



An Update on Mitophagy Facilitating Substances: Their Future for Facilitating Healthy Ageing Along with Treating NDG (Parkinson's Disease; Alzheimer's Disease), Cancer, Ovarian Ageing: A Mini Narrative Review

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ABSTRACT

The elimination of injured mitochondrial constituents via an event called mitochondrial autophagy (alias mitophagy) is necessary for appropriate mitochondrial working. Thereby mitophagy is crucial for the health of all the aerobic animals inclusive of humans. To our misfortune reduction of mitophagy takes place with age. A plethora of age related diseases for instance Alzheimer's disease, along with Parkinson's diseases have the properties of accrual of injured mitochondria in addition to oxidative injury. Thereby utilizing small molecule pharmacological agents, for activating mitophagy is an upcoming approach the treatment of myriad of diseases. Recent studies have isolated natural agents, as well as synthetic agents which facilitate mitophagy. Categorization of such substances have been done in the form of mitophagy stimulators inclusive of i) antioxidants ii) mitochondrial uncouplers iii) complex I hampering agents iv) redox manipulators v) metabolic manipulators vi) neuronal manipulators vii) autophagy manipulators viii) antibiotics along with anti fungal agents ix) reactive oxygen species (ROS) producers. Their influence on stimulating the prolongation of life- along with healthspan in addition to mechanistic modes is further illustrated if acknowledged. Lastly, mitochondrial biogenesis leads to harmony amongst mitophagy for guaranteeing appropriate mitochondrial network homeostasis. Intriguingly, mitochondrial biogenesis activation might be caused by akin molecules stimulating mitophagy for instance, resveratrol in addition to metformin. Although remarkable work has been undertaken regarding acquisition of insight regarding such events, plethora of information needs unraveling, specifically in the context of acquisition of insight of their interassociation at the level of organism along with evaluation of combination of such agents which target mitophagy as well as biogenesis. Future assessment of such field might be

unveiling the manner such combinations might be influencing lifespan along with healthspan in different biological models.

Keywords: mitophagy, injured mitochondria, Parkinson's disease, Alzheimer's disease.

INTRODUCTION

The manner Art portrays the depletion of the non-essential (as per Picasso) akin similarity is to mitophagy for the mitochondrial networks. Healthy mitochondria are necessary for the plethora of foundational events in the aerobic cells inclusive of conversion of the biomolecules, chemical energy to adenosine triphosphate (ATP)- through oxidative phosphorylation (OXPHOS) [1], generation of heme [2], breakdown of fatty acids via oxidation [3], controlling calcium [4] in addition to iron homeostasis, as well as regulating cell demise by apoptosis [6]. Furthermore, mitochondria produce reactive oxygen species (ROS), possessing key working in various cellular in addition to physiological events inclusive of redox homeostasis along with immunity [7]. Conversely the injured mitochondria result in elimination of ATP [8], dysfunctional metal ion homeostasis [9], escalated ROS generation [8], along with the activation of the cell demise via the liberation of cytochrome c [8,10]. Thereby depleting damaged mitochondria by an event referred to mitochondrial autophagy (alias mitophagy) is key for the appropriate cellular actions in addition to health.

Earlier we had reviewed part of SIRT 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, SIRT signaling pathway the significance of SIRT signaling pathway with NAD metabolism regarding improving oocyte quality, mitophagy part in treating HBsAg&PCOS.Detailed autophagy in Bile acid metabolism in cancer &in diabetic cardiomyopathy&T1DM [11-21]. Numerous mitophagy pathways implicate various signaling molecules, enzymes as well as adapter proteins. Here we detail concisely with availability of considerable comprehensive reviews with regard to various mitophagy pathways [22].

METHODS

Here we conducted a narrative review utilizing search engine pubmed,google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like Sirtuins; maternal ageing; Oxidative stress (OS); organs ageing; oocytes quality; natural mitophagy agents; synthetic agents; mitochondria function; Epigenetics; DNA methylation; Histone deacetylation; DNA healing; chromatin remodeling; cellular senescence; immunecell working ; melatonin; resveratrol; astaxanthin; nicotinamide mononucleotide; urolithinA; nicotinamideriboside; from 1985 to 2024 till date.

