MITOCHONDRIAL DYSFUNCTION IN AGING RELATED DISEASES; *potential mitochondrial based therapeutics in Sarcopenia and Age-related Macular Degeneration.*

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ABSTRACT

Aging represents a major scientific and social hurdle of mankind since the inception of life. This is as a result of decline in metabolic function and organelle power leading to varying degrees of aging related disease such as neurodegenerative disease, cardiovascular disease, optical defects, neuromuscular compromise etc. Of utmost interest in this review is aging-related disease sarcopenia and the eye deteriorating Age-related Macular Degeneration. Sarcopenia is a major muscle threatening condition emerging as a result of low muscle mass and muscle function and Age-related Macular Degeneration is a great cause of blindness globally. Previous studies have reported sarcopenia and age-related macular degeneration as a multi factorial disease induced by various mechanism such as physical inactivity, oxidative stress, mitochondrial dysfunction, inflammation, insulin resistance, cigarette smoking, sunlight exposure, genetic factors, and endocrine factors, all resulting in the pathogenesis of frailty associated with aging, thus reducing the quality of healthy life. Despite the growing risk factors in age-related diseases, there are increasing reports implicating mitochondrial dysfunction playing a prominent role in sarcopenia and Age-related Macular Degeneration. In addition, various therapeutics have been reported in management of age-related diseases most notably exercise, protein supplements, drugs, vitamin D and gene therapy. Recent studies points at mitochondrial based therapeutics as a promising prospect in managing age-related diseases. In lieu of that, this review affirms the plausibility of mitochondrial and aging, and examines the role of mitochondrial dysfunction in aging related diseases. Finally, explores some potential mitochondrial based therapeutics in management of sarcopenia and Angular Macular Dysfunction

Keywords: Aging, Mitochondrial Dysfunction, Sarcopenia, Age-related Macular Degeneration, Therapeutics.

1.0 INTRODUCTION

The fuss emanating from aging can be attributed to human desires to increase active life expectancy. Interestingly, healthy aging is achievable through resound planning and great care of health from birth. Thus, aging represents a great concern for all boughs of sciences and mankind. Aging may be defined as degenerative process that could decrease functional, physical activity and subsequently death. Several aging theories have been proposed [*1-5*], but a central theory of grave significance is the Mitochondrial Free Radical Theory of Aging (MFRTA) [*1*]. Owing to the multitude of metabolic processes and signaling cascade attributed to the power house (Mitochondrial), MFRTA thus avouch that the generation of excess free radicals is central to aging processes [*1*]. Accordingly, excess free radical generation results in oxidative damage to biomolecules, mutation to mitochondrial DNA and finally mitochondrial dysfunction attributed to aging related diseases [*6-9*]. Sarcopenia and Age-related Macular Degeneration (AMD) are two of several aging related diseases attributed to mitochondrial dysfunction [*10*]. Sarcopenia is generally accepted to be a muscle derailing disease associated with

aging [11]. It is proposed to be a mildly progressive ailment after the age of 30 years, termed severe with loses approaching 2% per year [12]. Conversely, AMD is termed a dismay cause of vision loss/ blindness of great concern. It is attributed to age-related accumulation of oxidative stress causative factors leading to oxidative damages [13-15]. Evidences affirms mitochondrial dysfunction as a hallmark of impaired mitochondrial biogenesis, unbalanced mitochondrial dynamics, decline in optimal mitochondrial function all linked to sarcopenia, AMD and other aging-related disease [16-20]. This review affirms the plausibility of mitochondrial and aging by evaluating various mitochondrial processes and further explains the underlying mechanism of mitochondrial dysfunction in sarcopenia and AMD. Although, increased physical activity, exercise training, gene therapy has been studied to attenuate aging in sarcopenia and AMD, this study further explores mitochondrial based therapeutics in sarcopenia and age-related macular degeneration.

1.1 THE POWER-HOUSE & AGING; PLAUSIBLE?

Undisputedly, aging represents a major scientific and social challenge of mankind with a global demographic change due to an increase in child-birth [21]. This process (aging) is marked with increased risked of fatality, neurodegenerative disease, cancer, and cardiovascular disease [22]. The fight to extend healthy lifespan and reduce the risk of morbidity has been active since the emergence of science leading to the development of various life interventions. A forth-put mechanism of aging is the age-dependent mitochondrial pathway [23,24], thus, the question mitochondria and human aging process plausible? With the mitochondria renowned as an omnipresent intracellular organelle, characterized by a double layered cell membrane encoding several essential proteins in a minuscule 16.5kb chromosome of DNA [25] which has been implicated in several aging causative factors described below.

1.1.1 MITOCHONDRIA BIOGENESIS & AGING

Referred to as the power house due to it highly energetic sensing systems in eukaryotic cells responsive to metabolic demands, immune responses and various regulatory processes [26], the biogenesis of the mitochondria is thus an intricate process [27]. It is a transcriptionally strictly regulated complex process that mediates the synthesis and replication of mitochondria DNA (mtDNA) [28] and controls the transfer of cytoplasm-based macromolecules majorly proteins & lipids to the mitochondria [29,30]. This process has thus been implicated in cell proliferation [31] and programmed cell death [32].The intricacy behind the regulation of mitochondrial biogenesis entangles gene expression, nuclear transcriptional factor orchestration, cellular mutualism and alteration of 20% cellular proteins [33]. The ubiquitous transcription factors (SP1, YY1, CREB, MEF-2/E-box), nuclear respiratory factors (NRF-1, -2, REBOX/OXBOX, MT-1 to -4) and coactivators (PGC-1a, -1b, PRC) allkey component of the PGC-1 family of co-transcriptionfactors[33] are crucial member of Mitochondrial transcription factor A (TFAM)&mitochondrialtranscription factor B1 and B2 (mtTFB-1 and mtTFB-2) [34]. TFAM, a nucleoprotein associated with mtDNA [35], is characterized by a presumed strong affinity to non-specific DNA [36] which is essential in mtDNA packaging [37] & architectural or scaffolding function [38,39] whichare critical inthe control of replication, transcription and maintenance in mitochondrial biogenesis [40].

