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Exciting Hope for Professional Women Marrying Late - Manipulating NAD$^+$ Metabolism: A Bright Future Prospect - A Narrative Review

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ABSTRACT

Nicotinamide adenine dinucleotide (NAD+)- portrays a key coenzyme implicated in cellular redox reactions, is intricately correlated with age correlated working disease degeneration along with metabolic disease. NAD directly as well as indirectly impacts a plethora of critical cellular working inclusive of metabolic pathways, DNA healing, chromatin remodeling, cellular senescence along with immune cells working, such cellular events as well as working are imperative for the sustenance of metabolic homeostasis in addition to healthy ageing. Numerous age correlated diseases have been corroborated to be correlated with diminished NAD+ quantities and plethora of age correlated diseases, that has been validated by separate approaches, with objective of escalating NAD+ quantities in the preclinical scenario. Ovarian ageing is a putatively natural event that has the properties of a reduction in the follicle numbers & working leading to diminished estrogen generation resulting in menopause. Regarding this it becomes essential to explore the numerous factors implicated in this complex event, which might possess the capacity of resulting in improvement of fertility in women with advancement of age. In the context of reduced NAD+ quantities with the propagation of age, favorable, encouraging outcomes with NAD+ precursors have been unveiled to facilitate NAD+ biogeneration are presented that might considerably result in improvement of oocytes quality along with ameliorate ovarian ageing; Therefore, to gain understanding into NAD+ metabolism, here we provide factors implicated in ovarian ageing, properties of NAD+ precursors, & their supplementation, present status of research in ovarian ageing.

Introduction

Continuing advances in reference to nicotinamide adenine dinucleotide (NAD^+)- biological work is persisting to unravel the mechanistic modes behind age correlated diseases, NAD^+ portrays the reduced kind of NAD which is a ubiquitous coenzyme observed in each human cell. It possesses a key part in sustenance of energy as well as redox homeostasis, controlling a considerably large networks of system over variety of cellular chambers along with tissues [1]. Apart from energy metabolism NAD^+ is believed to be a putative signaling molecule in addition to work in the form of restricting substrate in reference to a plethora of enzymes implicated in healing, epigenetic controlling, post-translational modifications as well as metabolic adaptation [2]. The reduction in NAD^+ quantities with ageing has been exhaustively displayed [3], along with its supplementation, with precursors of NAD^+ have been demonstrated to possess the capacity of escalating NAD^+ quantities *in vitro* as well as *in vivo*, working in the form of an attractive approach for tackling age correlated impairment in addition to disease.

The pioneer work regarding correlation amongst NAD^+ quantities as well as health was demonstrated practically a century back by Elvehejem et al. [4], in 1937 they invented the etiological factor of pellagra (displaying it occurred secondary to niacin deficiency) leading to reduction in NAD^+ quantities [4]. Studies which followed, displayed the association amongst lesser NAD^+ quantities in separate disease situations inclusive of metabolic conditions, neurodegenerative diseases along with ageing [5]. Sequentially, a remarkable attraction has been observed for unraveling the influence of NAD^+ metabolism on the origination of diseases, specifically age correlated diseases. In the present time supplementation with NAD^+ precursors have been believed to be favorable therapeutic strategy for the age correlated diseases [6], the manner corroborated by the advantageous actions seen in rodent models.

Ovarian ageing, having the characteristics of reduction in quantities in addition to quality of oocytes as well as diminished total ovarian actions [7], is responsible for considerable problems in reference to female reproductive health. Although, continued work is going on, the mechanistic modes behind ovarian ageing as well as longevity continue to be uncharted in addition to the association amongst different factors along with ovarian health warrants greater evaluation. At the time of birth women are endowed with around 2 million oocytes which decrease to just 1000 primordial follicles(PF) at menopause[8].Postponement of conception has the capacity of leading to fertility botherations for the women in the group with advancement of maternal age in view of association of their diminished ovarian reserve(DOR) had correlation with greater rates of aneuploidy along with sub idealization in embryonic generation in addition to maturation subsequent to normal pregnancy as well as following assisted reproductive technology(ART[9].A rapid escalation of studies which are evaluating different perspectives of ovarian ageing inclusive of stress, genetic ,diseases, dietary habits in addition to lifestyle factors are being conducted. Getting an exhaustive insight of such factors as well as their mechanistic modes is key regarding expansion of reproductive longevity along with escalating women's health.

Approaches concentrated on diminishing escalated ovarian ageing in addition to escalating quantities as well as quality of oocytes have undergone remarkable progression in current decades [10]. Acknowledged that mitochondrial impairment in addition to Oxidative stress (OS) mirror crucial factors in ovarian ageing, isolation of agents which possess the capacity of ameliorating ovarian condition might be possessing key part in tackling ovarian ageing. Such agents might work in the form of antioxidants or in form of molecules which are implicated in modulating cellular signaling pathway for avoidance of ovarian cells exposure to OS. Antioxidants are melatonin [11], Coenzyme Q10(CoQ10) [12], folic acid [13], resveratrol [14], Vitamin C along with E [7,15]. Despite, growth hormone (GH)does not come under the categorization of antioxidants, it possesses the capacity of influencing OS at the cellular level [16]. Clinical utility of small molecules or methodologies

implicating in mitochondrial transfer/mitochondrial replacement for escalating mitochondrial working was illustrated to possess efficacy in declining Oxidative injury in ovaries [17].

Earlier we had reviewed part of SIRTs in the form of epigenetic modifiers regarding postponement of Diabetic Kidney Disease (DKD)& in placental growth in pregnancy besides how resveratrol could be used in numerous chronic inflammatory diseases and Autoimmune Diseases, Part of NLRP3 Inflammasome, Telomeres Dynamics in Reproduction [18-24]. Here we have tried to review the significance of SIRT signaling pathway with NAD metabolism regarding improving oocyte quality.

Further work in this arena has illustrated NAD in the form of an attractive controller in attenuating age correlated diminished working. Apart from leading to improvement of mitochondrial working such molecule escalates different other cellular events along with working correlated with antiaging actions. What has been inspiring is that some studies have illustrated the probability of NAD precursors in the form of methodology for supplementation of body's NAD quantities. Moreover, clarity in reference to association amongst NAD quantities in addition to ovarian ageing has emerged over time period, with studies pointing those methodologies for buttressing NAD^+ might be efficacious in abrogating ovarian ageing, result in improvement of quality of oocytes in addition to escalate fertility. However, the particular mechanistic modes implicated behind such actions continue to be uncharted, thus making it imperative to evaluate further for getting greater clarity [5,25,26]. Here we provide an exhaustive review for finally achieving greater insight in reference to NAD^+ biology as well as metabolism, the factors impacting ovarian ageing, the NAD^+ precursors in addition to therapeutic plausibility of buttressing NAD^+ for tackling ovarian ageing.

Methods

Here we conducted a narrative review utilizing search engine PubMed, google scholar ;web of science ;emblaze; Cochrane review library utilizing the MeSH terms like Sirtuins; maternal ageing; Oxidative stress(OS); organs ageing; oocytes quality; embryo quality; implantation ; mitochondria function; Epigenetics; DNA methylation; Histone deacetylation ; DNA healing; chromatin remodeling ; cellular senescence; immune cell working ;melatonin; resveratrol ; nicotinamide mononucleotide ; nicotinamide riboside ; from 1914 to 2024 till date

Results

We found a total of 1000 articles out of which we selected 193 articles for this review. No meta-analysis was done.

2. Factors Impacting Ovarian Ageing,

2.1 Mitochondrial Impairment along with Oxidative Stress (OS)

The mitochondrion portrays a key organelle in oocytes, possessing a pivotal part regarding energy generation as well as estimating cellular fate [27]. Taking into account that it is a semisoveireign structure along with its DNA, the orchestrating crosstalk amongst the nuclear along with mitochondrial DNA (mtDNA) is critical for the appropriate working of mitochondrion [28]. Dysfunctional mitochondria possessing the properties of accrual of mtDNA mutations, diminished oxidative phosphorylation (OXPHOS) action, escalated oxidative injury, changed mitochondrial quality regulation, reduced biogeneration in addition to effectiveness of clearance, as well as disturbed mitochondrial dynamics have been correlated with mitochondrial ageing [29] (see Figure1) [rev in ref 30].