RESULTS

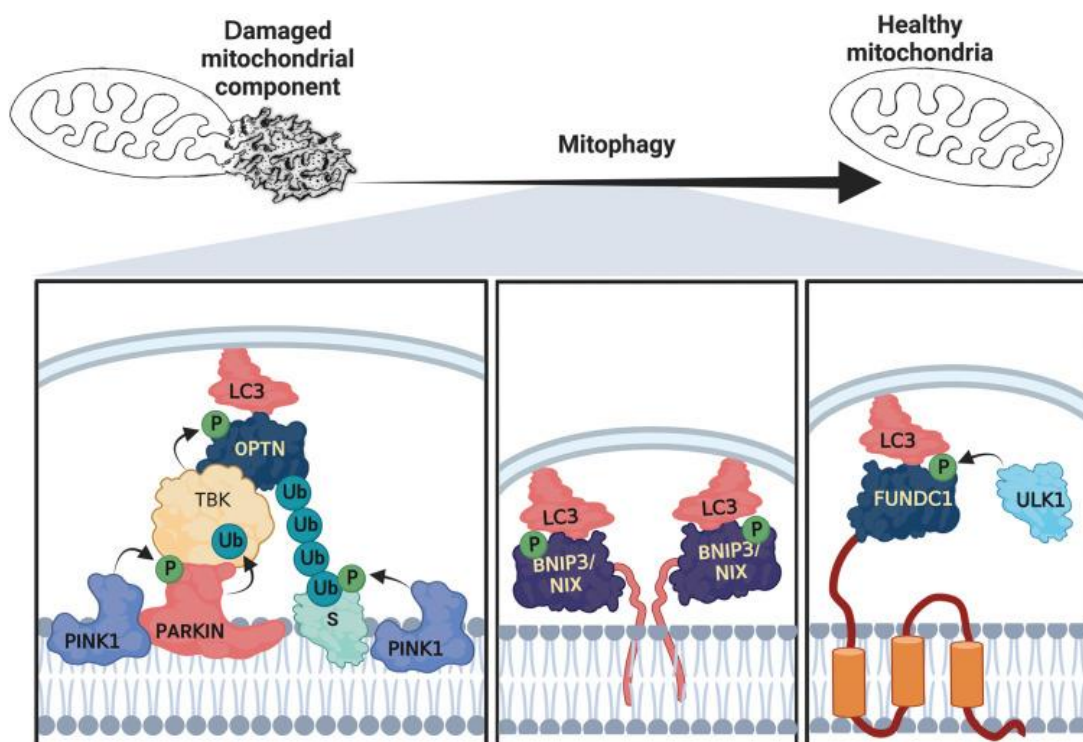
We found a total of 1000 articles out of which we selected 90 articles for this review. No meta-analysis was done.

PINK1/PARKIN Based Mitophagy

In healthy mitochondria phosphatase as well as tension homolog (PTEN) induced kinase [PINK1] gets imported to the inner mitochondrial membrane (IMM), along with thereby

targeted for breakdown by the presenilin associated rhomboid-like protein (PARL) as well as the cytosolic proteasome. Nevertheless, once mitochondrial membrane potential (MMP) diminishes, PINK1 accrual takes place at the outer mitochondrial membrane (OMM), in addition to its activation takes place via autophosphorylation [23]. Phosphorylation of ubiquitin results by PINK1 followed by enrollment of E3 ubiquitin ligase Parkin to the OMM [23,24]. Furthermore, it possesses the capacity of completely activating Parkin via direct phosphorylation on the serine 65 (in the ubiquitin like domain) whose escalation further takes place on the binding of the Parkin to the phosphor-ubiquitin [25]. Parkin possess the capacity of ubiquitination of numerous OMM proteins inclusive of voltage dependent anion channels (VDAC), mitofusin 2 (MFN2) as well as TANK binding kinase (TBK) [26]. Ubiquitinated OMM proteins crosstalk with the cargo receptors for instance proteins that possess the capacity of concurrently crosstalking with autophagosome correlated Atg8/ light chain 3B (LC3) family of proteins in addition to ubiquitin [26] inclusive of optineurin (OPTN) as well as nuclear dot protein 52 (NDP52) [23,24]. (Figure1) [rev in ref 27].

Besides the detailed signaling pathways, the mitophagy modulated by PINK1/ Parkin might implicate other mitophagy receptors for instance prohibitin2 IMM protein [28].



Legend for Figure 1.

Courtesy ref no-27-Schematic illustration of three mitophagy pathways (left to right, inspired by [23]).