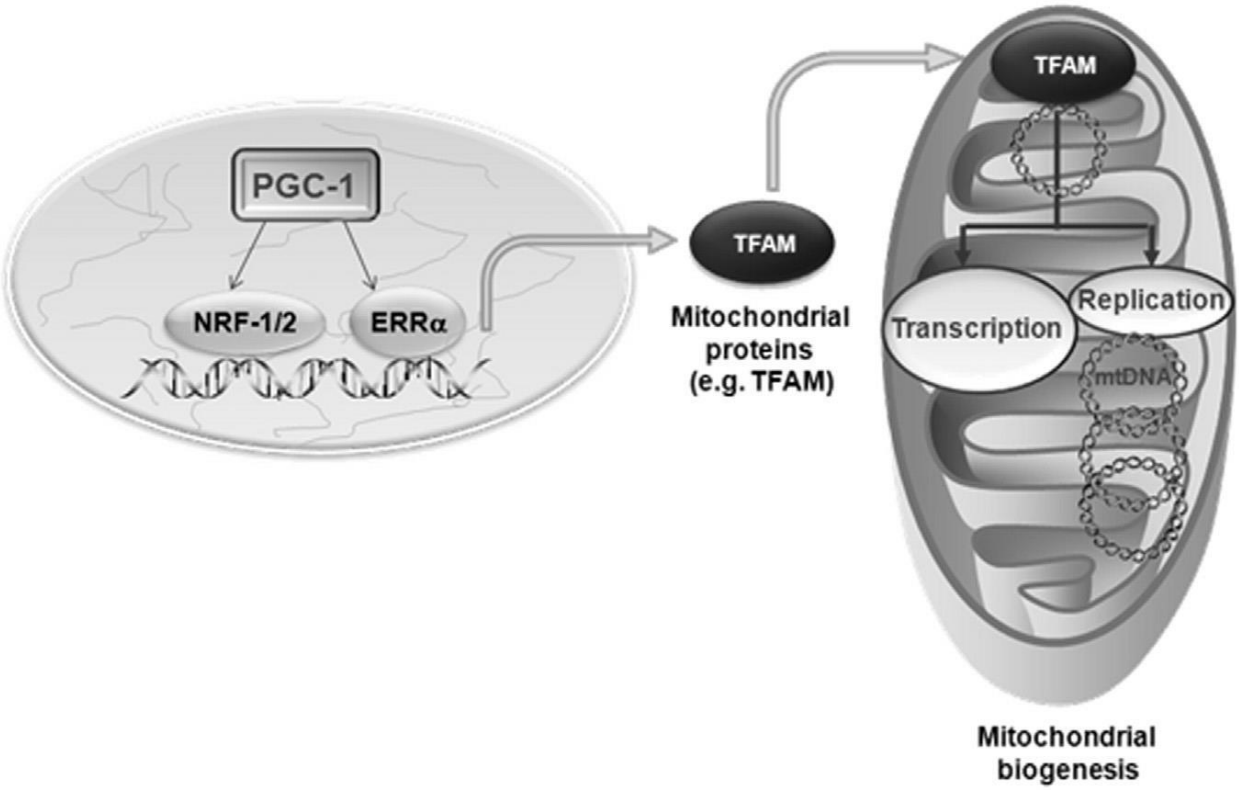

Fig 1; The major protein component ofthe nucleoids is TFAM highly essential in mtDNA packaging. PGC-1α an embodiment of ubiquitous transcription factor and nuclear respiratory factors is an activator of TFAM thus controlling replicational and transcriptional processes in the maintenance of mitochondrial biogenesis. Source; [*41*]

However, according to the mitochondrial theory of aging, aging is characterized by high mutation rate of mtDNA with less efficient DNA repair system [*1*], leading to mitochondrial impairment, declined ATP synthesis (due to altered expression of oxidative phosphorylation) necessary for homeostatic balance[*42*], and increased free radical generation [*43*].Among the plethora of biological phenomena affected by aging,the malfunction and decrease of biogenesis of mitochondria seemto exert some of the most potent effects on human. The disruption of biogenesis will slow mitochondrial turnover [*44*], accelerate oxidized lipids, proteins and mutant DNA synthesis [*45*], further aggravates the aging cascade. Previous studies have shown similar trend [*46,47,48*], although a study by Rogers & Rosia, 2014 reported a converse situation in which elevated mitochondrial biogenesis contributed to the longevity of mutant flies.

1.1.2 MITOCHONDRIAL DYNAMICS & MITOPHAGY IN AGING

Mitochondrial are dynamic organelles, shifting between a fragmented state and a tubular continuum, thus forming reticular structures inside the cell [*49*]. At a steady state, they undergo balanced fission and fusion to maintain integrity [*49*].Mitochondrial fusion,a dual process involving fusion proteins mitofusin (Mfn1) and (Mfn2) and optic atrophy 1 (OPA1),merging the inner and outer mitochondria by disunitable events where theouter and inner mitochondria fuse by separable events [*50*].Mfn1 and Mfn2 are mammalian homologues of yeast Fzo1 and Mgm1which are dynamin-related GTPases that are essential for mitochondrial membrane fusions and tethering [*51,52*] along with OPA1(localized in the inner mitochondria space).Mitofusins are required on adjacent mitochondria during the fusion process,implying that they form complexes in *trans* between apposing mitochondria [*52,53*]. A heptad repeat region of MFN1 has been shown to form an antiparallel coiled coil that is probably involved in tethering mitochondria during fusion [*53*]. Although the precise mechanisms still need to be elucidated, both OPA1 and MFN2 are involved in the regulation of mitochondrial respiratory chain coupling and oxidative phosphorylation[*54,55*].

Mitochondrial fission is anonymous to mitochondrial fusion in recruiting essential dynamin-related protein (Dnm1 in yeast and DRP1 in mammals) required inregulating peroxisomal fission [*56,57*]. DRP1 is a cytosolic large cytosolic GTPase protein that are mediated into the assembly of rings and spiral

responsible for the constriction of mitochondrial tubules [58], leading to eventual mitochondrial division into two mitotic daughter cells [59]. Although, the post-translational regulation of DRP1 is essential in elucidating its function along with its interaction with the four mitochondrial proteins; fission 1 (Fis1), mitochondria fission factor (Mff), mitochondrial dynamics protein of 49kDa (MID49) and MID51[59]. Thus, the equilibrium between the opposing fissional and fusional forces is known as Mitochondrial Dynamics.