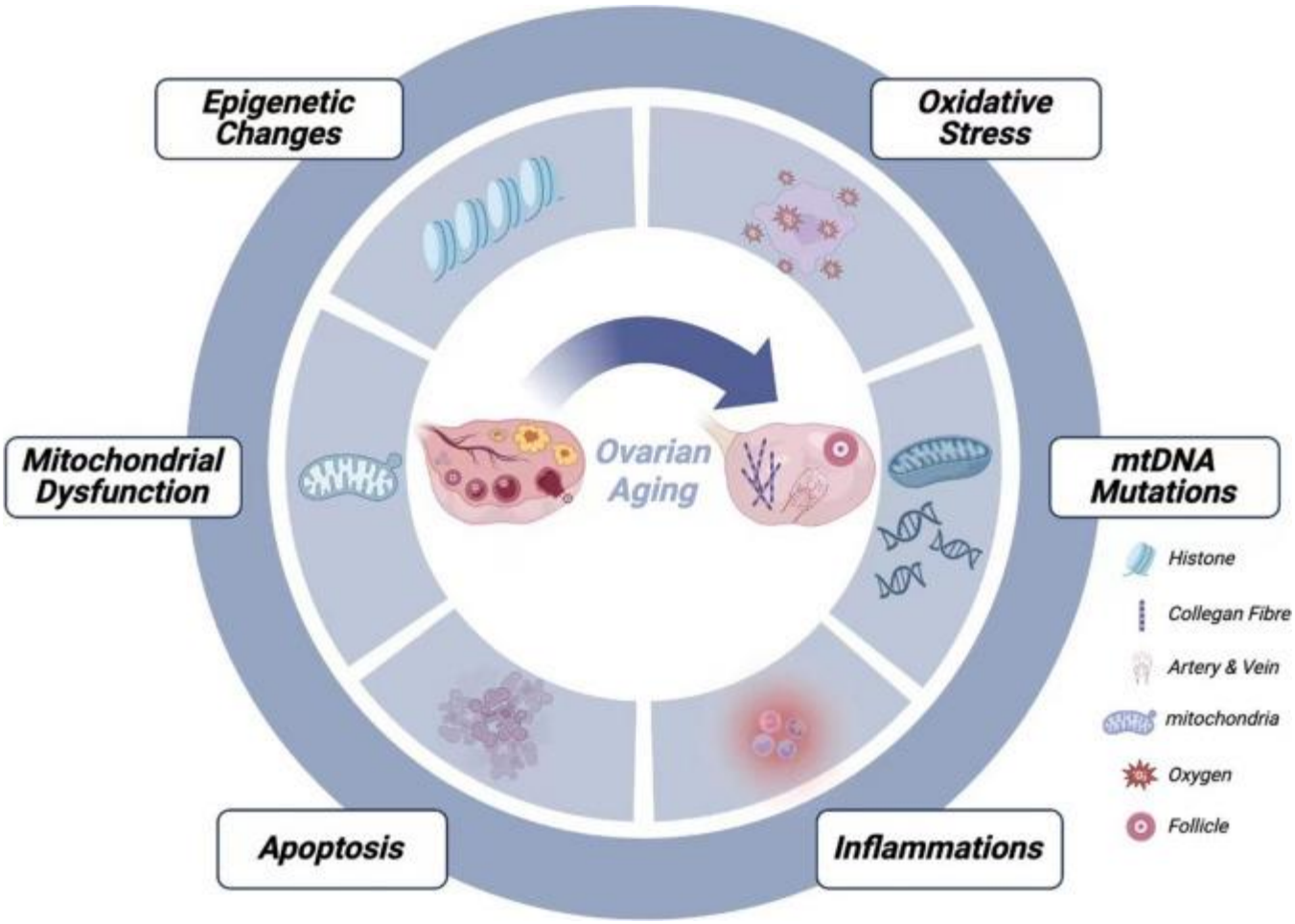


Figure 1: *Courtesy ref no 30-Factors affecting ovary aging. Many factors including mitochondrial dysfunction, apoptosis, inflammation, mtDNA mutations, oxidative stress and epigenetics changes have been shown linked to ovarian aging*

As per the free radicals posit, OS which takes place in view of escalated intracellular reactive oxygen species(ROS), portrays a key factor aiding in the mammalian senescence inclusive of reproductive ageing in female[31] .ROS comprise of free in addition to non-free radicals, basically formed in the form of byproducts at the time of metabolic events in eukaryotes[32].Moderate quantities of ROS are implicated in cell signaling ,possesses the capacity of facilitating cell survival, proliferation along with differentiation[33]. Nevertheless, once ROS quantities exceed a cell's oxidation resistance in addition to healing capacities they lead to induction of OS, oxidative injury to biological molecules in the cell, the milieu, resulting in ageing as well as of diseases generation [34]. In view of the positive association amongst ROS quantities in the human ovary along with age of the woman [35], human oocytes that continue to be dormant in the ovary over decades are specifically predisposed to OS. Endogenous antioxidants for instance superoxide dismutase (SOD) along with catalase existent in ovarian milieu are key for the ROS clearance. Nevertheless, a reduction takes place in their quantities with age resulting in incapacitating the ovarian capability of eliminating ROS [36,37]. In a study with the utility of single cell transcriptomics in case of non-human primates, it was pointed that oxidative injury portrays a crucial factor in aiding in age correlated diminished ovarian working [38]. ROS accrual in the ovary diminishes connection amongst oocytes as well as granulosa cell (GCs), stimulating induction of GCs apoptosis [39], aggravating corpus luteum

degradation [40], hampering oocytes maturation prior to ovulation [41], along with finally resulting in ovarian ageing. The well-illustrated association amongst telomere length of cumulus cells (CCs), in addition to oocytes as well as embryo quality [42], emphasizes that ovarian OS possesses the capacity of resulting in telomere shortening [43, rev by us in 24]. NAD possesses a crucial part in cellular redox reactions along with diminished NAD quantities are correlated with mitochondrial impairment in addition to production of oxidative injury.

2.2 mtDNA Conditions

Mitochondria possess a crucial part in generating the energy rich molecule adenosine triphosphate (ATP)via OXPHOS, yielding energy for maintenance of cell actions [44,45]. Leakage of electrons from the mitochondrial respiratory chain, portrays a reasoning for intracellular ROS generation. The exposition for such proneness takes place from the lack of histones which confer protection or DNA binding protein in mtDNA that resides amongst mitochondria, escalating its predisposition to ROS injury [46]. ROS formation as well as mtDNA injury are intricately interlocked with ROS formation usually overlapping the latter. Sequentially mitochondrial fission in addition to mitochondrial injury escalate which basically impact the stromal aspect of inner mitochondrial membrane (IMM) [47]. The slow dysfunction that takes place over a time period in the respiratory chain that is a result of mtDNA resulting in an aggressive escalated OS, particularly with age. Female mice having a shortening of lifespan as well as accelerated ovarian senescence secondary to accrual of mtDNA mutations in the germline [48] (Fig1)]. Additionally, younger women demonstrated a greater mtDNA copy count/ oocyte in contrast to older women, suggesting, declined mtDNA in aged ovaries at the time of ageing [49]. It has been illustrated that autologous or allogenic mitochondrial transplantation results in improvement of quality of oocytes in addition to IVF results in human as well as animal spp [50].

2.3 Epigenetics

Epigenetic modifications have been correlated with reduction of oocyte quality with ageing [51] (Fig1). The expression of DNA methyltransferases (DNMT) along with histone acetyl transferases, influence epigenetic modifications in oocytes, with age [52]. For example, diminished quantities of DNMTs in 35-40wk old mouse oocytes in addition to preimplantation embryos cause lesser DNA methylation quantities [53]. Furthermore, ageing influences histone methylation in mouse germinal vesicles oocytes [54], whereas elderly women demonstrate an absence of some histone marks in contrast to younger women. The transcription of histone deacetylates (HDACs) gets downregulated in mouse oocytes that are ageing, whereas histones continue to beacetylated in 10 mth old female mouse oocytes [55]. Such observations pointed that histone modification in ageing oocytes might be influenced before ovulation, with the probability of resulting in embryonic demise at the time of generation [56]. The expression profile of human 2nd meiotic division oocytes is correlated with ageing in addition to has a higher negative influence on histone acetylation, the moment woman's ageing takes place. Escalated corroboration in reference to microRNAs (miRNAs)- possess a critical part in controlling oocytes DNA methylation as well as follicles generation over different spp [57]. Disturbance of miRNAs expression aids in the generation of ovarian ageing [58]. Declined cellular NAD quantities result in dysfunctional NAD based along with NAD utility responsible for DNA healing in addition to genome intactness plausibly aiding in ageing correlated mutations along with epigenetic alteration.

2.4 Apoptosis

The ovary portrays a complicated as well as heterogenous organ comprised of a variety of cell kinds; where CC's possess a critical part in the ageing events. The CC's are obtained from the GC s are held responsible in the age correlated events in apoptosis of oocytes [59] (Fig1). The soluble molecules generated by CC's possess the capacity of inimically influencing ageing oocytes that result in amplification of oocyte ageing in addition to dysfunctional oocyte generation as well as maturation probability [60]. *In vitro* animal studies have displayed that coculture with CC's might

result in improvement of oocytes maturation [61], whereas oocytes from the elderly women illustrate a considerable reduction in the survival rate in contrast to oocytes from the younger mice [62]. Human studies have further displayed that GC s from the younger women display significantly lesser quantities of apoptosis in contrast to the ones from the elderly pts [63]. Furthermore, animal experiments have displayed escalated apoptosis quantities in GC lead to considerable reduction in ovulation along with fertility [64]. B cell lymphoma-2(Bcl2), a critical anti apoptotic factor was observed to be significantly upregulated in mature oocytes in contrast to immature oocytes that further buttresses the part of CC's in amplification of apoptosis in oocytes in addition to ageing of ovary [65]. The current work points that apoptosis along with autophagy in ageing cells aids in the reduction of NAD quantities in the organism [66,67].

2.5 Inflammation

Current work emphasizes inflammation in the form of emblem of ovarian ageing [68] (Fig1). Inflammatory ageing portrays chronic low grade inflammation status which is correlated with ageing as well as influences different parts of ovarian ageing for instance oocytes maturation [69], ovulation [70], implantation [71], in addition to delivery [72]. Animal experiments have displayed escalated gene expression associated with chronic inflammation with age [73]. At the time of ageing events, observation of escalated CD4+ cells, Bcells, as well as macrophages populations have been seen in the ovary, along with serum in addition to intraovarian quantities of mRNA of proinflammatory cytokines for instance, tumor necrosis factor alpha (TNFα), interleukin-6(IL-6), as well as IL-1α/β, along with nucleotide-binding domain, leucine-rich-repeat containing family, pyrin domain-containing (NLRP3) inflammasome as well as ASCgene [68]. NLRP3 inflammasome activation is correlated with age correlated inflammation in addition to impairment in different organs. studies where knockout (KO) of NLRP3 inflammasome as well as ASC gene was performed, displayed diminished intraovarian proinflammatory cytokines expression in addition to significant enhancement of follicles numbers, pointing that inflammation aids in age correlated reduction of ovarian reserve as well as anti-inflammation might result in avoidance of ovarian insufficiency [74]. The current work points those therapeutic strategies with the idea of escalating cellular NAD quantities at the time of ageing might be efficacious in diminishing inflammation along with both of senescent cells [75].

2.6 Telomere length along with Telomerase

Telomeres portray a dynamic nucleoprotein DNA structure having placement at the end of eukaryotic chromosomes, critical for the sustenance of genome intactness along with chromosomal stability [76]. Shortening of telomere length takes place with every cell division. Telomerase represents the telomerase reverse transcriptase (TERT) enzyme, aiding in the lengthening of the remarkably repetitive DNA sequences of telomeres [77]. Escalated telomere shortening has been displayed in studies to aid in cellular ageing as well as is intricately correlated with reproductive lifespan in addition to total longevity of life [78]. It has been the observation of scientific researchers that leukocytes attained from the post-menopausal women possess shorter telomeres in contrast to age matched controls still experiencing menstruation. Furthermore, women having lengthier telomeres have a tendency of getting into menopause at the later part pointing that the telomeres length is a significantly great biomarker in reference to reproductive ageing [79]. evaluation of human GC's has correlated telomere shortening as well as diminished or lack of telomerase with occult ovarian insufficiency or premature ovarian insufficiency (POI) [80].