PINK1/Parkin-dependent mitophagy: The decrease in membrane potential in damaged mitochondrial regions leads to the accumulation of PINK1 on the outer mitochondrial membrane (OMM), where it recruits Parkin. PINK1 activates Parkin by phosphorylating it within its ubiquitin-like domain, releasing its activity. Parkin then ubiquitinates OMM

substrates (S) such as MFN-2 and Vdac1. These ubiquitinated substrates are bound by cargo receptors such as OPTN1 and NDP52, which interact with membrane-anchored LC3 (LC3B-II) to promote mitophagy. The recruitment of TBK1 to the OMM promotes the binding of OPTN1 and cargo receptors to the ubiquitinated substrates, thus initiating mitophagy. BNIP3/NIX-dependent mitophagy: BNIP3 undergoes phosphorylation on residues S17 and S24, which are adjacent to the essential tryptophan residue at W18. This phosphorylation event promotes the interaction of BNIP3 with LC3B-II. FUNDC1-dependent mitophagy: The phosphorylation of S17 on FUNDC1 by ULK1 promotes its interaction with LC3B-II.

FUNDC1 Based Mitophagy

FUN14 domain containing (FUNDC1) portrays an OMM protein whose conservation has been going on from the nematode *Caenorhabditis elegans* (*C elegans* to the humans [29]. Current studies have illustrated that FUNDC1 possesses a key part in hypoxia stimulated mitophagy [30]. FUNDC1 possesses 3 transmembrane areas in addition to an amino terminal LC3 interacting region (LIR) having the capacity of crosstalking with the Atg8/ LC3) family of proteins]. (Figure1) [30]. Such crosstalk is strictly controlled by phosphorylation [31]. Once oxygen is not the restricting factor (normoxic situations) SRC in addition to CK1 phosphorylate FUNDC1 at tyrosine 18(Y18) as well as serine 13(S13) respectively thereby diminishing its proneness to LC3) [31]. Nevertheless, in case of hypoxia such residues get dephosphorylated. Therefore, there is escalation of LC3 crosstalk. Conversely, phosphorylation of the serine 17(S17, intricately placed with the LIR sequence motif) by the Unc 51 like autophagy activating kinase (ULK1) significantly escalates its crosstalk with LC3[31].

BNIP3/NIX- based Mitophagy

Bcl2 interacting protein3(BNIP3) along with Bcl2 interacting protein3 Like (NIX) represent stress stimulated mitophagy factors which were referred to start with in the form of pro apoptoticBH3 proteins. Akin to FUNDC1, BNIP3/NIX portray mitochondrial transmembrane proteins (having a single transmembrane area) which protrudes their LIR motif into the cytoplasm, where it directly has the capacity of crosstalking with LC3 in addition to other Atg8/ LC3 family of proteins [32] (Figure1). Such crosstalk is controlled partly by phosphorylation of the serine residues intricate to LIR motif serine 17(S17) along with serine (S35) in the BNIP3 as well as NIX respectively [33]. BNIP3/NIX are further controlled at the transcriptional level. A key transcription factor (TF) which controls their actions is the Hypoxia inducible factor 1(HIF 1) specifically BNIP3 once the O2 quantities decrease below 2% [34].

Other Mitophagy Pathways

Recent studies isolated alternate mitophagy pathways. This is inclusive of B cell lymphoma-2(Bcl)2-13 as well as lipids (cardiolipin along with Ceramide) based mitophagy pathways [35]. The other pathways are not described here. Nevertheless, all the mitophagy pathways – result in akin end: the breakdown of injured mitochondrial constituents in addition to lysosomes. Thereby for simplicity each aberrant mitochondrial clearance pathways have been referred to in form of 'mitophagy'.

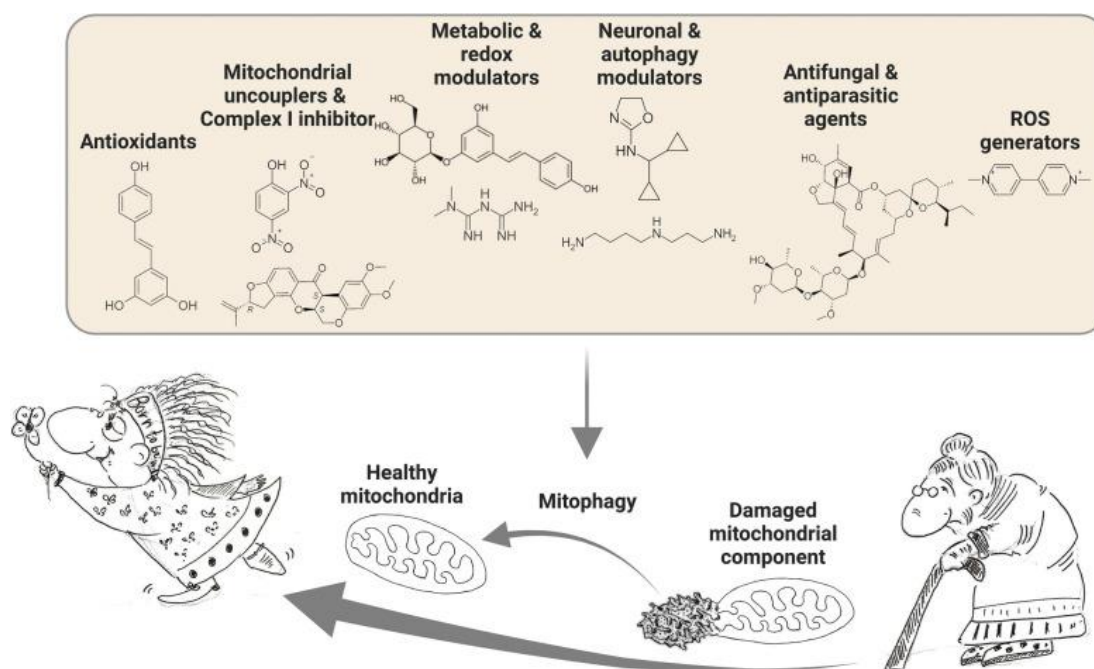
THE ACTIONS OF AGENTS WHICH ACTIVATE MITOPHAGY ON LIFESPAN ALONG WITH HEALTH SPAN