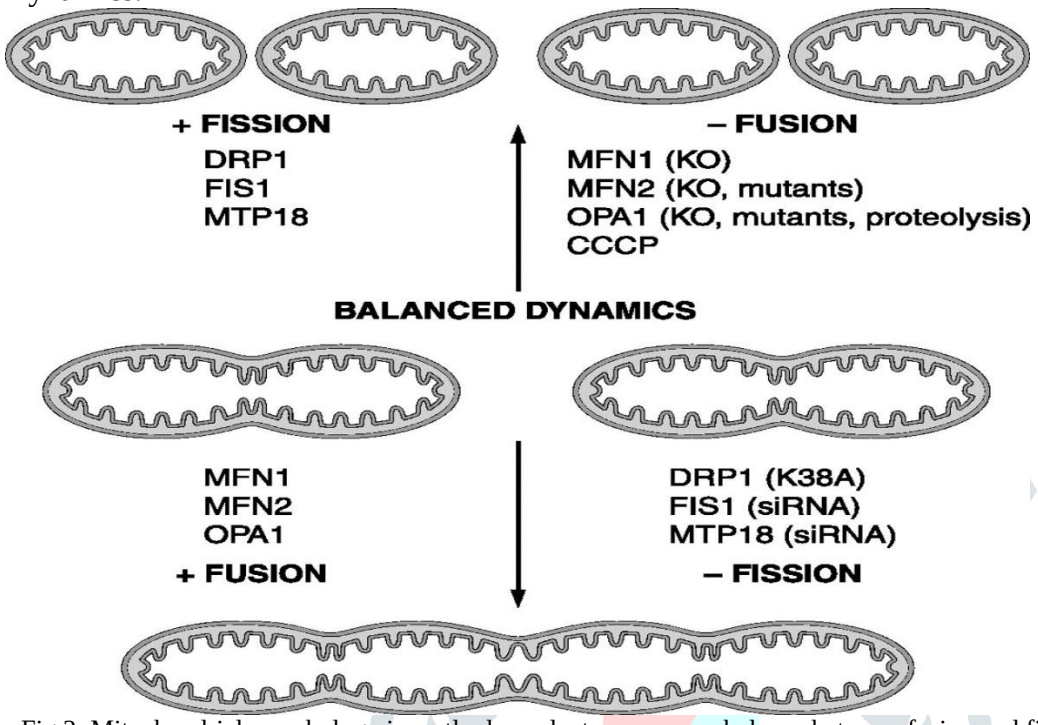

Fig 2; Mitochondrial morphology is partly dependent on a proper balance between fusion and fission processes. Schematic representation of mitochondrial morphology is shown in response to modulation of the activity of proteins involved in mitochondrial fusion or fission. Source [60].

Mitochondrial dynamics have been indicated to play essential roles such as maintaining mitochondrial bioenergetics [61], maintaining a functional mitochondrial population [62], proper mitochondrialredistribution in lymphocytes during chemotaxis [63], regulating apoptosis [64], and essential developmental functions [65]. Damage to mitochondrial are removed by mitophagy [66], a process involved in degradation by engulfment in autophagosomes. Although, this process is dependent on deactivation of fusion and induction of fissional forces and protein [66].This dynamic network is essential to maintain normal mitochondrial functions and participates in fundamental processes including aging [67]. Studies have revealed a compromise in mitophagy with increasing age, attributed to excess free radicals' production, decreased membrane potential and mtDNA damage [68,69].

1.1.3 MITOCHONDRIAL BIOENERGETICS, REACTIVE OXYGEN SPECIES (ROS) & AGING

The fundamentally ascribed role of the mitochondrial is the generation of ATP for various life processes via oxidative phosphorylation, and serves as an intermediate modulator to major metabolic pathways including the Krebs cycle, β-oxidation, metabolism of amino acids and the synthesis of iron sulfur clusters, hence the cruciality of mitochondrial bioenergetics. Oxidative phosphorylation, is made up of five complexes [70]. Complex I (NADH-ubiquinoneoxidoreductase), a multi subunit protein (about 45 dissimilar subunits) that catalyzes electron transfer from NADH to ubiquinone, coupled to membrane proton translocation thus contributing to proton motive force (PMF) of the cell [71,72]. Complex II (succinate dehydrogenase), a cardiolipin free tetrameric enzyme complex, providing a link between the kreb cycle and the electron transport chain (ETC) [70]. Converse to complex I does not contribute to proton gradient [70]. Complex III(ubiquinol-cytochrome c oxido-reductase), a loci multi subunit enzyme confined in the inner mitochondrial membrane (IMM) is responsible for the catalysis of electron transfer from membrane localized ubiquinol to water soluble cytochrome C [73]. Cytochrome c oxidase (CcO), a 205kDa transmembrane phosphatidylcholine, phosphatidylethanolamine, cardiolipin contains complex

of about 13 subunits [74]. However, only cardiolipin is found strongly bounded to this isolated complex [75, 76], essential for normal electron transport and proton translocation activity of this enzyme complex. Finally, complex V (mitochondrial F0F1 ATP-synthase) is shown to be a double functional multi subunit domain complex [70], The F0 domain confined in the IMM, and the F1 domain localized in the mitochondrial matrix utilizing the energy generated by the proton electrochemical gradient to phosphorylate ADP to ATP [77], essential for various metabolic and physiological processes.

Oxidative phosphorylation comes with additional cost, the production of ROS. Studies have implicated complex I & III as the major site of ROS production majorly superoxide anion (O2·-), which is ultimately dismutated by superoxide dismutase (SOD) to hydrogen peroxide (H2O2) [78,79,80], although Nitric oxide anion (NO·) is also produced by the mitochondrial nitric oxide synthase [81,82]. H202 produce has two fates [83]. It can be lysed into water molecule (H2O) by the catalase enzyme or undergo Fenton reaction in the presence of divalent cations to produce the highly mitochondrial injurious hydroxyl radical (HO·) [83].