Greater advancement by scientific researchers regarding assisted reproductive technology (ART), is immature oocytes possess significantly shorter telomeres in contrast to mature oocytes [81]. Telomere length in follicular cells display a positive association with oocytes along with embryo quality, in addition to diminished telomere length might be correlated with oocytes along with early embryo aneuploidy [42,82]. OS is believed to be the main etiological factor for the telomere shortening [43]. With escalated age quantities of ROS escalate in

ageing ovaries, escalating their susceptibility to oxidative injury, resulting in diminished generational capability. Utilization of antioxidant possess the capacity of hampering telomere shortening, fusion, DNA injury in addition to chromosomal instability in oocytes, hence ameliorating ROS modulated injury as well as sustenance of quality of ageing oocytes in addition to follicles [138,9].

3. NAD$^+$ biology along with Metabolism

3.1 History

The commencing of invention of NAD$^+$ occurred in 1906 by Harden &Young in the form of a low molecular weight substance that results in amplification of yeast extracts fermentation [84]. Its biochemical constitution was reported to be as an adenosine, phosphate along with a sugar group [85]. NAD$^+$ was reported to possess the capacity of switching hydride amongst molecules, that establishes it as a critical coenzyme in redox reactions, being an essential component of the energy metabolism in each organism [86]. NAD$^+$ possesses a controlling part in the working of dehydrogenases responsible for different catabolic pathways inclusive of glycolysis, fatty acids (FA)oxidation, glutamine breakdown. Besides its implications in energy metabolism, NAD$^+$ works in the form of a cofactor for the non-redox based enzymes for instance sirtuins, CD38, sterile alpha &TIR motif containing 1(SARM1), nuclear poly ADP ribose polymerase (PARP), ADP ribosyl transferase (ART's) in addition to RNA polymerases [87]. Such enzymes are key for the sustenance of intracellular homeostasis [67,88]. Reactions that use NAD$^+$ work in the form of a substrate or cofactor form nicotinamide (NMA) like a byproduct, that possesses importance for a plethora of metabolic pathways as well as cellular events. Numerous studies have illustrated the close in addition to dynamic part of NAD$^+$ metabolism, transport in addition to working, ensuring it a field of persistent scientific research [89]. NAD$^+$ becoming partitioned amongst cells is a complicated event, that implicates 3 primary subcellular pools in the i) cytoplasm, ii) nucleus as well as iii) mitochondria (Figure2).

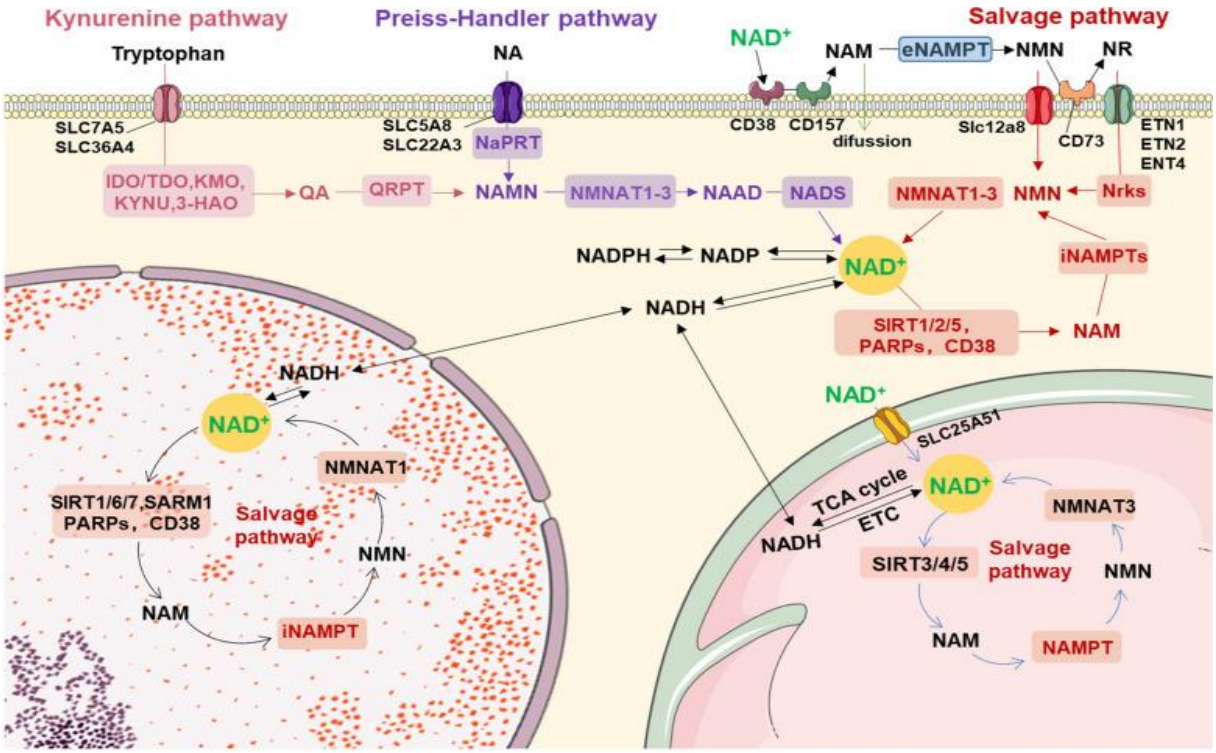


Figure 2

Courtesy ref no 30-Overview of NAD+ metabolism pathway. NA: nicotinic acid, NAM: nicotinamide, QA: quinolinic acid, NMN: nicotinamide mononucleotide, NR: nicotinamide riboside, IDO, indoleamine 2,3-dioxygenase, TDO, tryptophan 2,3-dioxygenase, KMO, 3-hydroxykynurenine (3-HK) by kynurenine 3-monooxygenase, KYNU, tryptophan 2,3-dioxygenase, 3HAO. 3-hydroxyanthranilic acid oxygenase, ETC, NAMN: nicotinic acid mononucleotide, NAD: Nicotinamide adenine dinucleotide, NADH: reduced form of NAD, NADP: Nicotinamide adenine dinucleotide phosphate, NADPH: reduced form of NADP, NAAD: nicotinic acid adenine dinucleotide, NAMPT: nicotinamide phosphoribosyl transferase, NMNAT: nicotinamide mononucleotide adenylyl transferase, QPRT: quinolinic acid phosphoribosyl transferase, NaPRT: nicotinic acid phosphoribosyl transferase, Nrk: nicotinamide riboside kinase, NADS: NAD synthase, PARP: poly (ADP-ribose) polymerase, TCA, tricarboxylic acid, ETC, electron transport chain

The probability of exchanging NAD^+ amongst the cytosolic along with nuclear pool is a putative fact, with such pools persistently documenting NAD^+ quantities that are practically akin [90]. Nevertheless, such capability of exchanging NAD^+ amongst the mitochondrial in addition to nucleocytosolic NAD^+ pool continues to be a debatable issue**.** Corroboration from yeast points that there is existence of NAD^+ transporters [91], whereas mammalian studies have illustrated mitochondria possess the capacity of picking up NAD^+ precursors in addition to complete NAD(H) [92]. Such observations point that mitochondrial NAD^+ pools have the capability of actually exchanging with other NAD^+ pools. The percentage controlling of such NAD^+ pools might differ considerably based on the organelles, tissue, cell kinds as well as age of the person with enzymes correlated with NAD^+ biogeneration in addition to breakdown is considerably restricted to compartments along with autonomously controlled [1,90,93].

3.2 NAD^+ biogeneration

Mammalian cells, but for neurons cells, lack the capacity of importing NAD^+ [94]. Thereby NAD^+ biogeneration takes place by using de novo pathway with use of tryptophan or the Preiss Handler pathway that implicates VitaminB3 products for instance nicotinic acid (NA) (Figure2). The implicated de novo biogeneration is basically expressed in the liver along with kidney [95]. De novo biogeneration pathway alias kynurenine pathway commences with the transformation of tryptophan to quinolinic acid (QA) followed by generation nicotinic acid mononucleotide (NAMN) as well as 5 phosphoribosyl-1 pyro phosphate (PRPP) that is catalyzed by the enzyme quinolinic acid phosphoribosyl transferase (QaPRT) [96]. NAMN might further get generated via the Preiss Handler pathway that consumes VitaminB3[97]. This molecule undergoes transformation into nicotinic acid adenine dinucleotide (NAAD) by the enzyme nicotinamide mononucleotide adenyl transferase (NMNAT). Following that NAD^+ synthase results in deamidation of NAAD resulting in generation of NAD^+ [98].

For the sustenance of intracellular quantities, thesalvage pathway (the primary pathway) is instrumental in the form of major sources using nicotinamide (NAM), Nicotinamide riboside (NR) as well as nicotinamide mononucleotide (NMN). NAM availability is from the food or generated by NAD^+ using enzymes [99]. Two reactions occur in its generation, i) first NAM transformation takes place catalytically into NMN by the enzyme nicotinamide phosphoribosyl transferase (NAMPT) along with PRPP [100]. ii)Subsequently NMN transformation takes place to NAD^+ by the conjugation of ATP's adenyl element that is catalyzed by the enzyme NMNAT [101]. NAMPT has broad placement in full NAD^+ correlated cellular chambers in addition to displays dynamic quantities [102]. This aids it in controlling the reactions of the body to nutritional status, stress, exercise as well as circadian rhythm, all being germane to the working of NAD^+ [103]. Thereby NAM is usually thought to be the NAD^+ precursors generally in cells. Placement of three

kinds of NMNAT isoenzymes in variety of subcellular chambers takes place for instance i) NMNAT1 in the nucleus [104].
ii) NMNAT2 in the cytoplasm as well as golgi apparatus iii) NMNAT3 in the mitochondria [102,105]. On the other hand, NR phosphorylation takes place via nicotinamide riboside kinase (Nrk) into NMN prior to transformation into NAD^+ by NAMPT [106].

