SASTA OLIPHANT SCIENCE AWARDS

SOUTH AUSTRALIAN SCIENCE TEACHERS ASSOCIATION

Prize Winner

Science Writing

Year 11-12

Aryan Parwal

Prince Alfred College

How have NAD+ supplements impacted society's quest for eternal youth

Introduction:

Australia's population is aging, with approximately 1 in 6 Australians being 65 or older as of 2020, and this percentage is projected to increase (Australian Institute of Health and Welfare, 2021). The risk of age-related diseases increases with age. The belief in the potential benefits of anti-aging supplements to delay the onset of these illnesses and provide anti-aging benefits has fuelled their popularity in the past decade. Nicotinamide Adenine Dinucleotide (NAD) is one such supplement believed to mitigate the negative effects of aging, such as the development of chronic diseases and the aging process itself. NAD^+ is a coenzyme essential for cellular energy production and repair in all human cells. This report will focus on the influence NAD+ supplements have on the medical, pharmaceutical and anti-aging industries.

Biological Background:

NAD^+ is a coenzyme that is crucial for carrying out chemical reactions within the body. Coenzymes are small molecules that aid enzymes in catalysing various reactions. Additionally, enzymes are proteins that catalyse biochemical reactions by reducing the activation energy required for reactions. This is achieved by inducing strain and distortion on the substrate bonds, making certain bonds weaker and more susceptible to breaking. This provides an alternate metabolic pathway for the reactants to turn into products. There are specific areas on the enzymes called active sites that bind to a particular substrate. The induced-fit model explains how the active site adjusts its shape to precisely fit the substrate, forming the foundation of enzymatic activity (Sigma Aldrich, 2024). NAD is the general name used to describe Nicotinamide Adenine Dinucleotide, which NAD^+ refers to the active biological form of NAD with catalytic abilities. NAD, after receiving electrons and a hydrogen ion, transforms into NADH (Concierge MD, 2022).

Aerobic respiration is a chemical process carried out by many living cells to produce cellular energy. During respiration, glucose is first broken down in the cytoplasm to form pyruvate. The next phase, the Kreb Cycle, is composed of many stages of biochemical reactions that are intended to release stored chemical energy in nutrients, so the energy released, forms ATP (adenosine triphosphate) (Bjyus, n.d). The cycle starts with Acetyl coenzyme A (a two-carbon-molecule) which reacts with oxaloacetate (a four-molecule-carbon) to form citrate (a six-carbon-molecule). The citrate is further transformed into Isocitrate which is an isomer of citrate. After the synthesis of α-Ketoglutarate but before the synthesis of Isocitrate, one molecule of carbon dioxide is produced and one molecule of NAD^+ is then converted into reduced NADH. Two additional NADH molecules are produced throughout one cycle of the Kreb Cycle and one molecule of oxidised flavin adenine dinucleotide ($FADH_2$) has been derived from flavin adenine dinucleotide (FAD). Additionally, one molecule of ATP is generated through substrate-level phosphorylation. The Kreb Cycle repeats twice, and so the end products after two repeats consist of two ATP molecules, four carbon dioxide, six NADH molecules, and two $FADH_2$ molecules (TMP, n.d). See Figure 1 below

Apart from aiding the production of ATP, NAD+ supplements also aid in other cellular processes such as DNA repair by decreasing the accumulation of endogenous DNA damage which improves DNA's repair capacity (DOI, 2020).