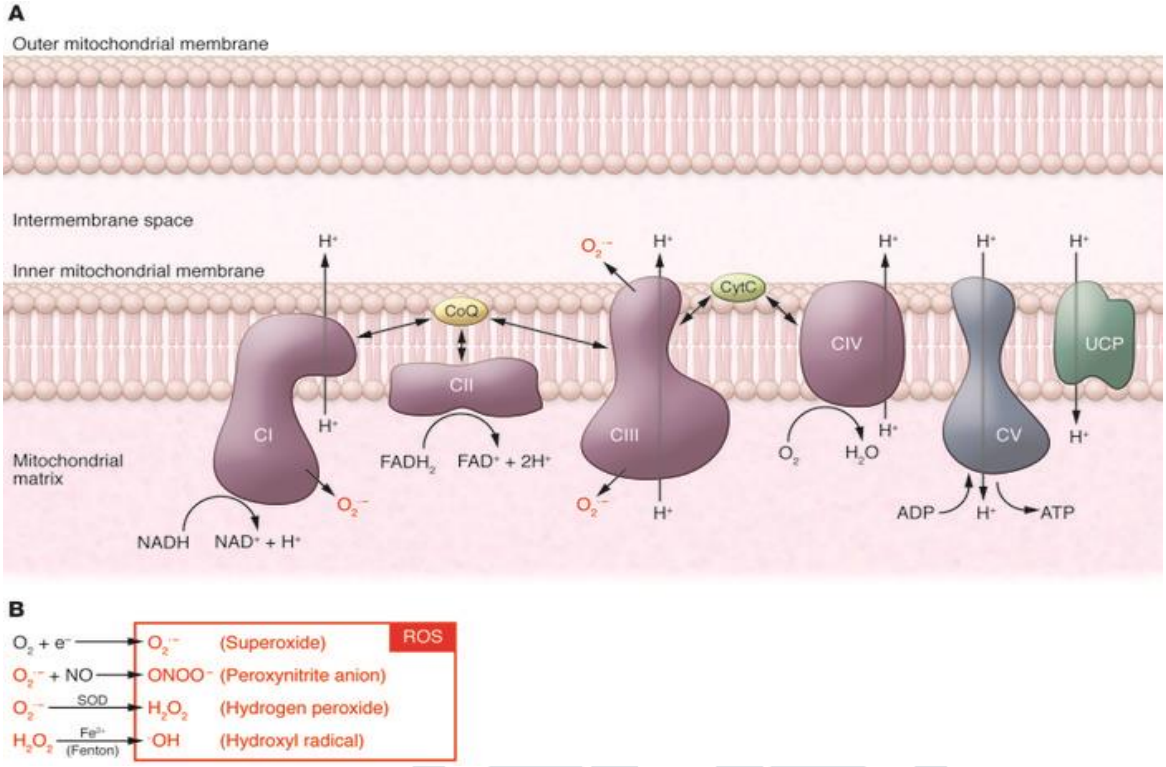

Fig 3; Schematic illustration of mitochondrial ATP synthesis via oxidative phosphorylation and the production of ROS which can be metabolically useful (important signaling molecules to promote longevity), although should be moderated. Source; [84]

Among the stochastic theories, the free radical theory of aging [1-5] explained that cells, continuously exposed to ROS, are more and more broken in their most essential biomolecules. The involvement of mitochondria both as producers and as targets of ROS has been the basis for the mitochondrial theory of aging [1]; this theory postulates that random mtDNA alterations in somatic cells are responsible for the energetic decline accompanying senescence.

2.0 MITOCHONDRIAL DYSFUNCTION IN SARCOPENIA

In ameliorating the intricacy behind the accumulation of inherent and extraneous damages during the degenerative aging processes, nine emblemsof aging related disease (genomic instability, telomere shortening,epigenetic alterations, loss in the homeostasis of proteostasis, dysregulatednutrient sensing, mitochondrial dysfunction, senescence, stemcell exhaustion, and altered intercellular communication) were proposed [85,86]. Several aging related diseases include,heart disease, type 2 diabetes, Alzheimer's disease, Angular Macular Degeneration (AMD), Sarcopenia [10] etc. Sarcopenia is described as a complex multifactorial condition (age, neuromuscular impairments, physical inactivity, mitochondrial dysfunction, insulin resistance, malnutrition [87]), characterized by adverse muscular changes accrued over the course of life, resulting in activation of skeletal muscles catabolic pathways [88], increased risk of metabolic disorders, and muscular failure [89]. A study by Denison et al., 2015 revealed that sedent

personalities are most prone to sarcopenia, averaging about 1-2% muscle mass loss per year from patients of 50-60 years, and about 3-5% per year at older ages. The study thus concludes that, physically inactive persons, can lose about 30-50% of muscle mass between the ages of 40-80 years over the course of their lifespan. However, due to the role of the mitochondrial as a loci hub in regulating aging-linked mitochondrial processes such as mtDNA preservation & repair, mitochondrial dynamics & mitophagy, mitochondrial bioenergetics and ROS synthesis [90,91], the dysfunction of the mitochondrial is thus eminent in aging related sarcopenia [88,92-96].

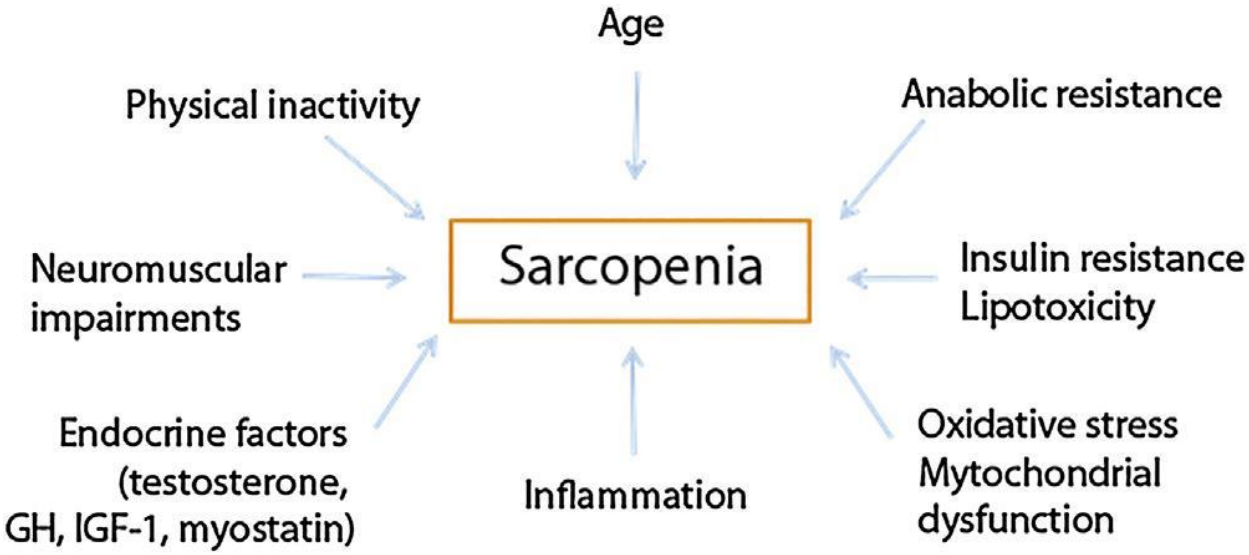

Fig 4: The multifactorial processes responsible for sarcopenia. These processes are complex but interdependent. Source; [97]

2.1 IMPAIRED MITOCHONDRIAL BIOGENESIS & SARCOPENIA

During skeletal muscle homeostatic condition, there is a balance between Insulin-likegrowth factor 1 (IGF-1)-PtdIns-3-OH kinase (PI3K)-Akt signaling activation of rapamycin (mTOR) pathway which in turn promotes protein translation [98] and catabolic muscular systems (ubiquitin-proteasome system (UPS), the autophagy-lysosome system and apoptosis) [88]. While the mTOR pathway is the master regulator of muscular protein synthesis, UPS degradation system is the proteolytic regulator of fission and fusion factors in mitochondrial membrane [99].mTOR is a serine/threoninekinase of the phosphatidylinositol kinase-related kinasefamily functioning as two signaling complexes in mammalian cells: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2)[100,101]. In response to several extracellular stimuli such as nutrients, cytokines, growth inducing factors and antigen receptor signaling, mTORC1 complex is activated via PI3K-AKT (protein kinase) complex [102]. Due to this activation, Tuberous sclerosis complex (TSC1) & (TSC2) which are repression mediating factors of mTORC1 complex becomes phosphorylated by Akt which concomitantly prevents the inhibition of mTORC1 activating factor Rheb [102]. The exerting effect of Rheb activation triggers the phosphorylation of P70-S6kinase (S6K) and eukaryotic initiation factor 4E-binding protein (4E-BP1) [103-105]. Thus, an increase in mTORC1activity results, promoting energetically expensive processes such asbiogenesis, translation [106] etc.