3.2 NAD^+ Breakdown

The sirtuin enzyme family portrays a crucial part in controlling a plethora of biological events inclusive of, metabolism, circadian rhythm, stress, as well as ageing [107]. Working of these molecules is basically in the form of NAD^+ based deacetylases, using the NAD^+ in the form of cosubstrates for the elimination of acyl groups from their substrates which result in the production of 2 O- acyl ADP ribose along with NAM. In case of mammals there are 7 sirtuin gene in addition to protein family members observed namely (SIRT 1-7), every one of them displaying unique cellular placement as well as working [108]. SIRT 1 along with SIRT6 have their placement in the nucleus where they conduct critical part in DNA healing, in addition to genomic stability. Compared to that SIRT 7 possesses placement in the nucleolus. SIRT3, SIRT 4, as well as SIRT5, are implicated in controlling of mitochondrial homeostasis. Cytoplasmic SIRT 1, SIRT 2, as well as SIRT5, conduct significant part in the circadian rhythm in addition to gene expression. Dependent on their unique Km levels for NAD^+; sirtuins might be classified into 2 groups; sirtuins which have Km levels lesser than normal physiological reference ranges of NAD for instance SIRT2, SIRT 4, SIRT5 as well as SIRT6 in addition to sirtuins which have Km levels considerably based on the NAD accessibility inclusive of SIRT 1 along with SIRT3. The remarkable significance of sirtuins is in view of their capability of impacting cell homeostasis, which establishes them via impacting NAD^+ quantities in the form of a favorable therapeutic target for antiaging treatment.
The working of the poly ADP ribose polymerase (PARP) family, is in the form of a necessary utilizer of NAD^+. PARP family is constituted of 17 members in humans along with 16 members in mice, in addition to it possesses significant part in DNA healing as well as in preservation of genome intactness. PARP's promote the cleavage of NAD^+ to generate NAM along with ADP ribose. This gets followed by the attachment of ADP ribose to PARP as well as other receptor protein generating a polymer bond in an event known as poly (ADP ribosyl) acylation (PARacylation) PARacylation mirrors a post-translational modification, possesses critical part in the sustenance of DNA healing in addition to genomic stability [109]. Placement of PARP's, PARP1, PARP2 along with PARP3 is in the nucleus which utilize remarkable quantities of NAD^+. With ageing there is escalation of DNA injury in addition to PARP actions. Out of PARP's just PARP1, PARP2 along with PARP3 have placement in the nucleus, of which PARP1 , along with PARP2 utilize maximum NAD^+ quantities. Once DNA injury takes place PARP1 is the sole one which aids in about 90% of the PARP actions [109]. In view of the reasoning that Km levels of PARP's is lesser than normal physiological reference ranges of NAD, PARP's possess a remarkable benefit of participating in vying for the restriction accessibility of NAD resources in contrast to sirtuins [110].

The cyclic ADP ribose (c ADPR) synthase comprise one more NAD^+ utilizer group, of which CD38 in addition to CD157 possess maximum quantities in cells. They have both glycohydrolase in addition to ADP ribose cyclase actions, which degrade NAD^+ into NAM along with adenosine ADP ribose that gets followed by generation of c ADPR [111].
Working in the form of an intracellular messenger, c ADPR influences calcium (Ca^{2+}) signal transduction, ROS generation, in addition to apoptosis [112]. Apart from NAD^+ , CD38 along with CD157 have the capability of utilizing NMN along with NR in the form of alternate substrates respectively[113]. Thereby hampering agents of CD38 as well as CD157 possess the capability of restoration of quantities of NAD^+ in ageing subjects in addition to for the treatment of metabolic conditions as well as age correlated diseases [114]. The ageing event results in

escalation of CD38 as well as CD157 quantities resulting in escalated consumption of NAD^+ [113,115]. This process is implicated in the diminished NAD^+ quantities in aged mice in contrast to younger mice**.** It has been illustrated in studies that mice having CD38 insufficiency deletes diminished quantities found at the time of ageing [116], therefore pointing to the probability of its use in age correlated diseases [67,117]. SARM1, basically expressed in neurons gets categorized in the form of a glycohydrolase, as well as cyclase in addition to its breakdown of NAD^+ is intricately correlated with axonal degeneration [118]. Moreover NAD^+ is responsible for the generation of RNA caps, nevertheless, its physiological germaneness continues to be uncharted

3.3 Working of NAD^+

3.3 A. Metabolism

NAD^+ mirrors an essential coenzyme which is closely implicated in cellular redox reactions, therefore has a significant part in cellular energy metabolism in aged mice. It is occupied in variable catabolic pathway reactions, for instance glycolysis, amino acids breakdown, along with fatty acids oxidation (FAO). Amongst such biochemical events, reduction of NAD^+ takes place by taking up hydride ions, thus generating NADH. This gets followed by switching of electron gained to the electron transport chain (ETC), ending in the ATP generation. Apart from its elemental part in redox reactions, NAD^+ demonstrates multifaceted actions, by getting phosphorylated to form NADP. Such phosphorylated product works in the form of an acceptor of hydrogen resulting in the generation of nicotinamide adenine dinucleotide phosphate (reduced form (NADPH), which has a key part in antioxidant defense as well as metabolic generational pathways .

Escalating corroboration is pointing to approaches that are used with the idea of manipulating NAD^+ breakdown or escalating NAD^+ quantities might be yielding therapeutic target for treatment as antiaging or for metabolic conditions [1]. Sustenance of the harmony amongst NAD^+ is imperative for the idealization of working of metabolic tissues [120]. Alteration or disturbance [121], of metabolic status for instance high fat diet (HFD), postpartum weight reduction in addition to circadian rhythm disruptions might result in reduction in NAD^+ quantities, influencing NAD^+ based cellular events. On the other hand, escalating NAD^+ quantities via exercise, restricting calories, along with intervention through healthy diet have been demonstrated to result in diminished stress in addition to facilitate metabolic normalization [122]. KO of PARP1 or CD38 or clinical utility of PARP1 as well as CD38 hampering agents in mice cause supraphysiological NAD^+ quantities in vivo. Such alteration result in escalated metabolic rate at the time of HFD feeding in addition to ageing in mice, with glucose metabolism continues to be germanely normal, which portrays advantageous actions in avoidance of obesity [113,123]. Mice fed a HFD diminished enzyme NAMPT, a critical enzyme in the NAD^+ salvage pathway which diminishes actions in this pathway, which might be the plausible mechanistic modes behind reduction in NAD^+ quantities in obesity subjects. Furthermore, in mice possessing adipocytes particular NAMPT insufficiency, reduction in NAD^+ quantities take place, escalated insulin resistance (IR), in addition to metabolic impairment might further get inimical in adipose tissue (AT) [124], which further corroborates the importance of NAD^+ homeostasis in metabolic actions. SIRT 2, the longevity protein has been observed to facilitate lifespan in a NAD^+ based way [100,125]. Escalated NAD^+ quantities further escalate actions of nuclear SIRT1 as well as mitochondrial SIRT 3, therefore controlling of mitochondrial working in addition to avoidance of diet stimulated metabolic conditions [126].

3.3 B. Inflammation along with Immunity

The association amongst chronic inflammation, immune cells along with metabolic cells is complicated [127]. Attempting to target macrophage immune metabolic pathways by manipulating NAD^+ biogeneration or breakdown is of considerable significance regarding controlling the inflammatory along with ameliorating diseases [128]. Recently studies have pointed that NAD^+ represents a critical controlling factor regarding working of macrophages in addition to proinflammatory M1 like macrophages might work

in the form of the basic sources of the proinflammatory cytokines production in aged tissues. Escalated CD38 expression in macrophage results in escalated NAD^+ utilization, leading to (M1) macrophage polarization. Blockade of NAMPT possess the capacity of hindering switching glycolytic event in M1 macrophages, restricting proinflammatory reactions in vitro, along with reduction in systemic inflammation *in vivo*. On the other hand, escalated NAMPT working results in escalated NAD^+ quantities, facilitates anti-inflammatory(M2) macrophage polarization [67].

At the time of ageing event, escalated CD38 expression as well as escalated NADase action in the liver along with adipose tissue (AT) aiding in reduction in NAD^+ quantities, in addition to accrual of proinflammatory M1 like macrophages [66,129]. Dysfunctional de novo NAD (+) biogeneration in ageing macrophages further impacts their working at the time of ageing [130]. Guiding of a vicious cycle of inflammation is performed by escalated proinflammatory cytokines, which aggravates tissue in addition to DNA injury that gets followed by activation of main NAD^+ utilizers for instance CD38 in addition to PARP's aggravating age correlated physiological diminished.

Conversely, NAD^+ has been held responsible in the stimulation of cell demise in T cell subsets [131], along with that it possesses the capacity of impacting T cell polarization [132], which demonstrates double part of NAD^+ in immune controlling. The exact part of NAD^+ in adaptive immune working continue to be uncharted.

3.3 C. DNA Healing, Transcriptional Controlling, along with Epigenetics

The manner detailed previously the PARP protein family is a critical NAD^+ utilizer, has a central part regarding DNA healing, as well as genome intactness. Accrual of PARP takes place at the region of single strand DNA breaks in cellular DNA in addition to starts the DNA healing events by consuming NAD^+ with the idea of auto ADP (ribosyl)action. Thereby PARP is believed to be a main NAD^+ utilizer at the time of ageing event. Overactivation of PARP might be observed at the time of ageing or subsequent to DNA injury [133], along with such escalated activation might aid in age-based NAD^+ elimination. Pharmacologic hampering or PARP genetic insufficiency result in avoidance of NAD^+ elimination at the time of ageing in addition to nutrient stress [133]. NADP, working in the form of an endogenous hampering agent of mammalian cells, has been demonstrated to be a negative controller of PARylation, DNA damage healing in cancer cells [134]. Supplementation of NAD^+ precursors possess the capacity of diminishing DNA injury found in the hippocampal neurons of Alzheimer's disease mouse model [135]. Besides its part in DNA healing, PARP further possesses a part in the form of a chromatin modifier, a controller of DNA methylation at the time of transcription of proteins [136]. Accessing harmony amongst facilitating along with hampering of PARP actions regarding acquisition of DNA healing as well as transcription of proteins controlling is key for hampering ageing.

The sirtuin enzyme family is one more main NAD^+ utilizer, which apart from being implicated in healing of DNA injury events is further implicated in epigenetic modifications correlated with ageing. Avoidance of DNA injury gets attained by sirtuins by hampering mitochondrial ROS generation in addition to causing activation of foraging enzymes [137]. They further facilitate DNA injury healing via mechanistic modes for instance PARP activation [138], replenishing glutamine metabolism intermediates [139], along with homologous recombination modulated double-strand DNA breaks (DSBs) healing [140]. Maximum noticeable working of sirtuins is deacetylation of histones. Deacetylation of histones at H4K16, H3K9 as well as H3K56 by sirtuins aids in escalation of lifespan [141, rev in detail by us in ref 22]. The sirtuins further might result in activation of the DNA methyltransferases as well as facilitate DNA methylation [142].