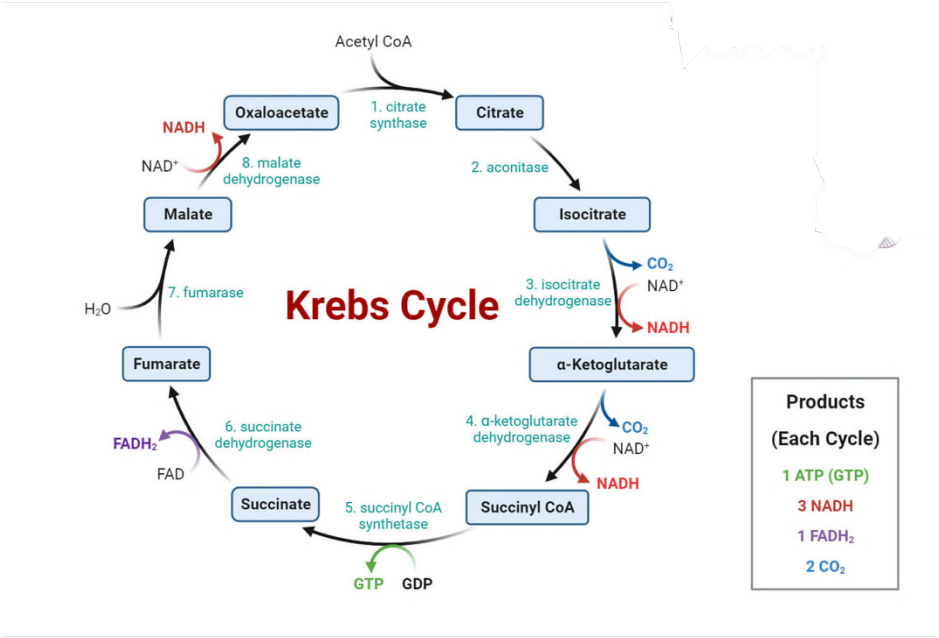

Figure 1: This figure illustrates the process of the Krebs Cycle, detailing the reactants and products generated at each stage (Microbe Notes, 2020).

Influence on Science and Society:

NAD+ supplements have influenced the scientific and medical fields due to recent theories about regulating life processes in organisms. Shinya Yamanaka demonstrated the feasibility of cell reprogramming through extensive experiments in mice, showing that it could enhance health and resilience in human cells. Throughout history, countless people have attempted to halt the aging process. Yet, scientists have long grappled with uncovering the underlying factors that contribute to the process of aging. From 1558, when women first discovered the wrinkle-reducing properties of meat applied to the face, to the early twenty-first century, when creams and pills became readily available in pharmacies, humanity has incessantly pursued to look more cosmetically appealing (Harpers Bazaar, 2016).

NAD was first discovered in 1906, but it became more widely known in the early 21st century, especially after the discovery of sirtuins in 2000. Sirtuins are proteins that depend on NAD^+. The concept of "NAD World" emerged, suggesting sirtuin 1 as a key regulator of aging and longevity in mammals. This sparked increased interest in the coenzyme NAD+ and led to a revolution in the anti-aging industry (DOI, 2000).

As organisms age, their tissue and cellular NAD^+ levels gradually decrease, impacting various model organisms like rodents and humans. Numerous age-related illnesses, such as sarcopenia, cognitive decline, and frailty, are directly linked to this drop in NAD^+ levels. Numerous illnesses may be slowed down or even completely cured by raising NAD^+ levels. Thus, focusing on NAD^+ metabolism has become a viable treatment strategy to reduce age-related illnesses and increase human lifespan and overall health (DOI, 2020).

Moreover, the popularity of anti-aging supplements, including NAD+ supplements, is increasing as many people strive to look and feel younger. This trend has significantly influenced both the

pharmaceutical and cosmetic industries and the anti-aging sector. NAD+ supplements can delay the onset of age-related diseases such as cancer and metabolic diseases, thereby reducing biological age and reversing age-related immune system decline (DOI, 1993).

As NAD^+ plays a pivotal role in numerous metabolic processes, NAD+ supplements have emerged as agents for rejuvenating aging cells, targeting pivotal mechanisms like damaged DNA and inefficient mitochondria (DOI, 2018). As a result, it has influenced the research into NAD^+ boosters, with trials underway to seek FDA approval for drugs aimed at combating aging (FDA, 2023). Moreover, these trials have spurred and influenced the development of other scientifically supported anti-aging medications, like recent trials involving metformin, originally a diabetes treatment. Successful outcomes from these trials could incentivise major pharmaceutical firms to invest more in anti-aging research, particularly in NAD+ supplements. Consequently, the emergence of NAD^+ boosters has influenced not only the pharmaceutical industry but also legislation in both the pharmaceutical and anti-aging sectors (Cosmos, 2023).

The utilization of anti-aging products such as NAD+ supplements within the scientific community has significantly reshaped public perceptions that were once steeped in negativity toward anti-aging interventions. Historically, the anti-aging industry bore a heavy stigma, partly due to marketing tactics employed by cosmetic companies. Additionally, these products are merely showcased through societal influences propagated by the media, promoting the idea of maintaining a “youthful look”, which undermines the concept of embracing the “natural aging” process gracefully. However, with the increasing prevalence of NAD+ supplements and their “scientific backing”, the industry and public perception of anti-aging is shifting from gimmicky products to promoting lifelong health by preventing diseases typically associated with aging. This evolving perspective may pave the way for more scientifically substantiated anti-aging products to enter the market, providing consumers with informed choices (Business Today, 2023).