Converse to mTORC1 protein synthesis dependent activation, activation of mTORC2 occurs upstream of Akt serine 473 phosphorylation [107]. This signaling cascade (mTORC2) is involved in the upregulation of anti-apoptotic factors and reorganization of cytoskeleton [107,108], via the activation of serum glucocorticoid-regulated kinase 1 (SGK-1) and protein kinase c alpha (PKCα).

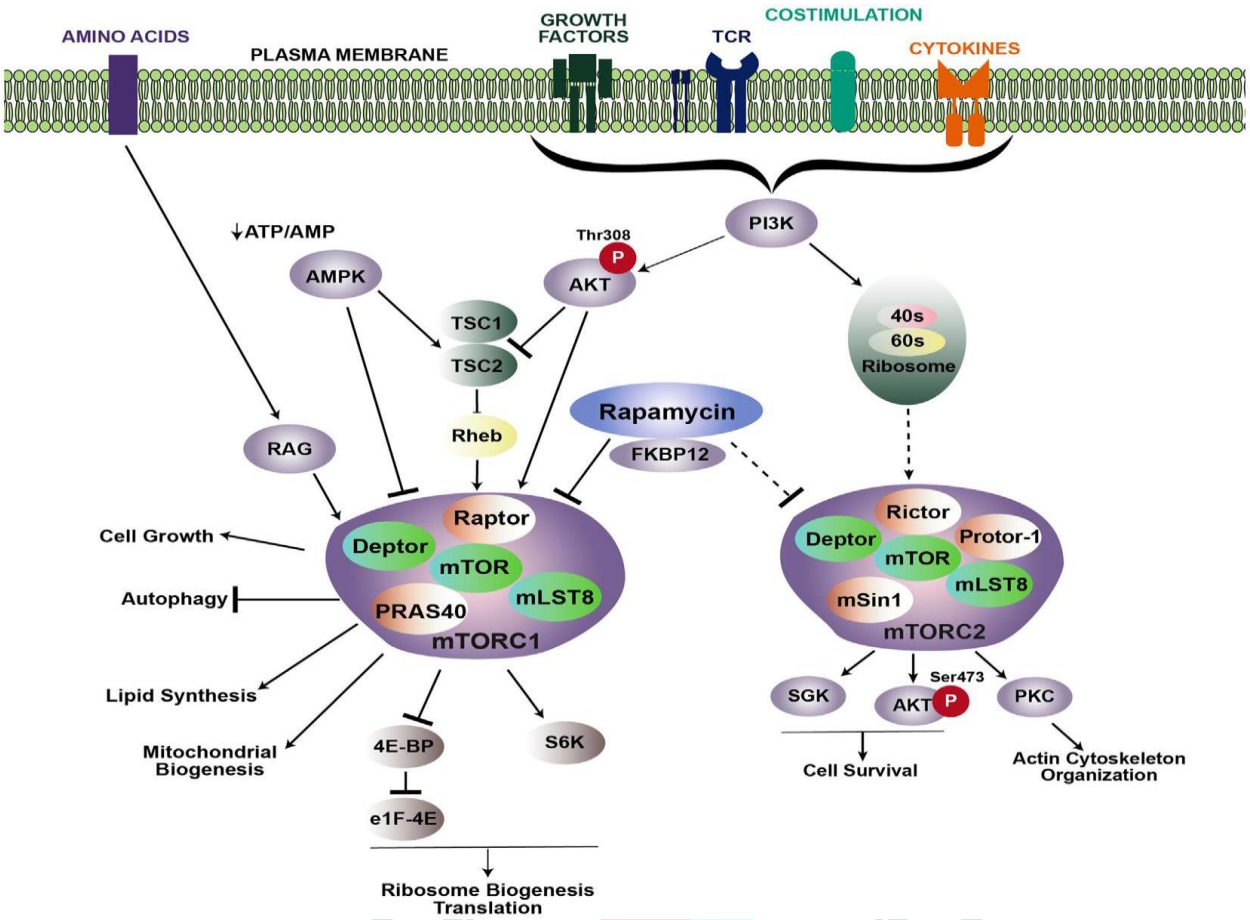

Fig 5; Illustration of the mTOR complex in mammalian cells. mTORC1 is constituted of scaffolding protein, regulatory-associated protein of mTOR (Raptor), DEP-containing mTOR interacting protein (Deptor), mammalian lethal with Sec13 protein (mLST8), and the Proline-Rich AKT substrate (PRAS40) with its activation occurring downstream of Akt following phosphorylation at threonine 308 (T308). In the absence of nutrient, mTORC1 activity is inhibited, this is in response to higher AMP- ATP/ADP ratio thus AMP- activated protein kinase (AMPK) becomes activated, and in turn, inhibits the phosphorylation of TSC2 or Raptor. mTORC2 comprises mTOR, Deptor, mLST8, scaffold protein Raptor-independent Companion of TOR (Rictor), the Protein observed with Rictor (Protor-1), and the mammalian stress activated protein kinase-interacting protein 1 (mSIN1). This signaling cascade relies on association with ribosomes and along with mTORC1 can be inhibited by prolonged exposure to rapamycin. Arrows and bars represent activation and inhibition, respectively. Dashed lines indicate that the exact mechanism is unknown. Source; [*109*].

However, sarcopenia is attributed to impaired signaling through mTOR pathway resulting in increased protein degradation and decreased protein synthesis [*110,111*]. Reduced expression of key proteins such as sirtuin 1 (*SIRT1*), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), NRF1, AMPK, TFAM, all of which leads to impaired mitochondrial biogenesis and decline in mitochondrial bioenergetics have all been implicated in aging related sarcopenia [*111*]. PGC-1α has been affirmed as a master regulator of mitochondrial biogenesis due to its important role in mitochondrial proteostasis [*112*], regulation of muscle fiber type [*113*], promoting mtDNA regulator (TFAM) [*114*], connecting mitochondrial function to muscle integrity [*115*], and regulating autophagy in prevention of muscle atrophy [*115*]. However, mutations of TFAM, linked with decline in mtDNA function has been attributed to sarcopenia [*116*]. Handaschin et al., 2007, reported impaired muscle function and reduced oxidative metabolism in PGC-1α knockout mice, Similarly, Anderson &Prilla 2009, asserted a decrease in PGC-1α levels in skeletal muscle during aging. Although, Wenz et al., 2009 reported a converse result, recording the amelioration of sarcopenia triggered by the over expression of PGC-1α. Finally, PGC-1α suppresses FOXO3-mediated transcription of various E3 ubiquitin ligases, thereby attenuating protein degradation and muscle atrophy during aging and sarcopenia [*117*].