Over time period a reduction in mitophagy takes place with age [36]. Sequentially the accrual of injured mitochondria aids in the cellular injury that might result in generation of different

disease status for instance Alzheimer's disease [37], Parkinson's diseases [38], idiopathic pulmonary fibrosis (IPF) in addition to ageing lung [39], cancer [40], along with sarcopenia [41]. Thereby escalation of mitophagy by pharmacologic intervening comprises of an upcoming approach for the therapy of diseases accompanied by escalating age.

The major objective of this narrative review is provision of updated resource for novice scientific researchers as well as experienced in the arena of mitophagy in reference to different agents i) stimulating the mitophagy event in cells ii) organisms along with iii) animals.

Classification of every agent is done dependent on its biological actions. This has been a bothersome in view of maximum agents (or practically each possess greater than one biological action. Nevertheless, in reference to clarification every agent has been divided in a particular group. All of these possess a natural origination. Such mitophagy activating agents have been further classified in the form of i) antioxidants ii) mitochondrial uncouplers iii) complex I hampering agents iv) redox manipulators v) metabolic manipulators vi) neuronal manipulators vii) autophagy manipulators viii) antibiotics along with anti fungal agents ix) reactive oxygen species (ROS) producers (Figure 2).) producers use of small molecule pharmacological agents,



Legend for Figure 2.

Courtesy ref no-27-Healthy mitophagy activation by natural and synthetic substances.

A variety of natural and synthetic substances induces mitophagy. Selectively removing damaged mitochondria ensures cellular health and presents an emerging therapeutic strategy to promote healthy aging.

Noticeably, a plethora of natural agents which stimulate the mitophagy pathways are polyphenols. Polyphenols portray a variable group of naturally existent constituents observed in plants with substantial enrichment in addition to are believed to be the maximum broadly

accessible phytochemicals amongst every plant dependent source. Overall, they have substantially come in lime light in view of their health facilitating characteristics inclusive of prolongation of lifespan [42]. The longevity facilitating actions of polyphenols are based on the structural properties of their carbo cyclic rings as well as the numbers of hydroxyl groups existent on the rings [43]. *Caenorhabditis elegans* studies pointed that working of polyphenols via the particular longevity pathway proteins for instance DAF-16/ fork head box protein O3 (FOXO3) in addition to SKN-1/NRF2 (nuclear factor erythroid-2-related factor-2) TFs along with SIR-2.1- SIRT1 [44,45]. Apparently, such proteins manipulate the prolongation of lifespan action of polyphenols activators of mitophagy for instance baicalein [46], catechinic acid [47], curcumin [48], myricetin [49], naringin [50], resveratrol [51], as well as urolithin A [52].

Interestingly, DAF-16 along with SKN-1 control the actions of mitophagy receptor DCT-1 (the *C. elegans* homolog of the mammalian BNIP3 in addition to BNIP3/NIX [53]. Noticeably, in this context it is significant to point that activation of mitophagy confers protection from oxidative damage [54]. A plethora of dietary polyphenols portray robust antioxidant actions of polyphenols [42]. Nevertheless, bioavailability of the polyphenols via the digestive system as well as effectiveness of transportation to cells promote such working *in vivo* continue to be debatable [55]. Therefore, a potential posit is antioxidant actions of polyphenols are partially manipulated for instance via indirect activation of mitophagy [56].