3.3 D. Cellular Senescence

With NAD^+ elimination, persistent accrual of senescent cells takes place in ageing tissues. Nevertheless, no studies have documented a direct association amongst accrual of inflammatory

senescent cells in addition to NAD^+ quantities at the time of ageing event. The particular mechanistic modes by which NAD^+ impact cellular ageing continue to be uncharted. Studies have documented that NAD^+ quantities impact age correlated senescence- associated secretory phenotype (SASP) of senescent cells [143]. Supplementation of NAD^+ precursor substances lead to escalated SASP resulting in escalated chronic inflammation. CD38 is believed to be the basic enzyme implicated in NAD^+ utilization [113] leading to diminishing NAD^+ quantities at the time of ageing. With escalation of age CD38 quantities further escalate despite mechanistic modes behind this continue to be uncharted.

It has been found that senescent cells along with their SASP result in the activation of CD38 in macrophages, facilitating CD38 based NADase actions [66,129]. Additionally, CD38 expression is escalated in macrophages cocultured with senescent cells or which had exposure to conditioned medium [67], pointing that macrophage might portray the cell population which reacts to SASP with diminished NAD^+ quantities. One further study that cells having mitochondrial impairment, start proinflammatory programs by liberating proinflammatory cytokines. Nevertheless, supplementation of NAD^+ precursors possess the capacity of partly attenuating the condition, partly by diminishing inflammation as well as partly by diminishing senescent cells quantities [75].

3.4 Controlling Mechanistic Modes Behind NAD^+ Metabolism in Ovarian Ageing

3.4A Modifications of the Characteristics of Enzymes Implicated in NAD^+ Biogeneration or Breakdown

The mRNA expression quantities of enzymes implicated in NAD^+ biogeneration in mouse oocytes undergoing ageing, for instance NAMPT, NaPRT, Nrk, along with NMNAT1/3 display no significant alterations in contrast to that of young oocytes. Nevertheless, the mRNA in addition to proteins expression of NMNAT2 significantly diminish [144]. Greater assessment displayed that KO of NMNAT2 in oocytes result in diminished NAD^+ quantities, disturb assembly of meiotic spindle, as well as interfere with metabolic actions. Attempting to rescue the ageing phenotype of oocytes where NMNAT2 had been KO via SIRT1 overexpression point that NMNAT2 might be controlling the oxidative- redox homeostasis of the ageing oocytes by manipulating NAD^+ quantities, therefore repressing the ageing phenotype of oocytes. Furthermore, downregulating NMNAT2 possesses the capacity of conferring protection to cells against p53 based cell demise in reaction to DNA injury [145].

SIRT's, PARPs along with cADPR represent the main NAD^+ using enzymes in cells. SIRT's have been demonstrated to influence oocyte quality by manipulating redox status. All SIRT's have been found to get expressed in mouse oocytes as well as their quantities diminish over time period till blastocyst stage gets reached. Different studies have documented that SIRT 1 in GV's have the capacity of countering OS via Fox-3 MnSOD axis in case of in vitro culture situations [146]. Hampering of SIRT 1 actions in *in vitro* culture oocytes escalates the probability of spindle, as well as of chromosomal aberrations. SIRT1, fork head box proteinO3a(FOXO3a) in addition to NRF-1 might generate a complex on the SIRT6 promoter, together taking into account the controlling ovarian follicle generation [147]. p53 expression takes place in arrested follicles in addition to SIRT1, possess the capacity of p53 acetylation as well as p53 modulated apoptosis. activation of SIRT1 results in diminishing of p53 expression, plausibly preservation of oocytes that were deemed to get eliminated [148]. Oocyte particular overexpression of SIRT1 in mice persistently activated FOXO3a as well as repressed mammalian target of rapamycin (mTOR), leading to escalation of ovarian reserve, escalation of ovarian lifespan along with escalated reproductive capacity [149]. Epigenetic hampering agents or RNAi that target SIRT1 decline oocytes survival by declining H4K16ac quantities, therefore pointing to a communication amongst SIRT1repression as well as oocyte follicle generation [150]. SIRT 3 that is a mitochondrial sirtuin [151], has declined expression in ageing oocytes ovaries resulting in mitochondrial impairment in addition to aberrant spindle assembly. It has been demonstrated in studies that

SIRT 3 in activation in in vitro fertilized along with embryos cultured escalated mitochondrial ROS generation, that gets followed by upregulation of p53, leading to generational arrest [152]. This points to SIRT 3 confers protection against OS generational arrest in preimplantation embryos cultured in vitro.

PARPs are implicated in sustenance of chromosome stability place at the time of meiosis, which possesses a key part regarding DNA healing [153]. Whereas studies that corroborate that controlling NAD^+ metabolism has the capability of diminishing DNA injury as well as genome stability [25,26,154], the particular part in addition to mechanistic modes behind PARPs actions continue to be uncharted.

CD38, an enzyme that portrays cADPR possesses the capacity of impacting cellular Ca^{2+} signaling, ROS generation, along with apoptosis. Expression of CD38 does not occur in ovarian follicles, however gets maximum expressed in ovarian immune cells, demonstrating age-based escalation of CD38 Expression. CD38 insufficiency leads to escalated NAD^+ quantities in the ovaries, NAM along with ADPR quantities in addition to positive controlling of NAD^+ metabolism. CD38 insufficiency escalates ovarian reserve as well as reproductive capacity in young female animals along with has the capability of abrogating inflammation in animals which aging by diminishing multinucleated macrophage giant cells post reproduction. Such advantageous actions are correlated with escalated ovarian NAD^+ quantities [155] (Figure3). Nevertheless, the precise mechanistic modes behind continue to be uncharted.

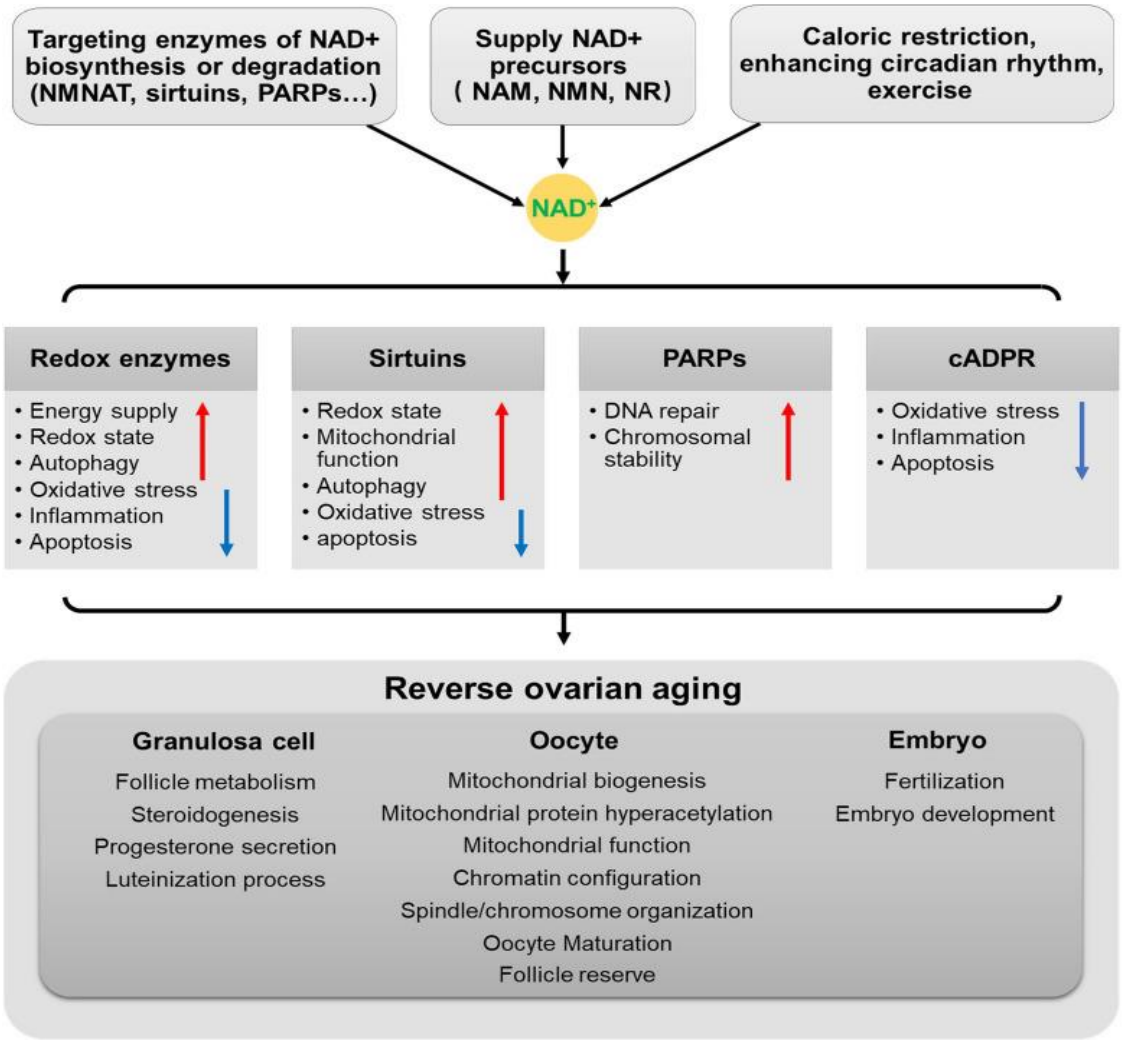


Figure 3: *Courtesy ref no 30-Mechanism of NAD + metabolism in ovarian aging. Modulating the properties of enzymes involved in NAD + biosynthesis or degradation, providing NAD + precursors, and altering lifestyle collectively govern cellular NAD + metabolism. In the context of ovarian aging, NAD + metabolism predominantly exerts a beneficial influence on granulosa cells, oocytes, and embryonic development through alterations in the redox state and the activities of NAD + -dependent enzymes. This ultimately manifests as the reversal of ovarian aging*

3.4 B. Supplementation of NAD^+ precursors

Protein acetylation quantities are aberrantly controlled in oocytes of ageing mice. SIRT's, that portray a family of class IIIHDAC's further target plethora of non-histone substrates. NAM gets generated by NAD^+ based enzymes; SIRT's, PARPs along with CD38 in addition to precursors for NMN as well as NAD^+ generation. NAM supplementation possesses the capacity of escalating cellular NAD^+ quantities along with non-competitively hampering deacetylase action of SIRT's. presently NAM is believed to be hampering SIRT1 in addition to SIRT2. SIRT1controls p53 acetylation along with p53 based apoptosis in reaction to DNA injury as well as OS [156]. SIRT2's part is in microtubule protein deacetylation [157]. In contrast to class I in addition to II HDAC's hampering agents NAM has the capability of acetylation along with deacetylation of microtubule protein in ageing oocytes at lesser quantities, significantly hampering the generation of aberrant microtubule structures at the time of ageing in addition to impacting age correlated phenotype correlated with the maturation [158].