AMPK, a crucial regulator of muscle metabolism, development and growth [*118*], whose activation inhibits the phosphorylation of TSC2 (a repressor protein of mTORC1 complex) involved mTOR complex in mammalian cells has been revealed to coordinate PGC-1α activity and sirtuin, thus decreasing overall protein synthesis during metabolic stress [*119*]. However, previous studies have

characterized sarcopenia and reduced mitochondrial biomarkers to AMPK-knock out in mice [120,121]. In aging cells, SIRT1 downregulation has been implicated in extending life span [122]. It co-interacts with mitochondria PGC-1α in down streaming [123], thus playing an essential role in increasing mitochondria protein synthesis.

2.2 OXIDATIVE DAMAGE& SARCOPENIA

Human mtDNA is a double stranded, multi copied, intron encoding (about 37 free genes), cyclic shut genome, translating into 13 polypeptides, 22 transfer RNAs, 12s & 16s ribosomal RNAs of about 16.5 kilobases [124], and encodes all proteins of oxidative phosphorylation, thus essential in the maintenance of mitochondrial integrity [125]. Unlike nucleosomes, mtDNA lacks the protective histone and its replication and transcription machinery depends on DNA polymerase γ (poly γ), mitochondrial DNA helicase, mitochondrial RNA polymerase (mtRPOL), or TFAM [126,127]. However,studies have reported that sarcopenia ensues in error-prone poly γ mice, causing mtDNA damage, mitochondrial dysfunction and muscle wasting [128-130]. Research has affirmed the vulnerability of mtDNA to its close proximity to oxidative phosphorylation machinery, the absence of protective histone, and a less robust DNA repair system [131,132]. With oxidative damage implicated as one of the hall marks of aging [85,86], deductions from the appreciable Mitochondrial Free Radical Theory (MFRT) thus asserts that, oxidative damage to mtDNA would results in compromised mitochondrial integrity, impaired oxidative phosphorylation processes, decreased mitochondrial bioenergetics and soar in ROS synthesis, all of which are indicative of sarcopenia [133,134]. Furthermore, Gonzalez-Friere at al., 2018 reported a decline in mitochondrial ATP synthesis in aged adults, thus supporting the induction of oxidative damage to sarcopenia. Notably, an increase in ROS impairs the mTOR pathway assembly [135], aggravates lysosome autophagy & UPS degradation machinery and finally induces muscle wasting. This results in disturbed mitochondrial fission and unbalances mitochondrial dynamics [136].

3.0 MITOCHONDRIAL DYSFUNCTION IN AGE-RELATED MACULAR DEGENERATION

A current ravaging ailment of great concern, causing impairment of vision is the Age-related Macular Degeneration (AMD) [137], with its prevalence projected to double in the next two decades [138,139]. Similar to sarcopenia, AMD is also a multifactorial inducing disease, some of which includes; Ocular risk factors (Previous cataract surgery [140] and darker iris pigmentation [141]), environmental & behavioral risk factor such as cigarette smoking [142], sunlight exposure, unhealthy dietary [143], unhealthy lifestyle induced cardiovascular disease and genetic factors [141, 144,145]. Clinically, AMD is indicted by alteration in Retinal Pigment Epithelial Cell (RPE), and the presence of drusen which is found between RPE & Bruch's membrane [137]. However, despite the enormous risk factors associated to AMD, recent studies have reported that its association with several environmental and genetic risk factors are responsible for increased oxidative stress [146,147,148]. Similarly, this leads to mtDNA damage of the RPE due to the decreasing antioxidant defenses associated with aging [149]. Thus, RPE degeneration is triggered in continual exposure to ROS induced oxidative stress, deteriorating the photoreceptors, leading to visual impairment associated with AMD [150].

3.1 RETINAL PIGEMENT EPITHELIAL CELL & VISUAL CYCLE IN AMD

RPE is the melanosome imparted brownish coloration, found between the light outer segments of the photoreceptor and vascular choroid [151]. It is separated from the retinal by the subretinal space, capable of forming a multi-layer retinal-like structure in cases of disturbed RPE-Retinal interaction [152]. RPE mediates several essential functions for normal retinal physiology which includes visual cycle participation & light absorption [153], maintaining structural integrity of the retinal by efficient defense against ROS, photo-oxidative exposure [154-156], maintenance of ion homeostasis of the subretinal space [157]. Vision starts with the absorption of a photon by the group of visual purple, 11-cis retinal [158]. After absorption of a photon, 11-cis retinal modifies its conformation into all-trans retinal and

rhodopsin becomes meta-rhodopsin in an exceedingly outlined time before its activity is terminated by phosphorylation. Following further reaction steps, rhodopsin is ready to exchange all-trans retinal for 11-cis retinal and will be activated again by a photon. Thus, all-trans retinal must be re-isomerized to conform a ample delivery of 11-cis retinal effective vision and visual desires [159,160]. Re-isomerization takes place within the RPE, hence all-trans retinal is delivered to the RPE, re-isomerized to 11-cis retinal and delivered back to photoreceptors. This procedure is termed the visual cycle of retinal [161].