A plethora of the synthetic agents are drugs, with certain of them getting FDA-approval, for instance aspirin, doxycycline hydrochloride, ivermectin, metformin, as well as rapamycin. Other agents are robust ROS inducers (paraquat in addition to sodium arsenite), Uncouplers of oxidative phosphorylation (2,4-dinitrophenol along with CCCP), metabolism modulators (dichloroacetate in addition to metformin), as well as and synthetic diamines (VL-004 along with VL-850).

Significantly the manner pointed for the natural agents, certain substances might be categorized in greater than one group. For instance, CCCP portrays a robust mitochondrial uncoupler and (therefore) inducer of oxidative stress in addition to [57]. Nevertheless, for sake of keeping things simple every material was clubbed into a single category. Akin to the natural agents, different synthetic 'compounds' actions are modulated by DAF-16 as well as SKN-1 TFs; for instance, ivermectin, sodium arsenite, aspirin, rapamycin, rilmenidine, 1,8 diamino-octane (VL-004), along with others. Studies by Srivastava et al. [54], in reference to synthetic diamine VL-004 illustrated that, minimally in *C. elegans*, extra TFs are the requirement for mitophagy-based antioxidant activity. That is, the hypoxia-inducible factor 1 (HIF-1), HLH-30/TFEB, and PHA-4/FOXO. Notably, these TFs are acknowledged to control regulate/manipulate lifespan in addition to healthspan in *C. elegans* [58], further corroborating the etiological causative working of mitophagy in lifespan controlling. A main hurdle is acquisition of insight regarding understanding the manner Such TFs actions get coordinated for the prolongation of life- along with healthspan.

Is it Feasible that Activation of Mitophagy by Utilizing Mitophagy Activating Compounds (MAC) Cocktail Escalate the Medical Advantages?

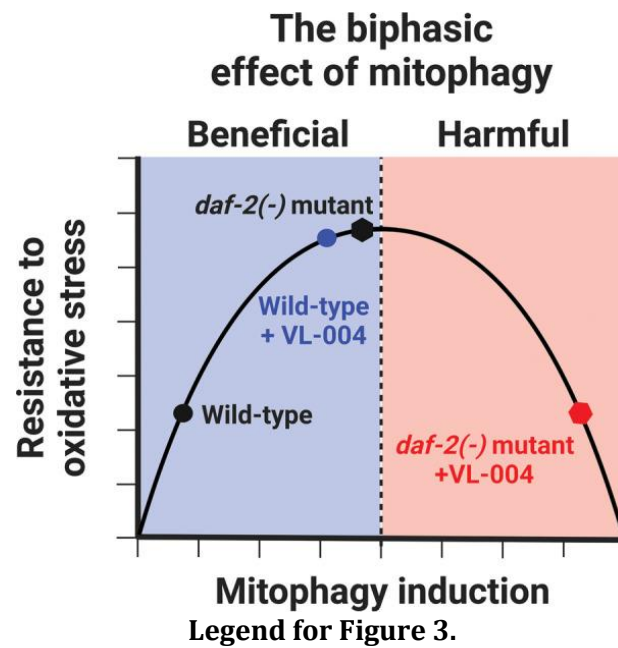
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synthetic diamine VL-004 illustrated that, minimally in *C. elegans*, extra TFs are the requirement for mitophagy- based antioxidant actions. That is, the hypoxia-inducible factor 1 (HIF-1), HLH-30/ HLH-30(homolog of TFEB in *C. elegans*) / transcription factor EB (TFEB), as well as PHA-4/FOXA (modulate feedforward loop at time of dietary restriction (DR)). Noticeably, these TFs are acknowledged to control regulate/manipulate lifespan in addition to healthspan in *C. elegans* [58], further corroborating the etiological working of mitophagy in lifespan controlling. A main hurdle is acquisition of insight regarding the manner Such TFs actions get coordinated for the prolongation of life- along with healthspan.

Earlier studies pointed that drug combinations might invoke therapeutic actions greater in contrast to the addition of the single agents [59]. Actually, there are proofs that targeting several constituents of the same cellular/physiological events might be advantageous [60]. An instance of such synergistic actions of two drugs working on the same target is the anticancer combination of cisplatin along with trabectedin. Trabectedin crosstalk with DNA as well as DNA healing repair systems in a separate manner in contrast to cisplatin. Specifically, trabectedin hampers DNA replication via a separate mechanistic mode, which diminishes the antagonistic action against cisplatin, resulting in a synergistic activity [60].