Additionally, NAM therapy significantly diminishes the effectiveness of germinal vesicles breakdown (GVBD), that generates akin actions on utilization of SIRT2 particular hampering agents. Nevertheless, following processes at the time of meiosis I, inclusive of spindle assembly in addition to chromosome alignment are uninfluenced. oocytes that had NAM therapy displayed greater expression of the anaphase facilitating complex Cdc-20 at the time of exit from meiosis I, which is correlated with reduction of cyclinB 1 quantities as well as escalation of hampering phosphorylation of cyclin dependent –kinase1(Cdk1), anticipated to result in inactivation of Cdk1 generating a mid-meiotic arrest in meiosis II [159]. Greater quantities of NMN cause advantageous actions instead of inimical sequelae in ovulated mouse oocytes [158] (Figure3).

Generation of NMN takes place as a result of NAMPT reaction, that portrays a key intermediate in NAD^+ homeostasis. In mice NMN supplementation possesses the capacity of escalating cellular NAD^+ quantities, reverting the ageing phenotype of oocytes in ageing mice, along with ameliorate the inimical actions of ageing on generation subsequent to NMN supplementation in culture medium [5]. Nevertheless, the precise mechanistic modes behind continue to be uncharted. SIRT2 via deacetylation in addition to stabilization of BubR1 possesses a part in sustenance of microtubule kinetochore attachment guaranteeing of chromosomal separation constancy. NMN advantages for oocytes in ageing animals gets basically attained by overexpression of SIRT2. NMN supplementation further has the capacity of escalation of fertilization capability of oocytes by sustenance of dynamics of the cortical granule ovastacin [25]. NMN supplementation for considerable time period results in upregulation of the expression of Peroxisome Proliferator Activated Receptor γ -Coactivator -1α (PGC-1 α), a protein correlated with mitochondrial working to some degree, reverting injury to granulosa cells in ovarian follicles [160].

Scientific researchers have demonstrated that NR supplementation has the capacity of escalating NAD^+ quantities in mouse ovarian cells, reverting ovarian ageing phenotype. Significant upregulation of the gene expression correlated with mitochondrial dynamics for instance i) mitochondrial fusion-related genes a) mitofusins 1 as well as 2(MFN1, MFN2), b) along with optic atrophy 1 mitochondrial dynamin-like GTPase (OPA1), ii) dynamin-related/like protein 1 (DRP1, also known as DMN1L), and mitochondrial fission

1 protein (FIS-1) that decline with ovarian ageing. Upregulation of intermediate metabolites, implicated in energy metabolism for instance citrate, isocitrate, D- fructose along with NAD^+ take place which result in escalated ATP generation. Additionally, mitochondrial biogeneration gets escalated in addition to expression of the mitochondrial autophagy correlated genes get upregulated for instance PINK1(PTEN-induced kinase 1), light chain 3B (LC3). Escalation of mitochondrial autophagy takes place subsequent to NR supplementation in addition to leads to improvement of mitochondrial dynamics as well as mitochondrial working in the ageing oocytes, finally resulting in improvement of quality of oocytes [26]. One more study recently performed by Lietal. [154], in 2023 documented that NR supplementation diminished ameliorated quality of oocytes which took place post ovulation. This study demonstrated that mRNA expression quantities of core proteins of mitochondrial OXPHOS chain got evaluated, with their observations pointing that NR therapy escalated the expression of Sdhb, Uqrc2 in addition to Atp5a1[154], that aids in avoidance of the mitochondrial correlated with ageing (Figure3).

4.Therapeutic plausibility of NAD^+ in Ovarian Ageing

4.1 Pharmacologic

The NAD^+ quantities in body get controlled by a fine harmony amongst biogeneration in addition to breakdown that gets impacted by ageing [1,161], The quantities of NAD^+ in different tissues might undergo modifications via dietary, lifestyle in addition to Pharmacologic intervening in some subjects. Presently 3 major approaches for escalating quantities of NAD^+ get used via Pharmacology i) improvement of the actions of enzymes implicated in NAD^+ biogeneration, specifically the ones which are crucial in the restricting step in both the de novo biogeneration in addition to the salvage pathway for instance alpha-amino-β carboxymuconate-ε -semi aldehyde decarboxylase(ACMSD) as well as NAMPT2,ii) hampering enzymes implicated in NAD^+ breakdown for instance PARP along with CD38 iii) supplementation of diet with NAD^+ precursors for buttressing NAD^+ generation via the salvage pathway. Studies performed in in *Caenorhabditis elegans* [133], flies [162], rodents [163], in addition to humans [164], have illustrated the plausibility of escalating NAD^+ quantities by provision **of** NAD^+ precursors (Figure4).

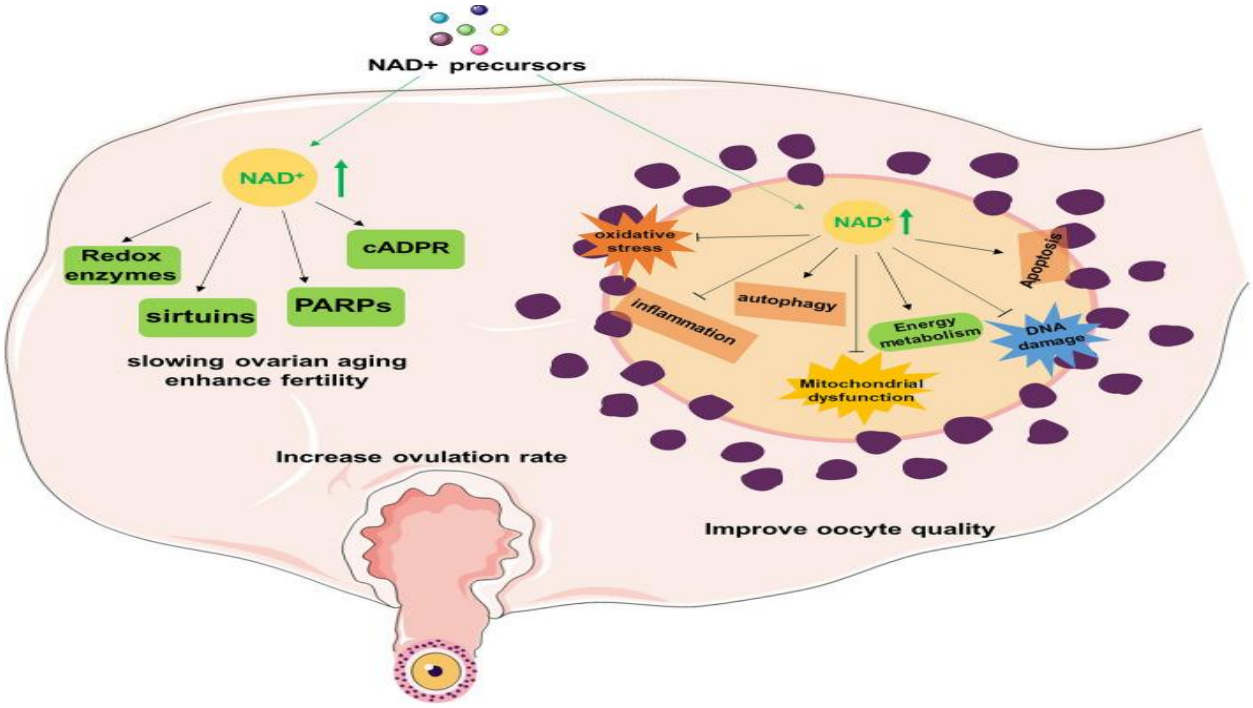


Figure 4: *Courtesy ref no 30-Therapeutic potential of NAD + in ovarian aging. Previous studies conducted in multiple model animals and humans have revealed the feasibility of increasing NAD + levels by supplying NAD + precursors, and the NAD + metabolomic pathway can enhance mitochondrial function, enhance autophagy levels, and maintain protein homeostasis in mitochondria and lysosomes, consequently decelerating the progression of ovarian aging*

4.2 Properties of NAD^+ Precursors

Till now the isolated NAD^+ precursors are inclusive of tryptophan, NA, NAM, NR, along with NM. Such precursors have attracted considerable interest in view of NAD^+ precursors possess significant part in NAD^+ biogeneration that has been escalatingly acknowledged [165]. None of the publications have isolated any particular predeliction of NAD^+ precursors. NA, in addition to NAM have a remarkably long association with pellagra [166], a disease whose avoidance is probable by ingesting a diet having enrichment of such precursors [167]. More recently NR, along with NMN have attracted considerable interest in view of germanely lesser inimical sequelae in contrast to NA, as well as NAM. Such precursors gain entry via variety of mechanistic modes for instance i) direct passage of NA into cells with the aid of membrane carriers like soluble carrier family5 members 8(SLC5A8), or SLC22A13 [168], whereas NR gain entry via equilibrated nucleoside transporters (ENTs). NAM might have direct entry or by transformation into NMN by NAMPT. Entry of NMN might result by particular transporters (Slc12a8) gene [169], by transformation into NAM or NR through CD38 or CD73 or via (ENTs) [95,113].