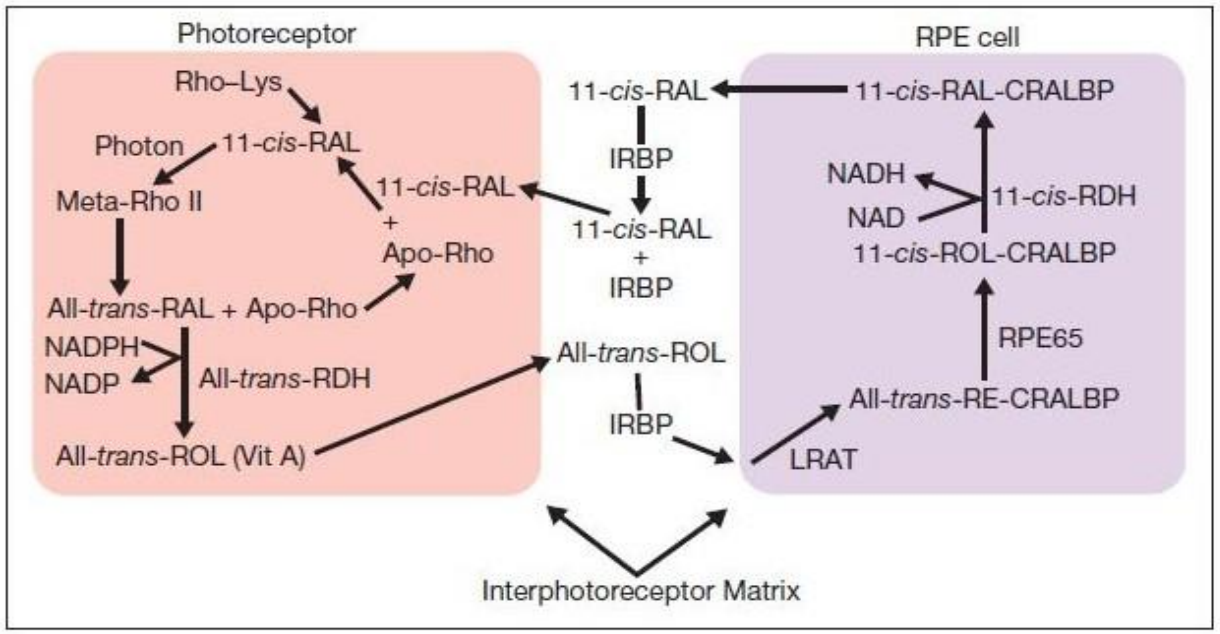

Fig 6;Illustrating the interactions between RPE and Visual cycle. visual cycle takes place in the photoreceptors (left), the retinal pigment epithelium (right), and the intervening interphotoreceptor matrix. RAL, retinal; RE, retinyl esters; ROL, retinol; CRALBP, cellular retinaldehyde-binding protein; LRAT, lecithin retinol acyltransferase; RDH, retinol dehydrogenase; Rho, rhodopsin; IRBP, interphotoreceptor-binding protein. Source; [162].

Thus, the RPE is the principal site of pathology in major causes of visual impairments, including age-related macular degeneration (AMD) and proliferative vitreoretinopathy (PVR) [162] that can lead to blindness. Furthermore, excessive formation of drusen, and pigment alterations in RPE are characterized by AMD, thus impairing the visual cycle [163].

3.2 OXIDATIVE DAMAGE & AMD

Aging has implicated with an overall damage increase in oxidative stress due to the accumulation of oxidized biomolecules in aged tissues [164], with the macular under extreme pressure during the continuous production of ROS [165,166]. However, it is notable to recall that the production of ROS and the induction of oxidative stress by the mitochondrial has been discussed earlier in this review. Malondialdehyde, carboxylethylpyrole, 4-hydroxyoneal, all of which are products of oxidative stress induced lipid peroxidation have been detected in the macula of AMD patients. Induced oxidative stress causes mtDNA dysfunction yielding a decline in ATP production, negatively effecting the protein homeostasis system [167]. AMD, Alzheimer's disease, Parkinson's disease and other age-related disease have their pathogenesis linked partly to loss of protein homeostasis system [168]. The protein homeostasis system includes UPS and Autophagy system. The UPS is a ubiquitin involving

energetically expensive proteasome system, responsible for the coordination of extralysomal degradation of cellular protein [169]. The rapid and strict regulation of the UPS maintains senescence, protein quality control, DNA repair [170] etc. However, UPS inhibition occurs in AMD, during the oxidative-stress during the oxidative stress induced homeostatic proteasome system loss, resulting in mitochondrial dysfunction and compromised oxidative phosphorylation [171]. Similarly, the downregulation of autophagy (induced by oxidative stress and mitochondrial dysfunction) has been reported in AMD patients [172]. Mitter et al., 2014, observed autophagy dysregulation in RPE and the neural retina of AMP patients. A similar study implicating autophagy in retinal degradation was also reported by Lie et al., 2015. Furthermore, accumulation of autophagosomes indicating the onset of autophagy in the retinal was reported by Mitter et al., 2012. Conclusively, the accumulation of peroxidase products in the macular area, lipofuscin, precedes the atrophy of outer retinal layers and vision loss in AMD patients [173, 174].

4.0 POTENTIAL MITOCHONDRIAL BASED THERAPEUTICS

With the growing role of the mitochondrial dysfunction as a risk factor of several life-threatening diseases, the need for therapeutics in preventing the malfunctioning of mitochondrial is thus essential. Although, several medical interventions have been reported in the management of sarcopenia and AMD, most notably exercise, healthy dietary intake, gene therapy [175,176]and topical formulations [177], mitochondrial based therapeutics has been obscure so far. Potential mitochondrial targeting therapeutics in the management of age-related sarcopenia and macular degeneration is discussed below.

4.1 ELAMIPRETIDE

Elamipretide is otherwise called Bendevia. It is a minute mitochondrial targeting tetrapeptide (D-Arg-dimethyl Tyr-Lys-Phe-NH2), capable of scavenging ROS species [178-180]. The modus operandi of Elamipretide is by penetrating the cell into the mitochondria, and protecting the essential protective lipid cardiolipin from undergoing peroxidation reaction during mitochondrial dysfunction. This action thus improves the coupling of the Electron Transport Chain by ameliorating the ROS producing complex I & III [181,182]. This study has earlier affirmed the dysfunction of mitochondrial has a prominent risk factor of sarcopenia and AMD, thus the protective role of Elamipretide would be effective in restoring mitochondrial bioenergetics and reduce the deteriorating effects of excessive ROD generation. As of march 2020, the drugbank database updated the completion of Elamipretide (Accession number; DB11981, Molecular Weight; 639.802g/mol) for clinical trials in the treatment of AMD and mitochondrial myopathies. The remarkable potency of this compound has however been reported in various animal model studies [183-185].