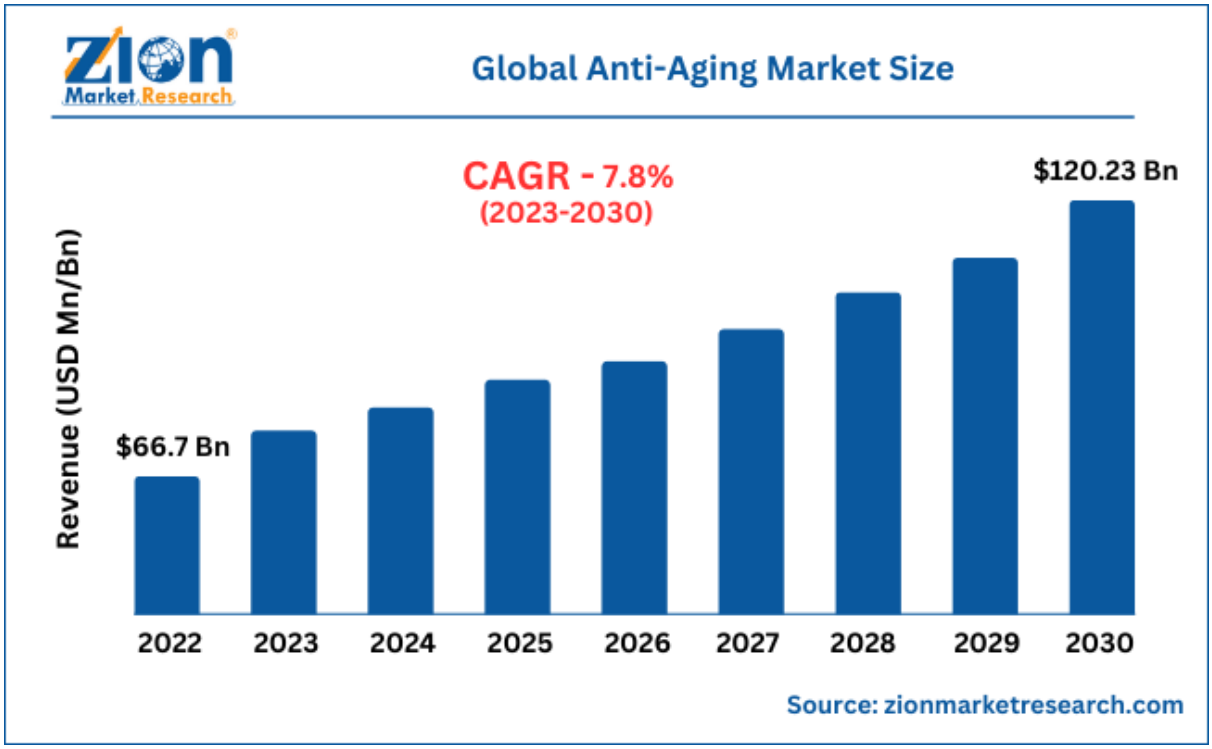

Figure 2: The global anti-aging industry is projected to experience rapid growth until 2030. (Zion Market Research, n.d)

Finally, products like NAD+ supplements have significantly boosted the economic development of the anti-aging industry, enabling a steady growth rate of 7.8% annually. See Figure 2

Currently valued at approximately sixty-six billion USD, the anti-aging industry is predicted to reach one hundred and twenty billion USD by 2030, clearly indicating that this industry will yield substantial economic benefits in the future. Furthermore, consumers recognize the importance of maintaining their health and preventing diseases before they arise, leading to increased spending on anti-aging supplements.

These products signify a recent breakthrough and stand out for their uniqueness. Consumers trust the scientific validation behind them, which attracts more buyers and establishes a new niche in the anti-aging market. This also contributes to the expanding 'natural products' segment. (Custom Market Insights, n.d).

Applications and Future Developments:

In addition to their anti-aging properties, NAD+ supplements can enhance energy levels and endurance by aiding mitochondria to produce NADH, the cell organelle responsible for ATP synthesis. By ramping up cellular metabolism and ATP production, NAD+ supplements can enhance physical performance and alleviate fatigue, making it particularly advantageous for athletes and individuals seeking to enhance muscle function and athletic ability. Additionally, NAD^+ has proven effective in addressing addiction and withdrawal symptoms by bolstering neurotransmitter production associated with addiction and mitigating oxidative stress, thereby curbing cravings, and fostering improved well-being during recovery. Furthermore, NAD+ supplements have been found to bolster immune function by bolstering the production and efficacy of immune cells, consequently bolstering overall health, and diminishing susceptibility to infections and ailments. This also leads to enhancements in the body's

metabolic processes, further contributing to overall well-being (AvizMedics, n.d). As well as curing certain illnesses and diseases, the future for NAD^+ is looking very promising. While there are many different areas of medicine NAD^+ may impact, the main area for potential NAD^+ application is the use of NAD^+ in prescription medication with tailored medication given to patients based on an individual's NAD^+ levels and metabolic profile.