In reference to pharmacokinetics, NAD^+ precursors document unique characteristics. Tryptophan, NA, in addition to NAM display the maximum quantities of plasma, overtaking 0.1μM, with NAM plasma quantities getting 10-fold greater in contrast to NA**.** Furthermore, in case of basal situations NR, along with NMN are practically negligible in plasma. This points towards liver being the main source of circulating NAM that is what reasons out 95% of tryptophan is implicated in NAM generation. Absorption, generation in addition to utilization of NAM along with NAD differ significantly in organs, with association with the expression of enzymes implicated in generation in addition to utilization of NAD. Delivery of greater quantities of NA result in escalated quantities of NAM that has greater half-life in contrast to NA [170]. Despite NAM possesses greater robust capability of escalating NAD^+ quantities, greater quantities of NAM might result in inimical sequelae for instance nausea, along with vomiting [171], in addition to might negatively influence NAD^+ utilizing enzymes for instance SIRT's, as well as PARPs [164]. Clinical studies have illustrated the efficacy of NA in escalating NAD^+ quantities in blood in addition to skeletal muscle, therefore abrogating systemic NAD^+ insufficiency in subjects with mitochondrial myopathy as well as leading to improvement of muscle working [172].

In agreement, oral ingestion of NAM possesses the capacity of pacey escalation of NAM along with NAD^+ quantities in blood [173]. Scientific researchers have further demonstrated that NMN has the capability of significantly escalating NAD^+ quantities in peripheral tissues possessing the capacity of crossing the blood brain barrier (BBB) for escalating NAD^+ quantities in brain [174]. On oral ingestion pacey absorption of NMN takes place from intestine into blood stream within 2-3', has fast organization in different tissues via circulation amongst 15'. Subsequent to15' plasma NMN quantities revert to basal quantities, whereas escalated NAD^+ quantities are found in liver, skeletal muscle along with cerebral cortex [175]. Furthermore, a clinical trial illustrated that single oral NMN supplementation possess the capacity of considerably escalating NMN in addition to NAD^+ metabolites in plasma [176]. Akin to that oral NR ingestion escalates NAD^+ quantities in blood cells illustrating 2-3-fold greater robustness in escalating ADPR in contrast to NAM [164].

4.3 NAD^+ Buttressing *in vitro*

Noticeably, the plausible advantages of NAD^+ precursors supplementation have attracted considerable interest regarding avoidance of in addition to treatment of age correlated diseases. However, the influence of NAD^+ precursors supplementation in reference to ovarian ageing have been studied inadequately. Occasional studies have evaluated part of NAD^+ precursors in ovarian ageing. For example, a study performed by Lee et al. [158], in 2013 displayed that provision of NAM to ageing ovulated mouse oocytes *invitro* possessed the capacity of hampering the generation of aberrant spindle as well as diminished cell fragmentation, pointing to the plausibility of postponement of ageing events. Moreover, buttressing NAD^+ biogeneration with NA was observed to result in avoidance of ageing events in oocytes that were aged [144]. Nevertheless, debatable outcomes have been documented in other studies. In particular a study conducted by Riepsamen et al. [159], in 2015 observed that NAM disturbed the controlling of Cdk1 in ovulated oocytes leading to dysfunctional entry into meiosis I in addition to generating metaphase II arrest [159]. Nevertheless, a study recently performed by Lietal.[154], in 2023 documented that NR supplementation had the capability of sustenance of oocytes quality [154]. NR possesses the capacity of hampering the reduction of NAD^+ quantities, overtakes the impairment, preservation of spindle in addition to chromosomal structure, reduction of ROS quantities along with DNA injury, therefore escalating oocytes quality in addition to embryonic generation plausibility as well as probability of escalating assisted reproductive technology (ART) success rate. The exact mechanistic modes behind NR supplementation continue to be uncharted. Akin to that a study observed that NMN therapy in embryo cultured reverted the negative influence of ageing on generation [5].

4.4 NAD^+ Buttressing *in vivo*

The assessment of the influence of NAD^+ precursors supplementation has been performed *invivo*. The outcomes have pointed that NMN supplementation possesses the capacity of escalating oocytes quality, the rate of ovulation along with fertility in aged mice [5]. It has been observed that treating preovulation oocytes with NMN for a 4-week time period had the capability of restoration of oocytes spindle assembly along with diminished aneuploidy incidence in addition to improvement of oocytes quality. Furthermore, the mechanistic modes behind improved ovulation using NMN therapy might be correlated with NAD^+ metabolism as well as actions of other tissues over follicles generation. Supplementation using lesser dosage NMN therapy has been observed to escalate pregnancy rates in addition to live birth rates (LBR) in aged mice, pointing that it caused idealization of NAD^+ quantities for fertility therapy. Additionally, NMN therapy further might guarantee normal dynamic of the cortical granule, improvement of sperm binding along with escalating the fertilization capability of aged oocytes [26]. The advantages of NMN therapy are basically believed to be due to escalating energy metabolism of oocytes despite an akin action was found in aged oocytes having transgenic overexpression **of** SIRT2. However, the outcomes from SIRT2 KO mice, pointed that SIRT2 protein might not be possessing a critical part in the working of oocytes [177]. Sequentially, greater work is imperative for unravelling if other SIRT members take part in modulating the actions of NMN.

A different study found akin actions on using NMN for buttressing NAD^+ biogeneration in aged mice [25]. Miao et al. [25], found that NMN supplementation resulted in escalation of antral follicles as well as ovulated oocytes whereas diminishing the generation of fragmentation of mature oocytes. NMN therapy escalated cytoplasmic maturation along with that of nucleus in aged oocytes therefore buttressing the maturation rates of oocytes. Via utilization of cell transcriptome profiling, they assessed the plausible effectors of NMN in addition to invented that the influence of NMN on aged oocytes might be in view of its actions over mitochondrial working. In particular the advantages of NMN apparently takes place by the restoration of mitochondrial working, diminished accrual of ROS along with repression of apoptosis (Figure4). A study recently performed by Huang et al. [160], in 2022 pointed that long

term treatment(20wks) in mice aged 40wks had the capability of escalating mitochondrial working, escalating autophagy quantities (In particular mitophagy) in addition to sustenance of protein homeostasis in mitochondria as well as lysosomes, sequentially diminishing rates of propagation of ovarian ageing [160]. Furthermore, persistent NMN supplementation was observed to diminish the expression of ovarian ageing biomarker P16, escalate the quantities of mitochondrial working correlated protein. Additionally, NR supplementation was observed to result in restoration of mitochondrial working, escalating energy metabolism resulting in enhanced ovarian reserve, enhanced plausibility of ovulation in addition to greater LBR [26]. Nevertheless, presently there is absence of adequate studies evaluating NAD^+ precursors supplementation in ovarian ageing.

5. Therapeutic Plausibility of NAD^+ in Clinical Trials over Ageing Associated Situations

Maximum rodent preclinical studies have displayed an advantageous translational plausibility in reference to NAD^+ buttressing treatment. NR as well as NMN are the ones maximum utilized clinical in trials [176,178], none of which have been demonstrated to possess inimical sequelae [179], whereas NA had the capability of leading to flushing along with pain [180]. Clinical trials where assessment of pharmacokinetics in addition to toxicology studies have yielded initial corroborating proof which validate safety of NAD^+ buttressing treatment [181-184]. However, the translation of the favorable therapeutic actions found in preclinical animal models to humans has been observed to be bothersome in view of mild in addition to debatable kind of attractive actions of NAD^+ precursors.

Positive outcomes have been obtained in clinical studies, pointing that human escalating pointing that NMN supplementation possesses the capacity of enhancing muscle insulin sensitivity in overweight/ obese prediabetic women, therefore improvement of insulin signaling as well as remodeling [184]. In a study recently performed by Huang et al. [185], regarding antiaging actions of NMN it was found NMN supplementation had the capability of significantly enhancing NAD^+ quantities in the serum of healthy persons. Additionally, NMN supplementation escalated insulin sensitivity, in the manner considerable diminished homeostatic assessment of insulin resistance (HOMA-IR) scores in contrast to the ones in the control groups, which emphasized the antiaging actions of NMN [185]. Nevertheless, a clinical study using a dose based NMN supplementation did not influence insulin sensitivity despite significant improvement was observed in those taking part [183]. Martens et al. [6], demonstrated short term NR supplementation possessed certain advantageous actions in addition to was well tolerated, elevating NAD^+ in healthy middle aged and older adults [6]. Additionally, long term NR supplementation demonstrated greater safety, tolerability as well as greater effectiveness regarding stimulating NAD^+ metabolism in healthy middle aged and older adults leading to decreased circulating quantities of proinflammatory cytokine [182]. certain studies performed in older adults have pointed that NAD^+ precursors supplementation via tryptophan, NA, along with NAM, did not result in improvement of mitochondrial or skeletal muscle working [181]. Furthermore, NR supplementation had in obese men practically negligible actions [178,186]. Intriguingly, a study illustrated that NA supplementation had the capability of restoration of escalating NAD^+ quantities in blood in addition to skeletal muscle, therefore abrogating systemic NAD^+ insufficiency in subjects with mitochondrial myopathy as well as leading to improvement of muscle working [172].