However, although the medical plausibility innates in the MAC cocktail approach it is believed to be a probable restriction. Srivastava et al. [54], in a recent publication illustrated that the diamine VL-004 possessed the capacity of prolongation of health along with lifespan of *C. elegans* [54]. Additionally, they illustrated that VL-004 conferred protection to *C. elegans* in addition to human obtained cell lines from oxidative damage [54]. Such protection conferring actions of VL-004 is based on the TF DAF-16, that gets negatively controlled by DAF-2; the *C. elegans* ortholog of the mammalian insulin as well as insulin like growth factor (IGF1) receptor (IIR) [61], DAF-2 hampers DAF-16, from entering nucleus. In view of that, once DAF-2 repression takes place, DAF-16 gets empowered in moving to the nucleus, reaching that place it gains the capacity of activating genes critical for stress along with elevated lifespan. Of these the gene sare represented by antioxidant genes; for instance, catalase 1 along with catalase2 in addition to superoxide dismutase3(SOD3) [62], whereas TF SKN is implicated in activation of plethora of antioxidant genes [63]. There by it does not come as amazing fact that worms presenting with loss-of-function mutations which hamper DAF-2 actions (daf-2 gene mutants) possess greater resistance to OS [64].

Interestingly, VL-004 does not escalate resistance of the daf-2 gene mutants to OS [54]. Conversely, it reduces the resistance to wild kinds of worm's quantities [54]. A posit expositioning that is that idealization of mitophagy result in sustenance of an efficacious harmony of the mitochondrial actions as well as ROS quantities. Further than these quantities, mitophagy is inimical, probably in view of it depletes non-damaged mitochondria in addition to/or disrupts healthy ROS signals((Figure3).



Courtesy ref no-27-The biphasic effect of mitophagy.

The basal level of mitophagy in wild-type worms is significantly lower than in *daf-2* mutants. Similarly, their resistance to oxidative stress is also lower, as represented by the dark circle and hexagon, respectively. Treatment with VL-004 increases the level of mitophagy in wild-type worms, moving it towards the optimal range of mitophagy, thereby increasing 'worms' survival in oxidative stress. This brings their survival rate similar to that of *daf-2* mutants (represented by the blue circle and dark hexagon). In contrast, treating *daf-2* worms with VL-004 leads to excessive mitophagy, moving it toward the harmful range. As a result, the survival rate of the *daf-2* animals decreases (represented by the red hexagon) to the level of wild-type worms before the VL-004 treatment. Actually, direct mitophagy determination illustrate that the baseline quantities in *daf-2* gene mutants is substantially greater, akin to that of wild kinds of worms which got VL-004 therapy [54]. The manner anticipated by the posit earlier, VL-004 escalates mitophagy in *daf-2* mutants, guiding it into non-healthy mitophagy zone. Parallel to this finding, it has been validated that escalated mitophagy might be inimical. For example, escalated mitophagy might working result in generation of heart failure in view of elimination of cardiomyocytes [65]. Additionally, it has been indicated that escalated mitophagy might work in the form of etiological factor of Huntingtons disease [66], along with stroke as well as Multiple Sclerosis (MS)[67]. Mitophagy might be working akin to that of walking on a tightrope as shown in movie Walk on ropes amongst 2 towers-meaning strict harmony needed. Therefore, planning of MAC cocktail has tobe precise in reference to not overtaking mitophagy threshold.

ARE MITOPHAGY ACTIVATING SUBSTANCES EFFICACIOUS IN ILLUSTRATING TREATMENT OF AGE CORELATED MEDICAL DISORDERS?

In reference to answering such a query the <https://clinicaltrials.gov/> databases which concentrated on studies meeting these criteria i) pure concentration on subjects ≥ 60 yrs older males as well as females using topic enhancement of longevity along with lifespan ii) both continuation of in addition to diseases finished human clinical trials. in case of accessibility of

plethora of studies(>3) our preference was for finished as well as publication of those clinical trials for guaranteeing accessibility of exhaustive outcomes .iii-)our assessment was restricted to substances utilized in their natural form amongst the study .Such criterion with efficacy deleted any kind of distracting actions resulting from extract or combination of substances, thereby escalated clarification of outcomes in addition to interpreting becoming simplified. Iv) plausible restriction related with any kind of treatments were further described, the illustrated in <https://clinicaltrials.gov/databases>. Such plausible restrictions were inclusive of i) numbers of subjects taking part in the clinical trials ii) time period of treatment of clinical trials of rest. Furthermore, we emphasize on any kind of the inimical sequelae found. v)The major objective was concentrating on diseases which have basically relevance in older age as well as are correlated with diminished mitophagy. See Table 1 for detailed results.