Conclusion:

In conclusion, NAD+ supplements have significantly impacted society's quest for eternal youth by providing promising strategies to address age-related illnesses and improve overall well-being. With Australia's aging population growing, there is a rising demand for anti-aging solutions. NAD^+, a crucial coenzyme essential for cellular energy production and repair, has become a symbol of optimism in this endeavour. Scientific progress in understanding NAD^+'s role in cellular processes and aging has spurred the creation of NAD+ supplements, shaping not only the medical and pharmaceutical fields but also altering public perceptions of aging. Further exploration of NAD+ metabolism and its potential for tailored treatments based on individual characteristics foreshadows exciting developments in anti-aging medicine.

Word Count: 1493

References:

Australian Institute of Health and Welfare (2021). *Older Australians, Summary*. [online] Australian Institute of Health and Welfare. Available at: https://www.aihw.gov.au/reports/older-people/older-australians/contents/summary [Accessed 25 Apr. 2024].

Beyond Market Insights. (n.d.). *The Booming Anti-Aging Market: Key Players and Strategies*. [online] Available at: https://beyondmarketinsights.com/report/anti-aging-market/ [Accessed 23 May 2024].

byjus.com. (n.d.). *What is the role of NAD+ in cellular respiration?* [online] Available at: https://byjus.com/question-answer/what-is-the-role-of-nad-in-cellular-respiration-1/ [Accessed 25 Apr. 2024].

cosmosmagazine.com. (2017). *Going to trial: anti-ageing pills*. [online] Available at: https://cosmosmagazine.com/science/biology/going-to-trial-anti-ageing-pills/ [Accessed 25 Apr. 2024].

Covarrubias, A.J., Perrone, R., Grozio, A. and Verdin, E. (2020). NAD+ metabolism and its roles in cellular processes during ageing. *Nature Reviews Molecular Cell Biology*, 22(2), pp.119–141. doi:https://doi.org/10.1038/s41580-020-00313-x.

datacommons.org. (n.d.). *Earth - Place Explorer - Data Commons*. [online] Available at: https://datacommons.org/place/Earth?utm_medium=explore&mprop=lifeExpectancy&popt=Person&hl=en [Accessed 22 Apr. 2024].

Davila, A., Liu, L., Chellappa, K., Redpath, P., Nakamaru-Ogiso, E., Paolella, L.M., Zhang, Z., Migaud, M.E., Rabinowitz, J.D. and Baur, J.A. (2018). Nicotinamide adenine dinucleotide is transported into mammalian mitochondria. *eLife*, 7. doi:https://doi.org/10.7554/elife.33246.

Imai, S., Armstrong, C.M., Kaeberlein, M. and Guarente, L. (2000). Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. *Nature*, 403(6771), pp.795–800. doi:https://doi.org/10.1038/35001622.

Kenyon, C., Chang, J., Gensch, E., Rudner, A. and Tabtiang, R. (1993). A C. elegans mutant that lives twice as long as wild type. *Nature*, [online] 366(6454), pp.461–464. doi:https://doi.org/10.1038/366461a0.

Morrill, H. (2016). *Charting: A Brief History of Anti-Aging*. [online] Harper's BAZAAR. Available at: https://www.harpersbazaar.com/beauty/skin-care/a14980/history-of-anti-aging/ [Accessed 22 Apr. 2024].

Palkovick, L. (2022). *What Is The Difference Between NAD, NADh, And NAD+?* [online] Concierge MD - Mobile Medical Services. Available at: https://conciergemdla.com/blog/difference-between-nad-nadh-and-nad-plus/#:~:text=Basically%2C%20NAD%2B%20is%20the%20biologically [Accessed 28 Apr. 2024].

Research, C. for D.E. and (2023). *Alive By Nature, Inc. - 607435 - 05/06/2020*. [online] Center for Drug Evaluation and Research. Available at: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/alive-nature-inc-607435-05062020 [Accessed 25 Apr. 2024].