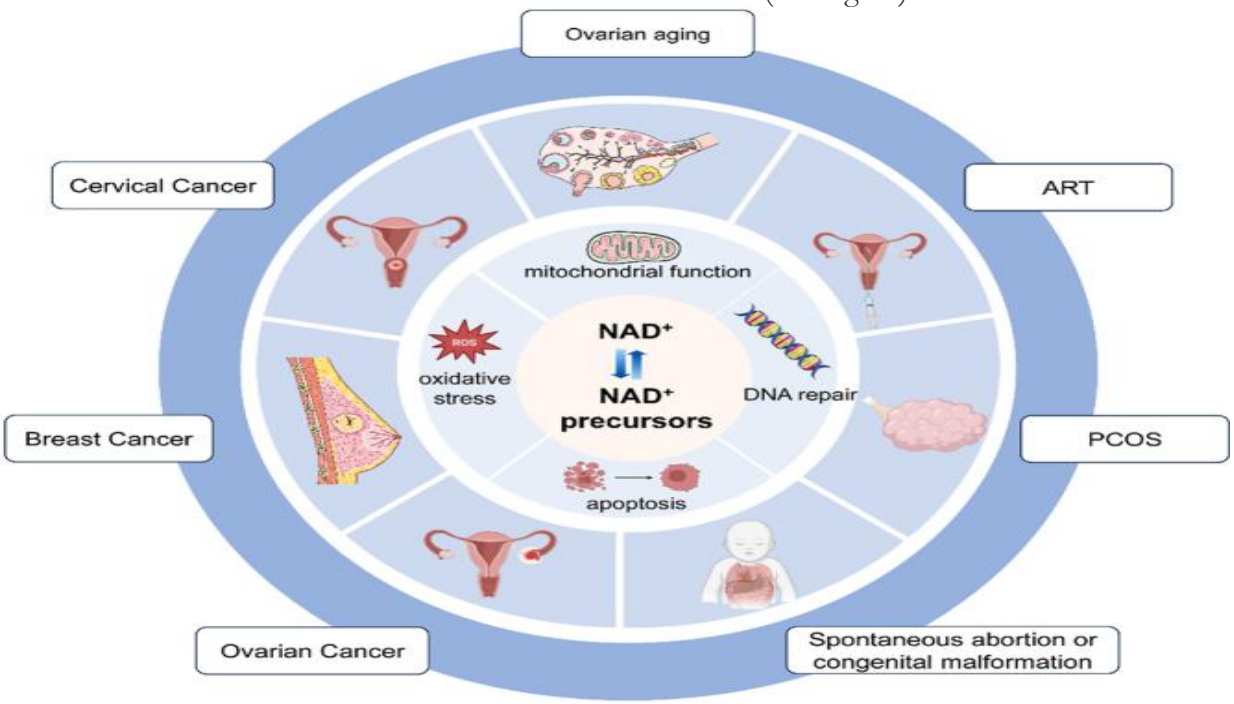
Therefore, the reasoning for the lack of advantageous actions of NAD^+ buttressing treatment in human clinical trials continue to be uncharted. This might be probably correlated with the incapacity of NAD^+ precursors in escalating NAD^+ quantities in particular tissues in human body [165,187]. Additionally, time period of studies might have been insufficient for achieving clinical advantages in addition to experimental fashioning

basically focused on healthy persons having normal baseline quantities. Therefore, greater future clinical trials are necessary for deciphering the ideal dosage regimens, treatment duration as well as long term toxicological results. There is requirement for subjects taking **part** have to be variable for efficacious overcome translational botherations correlated NAD^+ facilitating approaches.

Conclusions & Future Directions

Thus, here we have comprehensively summarized how NAD^+ possesses considerable significance In different disease models for instance cancer, neurodegeneration, diseases of different organs, ageing have received remarkable interest [120,188, 189]. For this imperative part of NAD^+ in the form of cofactor in key redox reaction are implicated in pivotal events for instance energy metabolism, cellular homeostasis, post-translational modifications, epigenetic alterations, along with RNA stability [190]. Studies in reference to NAD^+ buttressing by supplementation of NAD^+ precursors regarding ovarian ageing are emerging with remarkable excitement. Studies in animal models regarding ovarian ageing illustrated supplementation of NAD^+ precursors resulted in improvement of oocytes quality along with ameliorated resulting in improvement of fertility. Nevertheless, the mechanistic modes behind NAD^+ precursors supplementation continue to be uncharted. Variable queries have arisen inclusive of transportation of NAD^+, along with its precursors to ovarian cells in addition to its organelles, predeliction of ovarian cells for particular NAD^+ precursors, as well as the actions of particular metabolic pathways in health ageing ovaries along with healing mechanistic modes for the toxic metabolites generated by NAD^+ metabolism. At the present time the advantages actions of NAD^+ buttressing in human clinical trials are remarkably restricted, generating substantial queries which need to be answered.

Further extrapolating this deep knowledge, it might further be used for treatment of PCOS, variable cancers in particular ovarian and breast cancer where we recently emphasized the significance of utilization of PARP hampering agents in treatment of high grade serous ovarian cancers (HGSOC) [191]. Li et al. [192], has further detailed how NAD^+ / NAD^+ precursors supplementation might be used for treatment of different female reproductive diseases (see Fig5-7).



Courtesy ref no 192-Legend for Figure5-Graphical Abstract

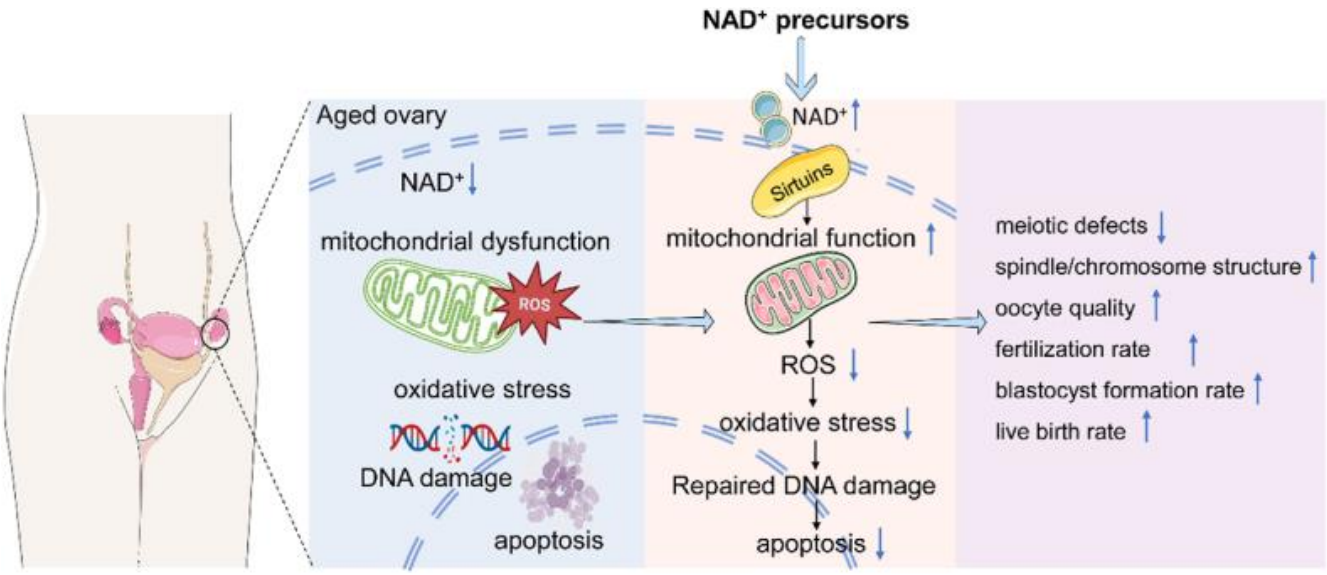


Figure 6: *Courtesy ref no 192-NAD+ precursors protect the ovary by improving mitochondrial function, lowering ROS levels, reducing oxidative damage and inhibiting damage and apoptosis . hydroxy-5-*

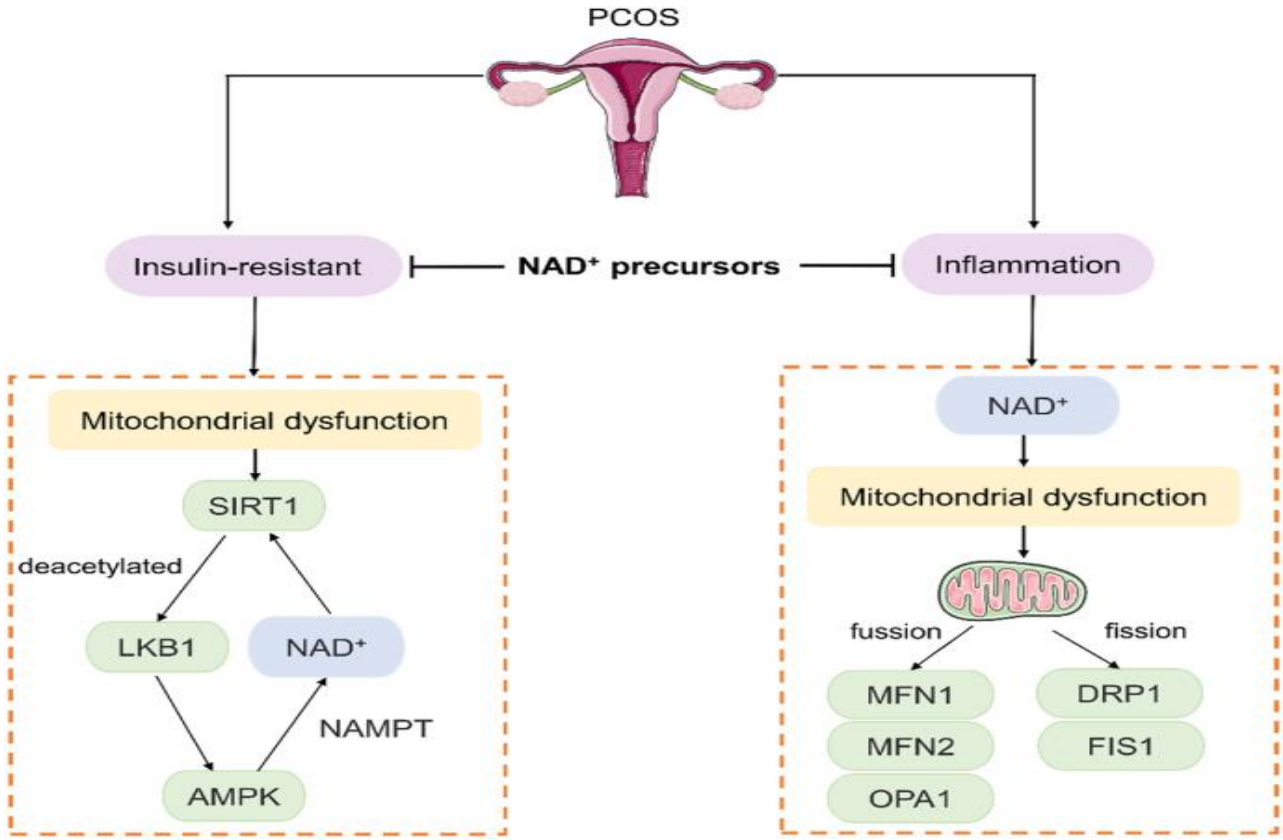


Figure 7: *Courtesy ref no 192-NAD+ precursors rescue PCOS by improving insulin resistance, inflammation and mitochondrial function*

Furthermore, recently Wang et al. [193], displayed that Astragalin from Thesium chinense worked in the form of an antioxidant by targeting IGFR, CD38, as well as Sirtuins [193].

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