Table 1: Actions of Mitophagy activators in clinical trials targeting elderly- associated situations

Mitophagyescalator	Study Title (NCT number)	Disorders	Dosage&Intervening	Evaluated Criterion	Outcomes	Inimical sequelae& restriction of study (if particularly pointing in clinical outcomes)
Curcumin	Curcumin as well as working in older aged adults (NCT03085680)	Physical working as well as cognitive working in older adults	DietSupplementation: Curcumin: Daily 1000 mg x 3 months.	Physical working- Walking and hand grip cognitive working attention as well as & memory, pain, inflammation-IL-6	Curcumin caused improvementof physical, cognitive, and immune working	
Curcumin	Actions of curcumin on microvascular reactions and tissue oxygenation (NCT04119752)	Cardiovascular risk factor	Dietary Supplementation: Curcumin powder: 10 g, and studies were performed 2 h subsequent to delivery	Alteration in microvascular reactivity, tissue oxygen saturation, as well as nitric oxide metabolites (plasma nitrate along with nitrite)	Curcumin Supplementation caused improvementof the older population's pre-frontal cortex oxygenation along with blood volume [68].	
Resveratrol	Impact of resveratrol on brain function and structure (NCT02621554)	Healthy	Dietary Supplement: Resveratrol: Daily 200 for 26 weeks.	Alteration from baseline verbal learning task scores at 6 and 12 months, mini-mental state examination, functional alterations on brain MRI images and plasma biomarkers	No significant variation in the treatment versus placebo [69]. Escalation of serum cholesterol along with Total health reductionin both treatments along with placebo.	Greater studies with prolongation of time period of the drug treatment along with larger sample size would be requirement drawing appropriate Conclusions
	Cardiovascular health of older adults and resveratrol (CORE) (NCT02909699)	Aging	Dietary Supplement: Resveratrol: 1000 mg of resveratrol per day (one pill three times daily). Or 1500 mg of resveratrol per day (one pill three times per day).	Speckle tracking analyses, flow-mediated dilation, autophagy, differential endothelin-1 protein expression, endothelial function endothelial nitric oxide synthase (eNOS).	No accessibility of outcomes	
Urolithin A	Bioenergetics and muscle function improvement with AMAZ-02 in elderly skeletal muscle (ENERGIZE Trial) (NCT03283462)	Dietary Supplement: Mitopure (Urolithin A): 1000 mg/day, and the studies were conducted at the baseline (start of the study, 2 months and 4 months).	Alteration in 6 min walking distance (6MWD), percent change from baseline in ATP max (maximal ATP synthesis rate) in hand skeletal muscle, percent change from baseline in contraction number during a hand muscle fatigue test, percent change from baseline in ATP max (maximum ATP synthesis rate) in leg skeletal muscle, percent change from baseline in contraction number during a leg muscle fatigue test, changes in Short Physical Performance Battery (SPPB) scores at the end of the study intervention compared with baseline, change in exercise tolerance compared with baseline (via cycle ergometry), change in hand grip strength, change in leg muscle strength (1-RM and 10-RM), change in muscle size (cross-sectional area of the muscles), changes in mitochondrial function on muscle biopsy samples, effect of AMAZ-02 on mitochondrial	Urolithin A is overall safe for consumption. 6MWD along with ATP production in hand skeletal muscle did not significantly differ between the placebo along with the treatment. However, long-term treatment benefitted muscle endurance along with plasma biomarkers [70].	Urolithin A is overall safe for consumption. 6MWD and ATP production in hand skeletal muscle did not significantly differ between the placebo along with the treatment. However, long-term treatment benefitted muscle endurance and plasma biomarkers [70].	In this study, overall, there was an increase in both placebos along with drug for alterations in 6MWD, which may be because the participation in this study motivated the participant to increase their daily activity, along with daily participant physical activity was not monitored. Secondly, the study was carried out in a small sample size along with justin the white population from Seattle, Washington area and thus not applicable to full elderly population [70].