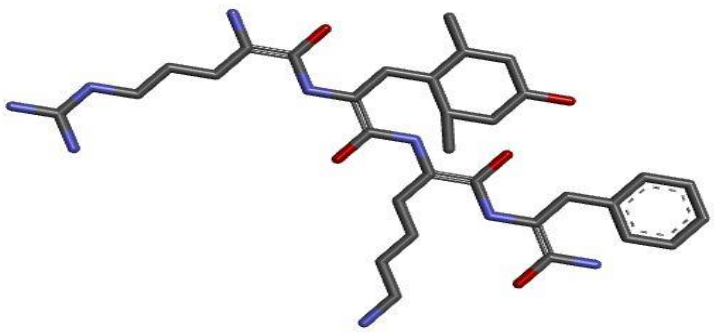

Fig 7; 3D structure of Elamipretide

4.2 NATURAL PRODUCTS OF AMPK ACTIVATORS

As earlier explained, the downregulation of AMPK signaling cascade results in decline in mitochondrial biogenesis and imbalanced mitochondrial dynamics, thus causing mitochondrial dysfunction. This process is however characterized in age-related sarcopenia and macular degeneration. Thus, the upregulation of AMPK would be essential in the management of this diseases. Several natural products known to upregulate AMPK includes Arctigenin, Berberine, Genistein, Spatholobussuberetus [*186*] etc. Arctigenin is a natural dibenzyl butyrolactone-type lignanolide, that increases glucose uptake in cultured L6 skeletal muscle cells and isolated muscles, inhibits lipid synthesis and gluconeogenesis, and thus produces a specific effect on respiratory Complex I [*186*]. Arctigenin have been revealed to inhibit the ROS producing complex I, via the activation of AMPK cascade [*187,188*]. Berberine, is an isoquinoline alkaloid found in various plants, an essential AMPK phytochemical [*189*]. It phosphorylates Thr 172 residue of AMPK in upregulating mitochondrial function, thus stimulating the activation of AMPK. Berberine was examined to produce the same effect as metformin and rosiglitazone by suppressing the ROS inducing electron transport chain complex I in in isolated muscle mitochondria and L6 myotubes [*189*]. Similarly, S. suberectus (Ss) an herb rich in polyphenolic compounds, steroids, quinones, fatty acids, and procyanidins has been widely used in soups, tea and wines, has been proven to upregulate AKT and AMPK pathways [*186*].

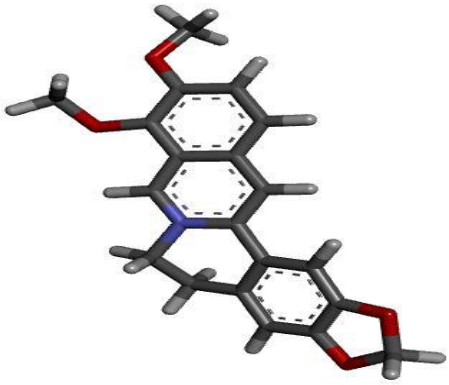

Fig 8a ;3D structure of Berberine

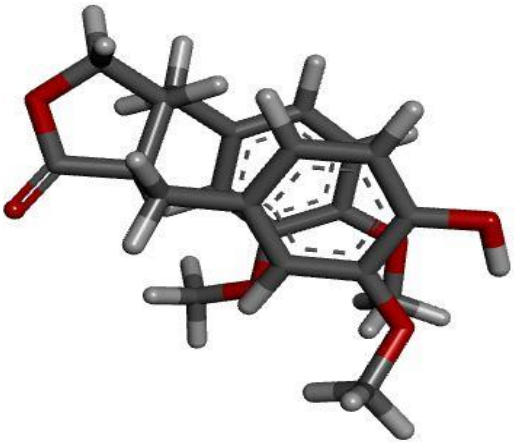

Fig 8b; 3D structure of Arctigenin

4.3 UROLITHIN A

An emblem of age-related sarcopenia and macular degeneration is compromised mitophagy, resulting in mtDNA damage [*88,92-96,149*]. Urolithin A(UA) is a first-class natural food metabolite compound, belonging to benzo-coumarins and dibenzo-α-pyrones class of organic compounds [*190*]. They result from gut bacterial transformation of ellagitannins, stimulating mitochondrial mitophagy and prevents the accumulation of dysfunctional mitochondrial [*191*]. Urolithin A precursors are pervasive, and includes strawberries, rose hip, pecans, mango, oak-aged red wine and raspberries [*190*]. Furthermore, in human respiratory cells, UA have been revealed to maintain mitochondrial biogenesis, improve mobility and

extend life span [*192*]. Finally, the first human clinical trial of UA affirmed that UA induces molecular signature of improved mitochondrial and cellular health [*193*].

Fig 8; 3D structure of UA

4.4 CURRENT CLINICAL TRIALS DRUGS

ROW	STATUS	STUDY TITLE	CONDITION	INTERVENTION	LOCATION
1	Recruiting	Sarcopenia in acute care patients: protocol for sarcopenia 9+	Sarcopenia	Diagnostic Test; EWGSOP 2	CHU Brugmann Brussels, Belgium. UZ Gent Gent, Belgium.
2	Recruiting	Understanding Acute sarcopenia	Sarcopenia	Drug: Antibiotics	Queen Elizabeth Hospital Birmingham Birmingham, West Midlands, United Kingdom.
3	Unknown	Clinical Trial to assess the preventive effects of ceptylpyrindilnum chloride on sarcopenia.	Sarcopenia	Drug: CPC Drug: placebo	Seoul National University College of Medicine Seoul, Korea.
4	Recruiting	Use of sit to stand task asa screening tool for sarcopenia.	Sarcopenia	Diagnostic Test;Dexa Scan	University of Bedfordshire Bedford, Bedfordshire, United Kingdom

5	Active	AMD in Vit D and Omega 3 - trial (VITAL)	AMD	Drug: Omega-3-fatty acids (Fish oil) Dietary supplement: Vitamin D3	Brigham and Women's Hospital Boston, Massachusetts, United States.
6	Active	A staged study of the safety of ASP7317 in senior adults, who are losing their clear, sharp central vision due to dry AMD	AMD	Drug: ASP7317 Other: Placebo Drug: Tacrolimus Drug: Mycophenolate mofetil (MMF)	Retinal Consultants of Arizona LTD, Retinal Research Institute Phoenix, Arizona, United States. Jules Stein Eye Institute Los Angeles, California, United States. Retina Consultants of Southwest Florida & National Ophthalmic Research Institute Fort Myers, Florida, United States.
7	Unknown	Prophylactic Ranibizumab for exudative AMD	AMD	Drug: Ranibizumab 0.5mg	Northern California Retina Vitreous Associates Mountain View, California, United States. Southern California Desert Retina Consultants Palm Desert, California, United States. Elman Retina Baltimore, Maryland, United States. Black Hills Regional Eye Institute Rapid City, South Dakota, United States.

Table 1; Adapted from https://clinicaltrials.gov/

5.0 CONCLUSION

It is clear that mitochondrial is a central hub to various metabolic processes and thus, any dysfunction of mitochondrial activity is conspicuous to several aging-related disease. Hitherto, aging and age related diseases have been linked to combined dysfunction in the structure and function of the mitochondria. Quite convincingly, this review has outlined few benefits of some compounds in circumventing the

development of age related reactions and mechanism associated with such dysfunction. While the challenge to conform various animal studies into human therapies still remains, natural products that promotes mitohormesis and their mechanism should further be elucidated. Furthermore, future studies should focus on the use of nanotechnology in the management of age-related sarcopenia and AMD.

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