Research, Z.M. (n.d.). *Anti-Aging Market By Age Geographic (Baby Boomer, Generation X, and Generation Y), Product (Botox, Anti-Wrinkle Products, Anti-Stretch Mark Products, Others), By Services (Anti-Pigmentation Therapy, Anti-Adult Acne Therapy, and Breast Augmentation), By Device (Microdermabrasion, Laser Aesthetics, Anti-Cellulite Treatment And Anti-Aging Radio Frequency Devices): Global Industry Perspective, Comprehensive Analysis and Forecast, 2020 – 2028*. [online] www.zionmarketresearch.com. Available at: https://www.zionmarketresearch.com/report/anti-aging-market [Accessed 23 May 2024].

Sapkota, A. (2020). *Krebs cycle / Citric acid cycle / TCA Cycle with steps and diagram*. [online] Microbe Notes. Available at: https://microbenotes.com/krebs-cycle/ [Accessed 25 Apr. 2024].

September 2019, N.L.-S.W. 10 (n.d.). *Could a Drug Cocktail Reverse Biological Aging?* [online] livescience.com. Available at: https://www.livescience.com/reverse-aging-biological-clock-drug.html [Accessed 22 Apr. 2024].

Siegrist, J. (2024). NMR Chemical Shifts of Impurities Charts. *Merck*, [online] 1(1). Available at: https://www.sigmaaldrich.com/MX/en/technical-documents/technical-article/genomics/cloning-and-expression/blue-white-screening [Accessed 25 Apr. 2024].

TeachMePhysiology. (n.d.). *The TCA Cycle - Steps - Krebs Cycle*. [online] Available at: https://teachmephysiology.com/biochemistry/atp-production/tca-cycle-2/#:~:text=Step%201%3A%20Acetyl%20CoA%20(two [Accessed 27 Apr. 2024].

Tru Niagen. (n.d.). *What Is NAD+ and How Does It Affect Aging?* [online] Available at: https://www.truniagen.com/blog/science-101/what-is-nad/ [Accessed 25 Apr. 2024].

Ullah, M. and Sun, Z. (2018). Stem cells and anti-aging genes: double-edged sword—do the same job of life extension. *Stem Cell Research & Therapy*, [online] 9(1). doi:https://doi.org/10.1186/s13287-017-0746-4.

Weintraub, K. (2016). *Aging Is Reversible—at Least in Human Cells and Live Mice*. [online] Scientific American. Available at: https://www.scientificamerican.com/article/aging-is-reversible-at-least-in-human-cells-and-live-mice/ [Accessed 23 May 2024].

Wilk, A., Hayat, F., Cunningham, R., Li, J., Garavaglia, S., Zamani, L., Ferraris, D.M., Sykora, P., Andrews, J., Clark, J., Davis, A., Chaloin, L., Rizzi, M., Migaud, M. and Sobol, R.W. (2020). Extracellular NAD+ enhances PARP-dependent DNA repair capacity independently of CD73 activity. *Scientific Reports*, 10(1). doi:https://doi.org/10.1038/s41598-020-57506-9.

www.azivmedics.com. (n.d.). *NAD IV Therapy - Treatment, Types, Benefits, and Cost*. [online] Available at: https://www.azivmedics.com/iv-therapy-packages/nad-infusion#:~:text=NAD%2B%20IV%20infusion%20therapy%20has [Accessed 25 Apr. 2024].

www.custommarketinsights.com. (n.d.). *Global Anti-Aging Market Size, Trends, Growth, Forecast 2030*. [online] Available at: https://www.custommarketinsights.com/report/anti-aging-market/#:~:text=The%20size%20of%20the%20global [Accessed 24 Apr. 2024].

www.medicalnewstoday.com. (2020). *Hormonal imbalance: Symptoms, causes, and treatment*. [online] Available at: https://www.medicalnewstoday.com/articles/321486#:~:text=Hormonal%20imbalances%20occur%20when%20there [Accessed 22 Apr. 2024].

www.sciencefocus.com. (n.d.). *Breakthrough anti-ageing cell discovery could help you stay younger for longer*. [online] Available at: https://www.sciencefocus.com/news/slow-ageing-t-cells [Accessed 22 Apr. 2024].

Yang, J.-H., Petty, C.A., Dixon-McDougall, T., Maria Vina Lopez, Tyshkovskiy, A., Maybury-Lewis, S., Tian, X., Ibrahim, N., Chen, Z., Griffin, P.T., Arnold, M., Li, J., Martinez, O.A., Behn, A., Rogers-Hammond, R., Angeli, S., Gladyshev, V.N. and Sinclair, D.A. (2023). Chemically induced reprogramming to reverse cellular aging. *Aging*, 15(13). doi:https://doi.org/10.18632/aging.204896.