			gene and protein expression in muscle tissue, the effect of AMAZ-02 on plasma acylcarnitines, the effect of AMAZ-02 on quality-of-life questionnaire (SF36), change from baseline in plasma lipid profile and change from baseline in plasma for circulating biomarkers (myostatin, follistatin)			
Nicotamide riboside (NR)	The effects of nicotinamide adenine dinucleotide (NAD) on brain function and cognition (NCT02942888)	Mild cognitive impairment	Dietary Supplement: Nicotinamide riboside: 250 mg (week 1), 500 mg (week 2), 750 mg (week 3), 1g (weeks 4–10).	Alteration in Montreal Cognitive Assessment (MoCA), cerebral blood flow, plasma NAD, Short Physical Performance Battery (SPPB), Instrumental Activities of Daily Living (IADLs), endothelial function, Geriatric Depression Scale (GDS), Geriatric Anxiety Scale (GAS), Clock Drawing Task Protocol (CLOX), Executive Interview (EXIT), Test of Auditory Processing Skills (TAPS) along with grip strength from baseline at 10 weeks	No accessibility of outcomes	
	Inflammation in COPD and the effect of nicotinamide riboside (NCT04990869)	COPD	Dietary Supplement: Nicotinamide Riboside: 2000 mg/day	Alteration in Interleukin-8, NAD+ levels, interleukin-6, interleukin-10, Tumor necrosis factor alpha, C-reactive protein along with matrix metalloproteinase-9	No accessibility of outcomes	
	Slow age: interventions to slow aging in humans (NCT05593939)	Aging	Dietary Supplement: Nicotinamide riboside: 2000 mg/day for 6 weeks	Alteration in Interleukin-6, CRP, TNF- α , NAD levels in plasma, alterations in fat along with lean mass, grip strength, gait speed, predicted age by studying DNA methylation, Blood age, transcriptomics, voice, along with photographs of the patient.	No accessibility of outcomes	
	NR supplementation and exercise (NCT04907110)	Overweight, obesity along with type 2 diabetes in aging	Niagen: 1000 mg/day. Studies were conducted three days prior to NR supplementation along with after 40 days of treatment.	Alteration in ex-vivo muscle mitochondrial function, maximal aerobic capacity, physical performance, skeletal muscle NAD content, (ex-vivo along with <i>in vivo</i>), intrahepatic lipid concentrations upper leg muscle mass, body composition, quality of life, blood metabolites, submaximal exercise energy expenditure, sleeping metabolic rate along with and exercise efficiency	No accessibility of outcomes	
Cannabinoid	The effect of cannabis on dementia-related agitation along with aggression (NCT03328676)	Agitation related to dementia	Avidekel oil drops given under the tongue: that contains 30% cannabidiol along with a1% tetrahydrocannabinol: 295 mg along with 12.5 mg per ml three times a day for 16 weeks)	Alteration in score of the Cohen-Mansfield Agitation Inventory (CMAI) and in the score of the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH)	The use of 'Avidekel' oil resulted in a notable reduction in agitation contrasted with placebo in patients experiencing behavioral disruption associated with dementia [71].	Inimical sequelaemight include drowsiness. the study had restriction due to a small as well as heterogenous participant group from a single medical center. It didn't compare variable dementia sub-types, impacting the safety profile evaluation of the product containing THC. Working dysfunction measures as well as pharmacokinetic indices were missing. A much extensive study

						with a larger sample size is required.
Astaxanthin	Actions of astaxanthin on patients with Alzheimer's disease (NCT05015374)	To assess the plausible advantages of astaxanthin on Alzheimer's disease	Dietary Supplement: Astaxanthin (350 mg/day) for 3 years.	Mini-Mental State Examination (MMSE), Cognitive Ability Screening Instrument (CASI), Clinical Dementia Rating (CDR), Neuropsychiatric Inventory (NPI), along with incidence of treatment-emergent adverse events (safety and tolerability)	No accessibility of outcomes	
Metformin	Metformin to augment strength training effective response in seniors (MASTERS) (NCT02308228)	Aging	Behavioral: Progressive Resistance Training. Drug: Metformin 1700 mg/day for 16 weeks	Percent alteration in type 2 myofiber cross sectional area (utilizing the muscle biopsies of the vastus lateralis) along with percent alteration in normal density muscle size by computed tomography	Metformin has a detrimental effect on the hypertrophic response to resistance training in healthy older individuals. The study showed that participants who received the placebo experienced significantly greater gains in lean body mass ($P = 0.003$) and thigh muscle mass ($P < 0.001$) compared with those who took metformin [72]. Patients who had higher levels of muscle fat (lipid) at the beginning of the study showed reduced gains in muscle mass and strength when they took metformin. Similarly, the individuals who experienced the greatest changes in muscle fat also had limited improvements in strength. This suggests that for people to get the most benefit from strength training exercises, their muscle metabolism needs to adapt along with reduce fat quantities. However, metformin seems to interfere with this adaptation process, leading to less effective results from both aerobic along with strength exercises [73].	Inimical sequelae may include nausea, diarrhea, along with flatulence. This study focused on non-obese individuals who were free from any metabolic disease. It excluded the sedentary group.
	Metformin and Muscle in Insulin-resistant Older Veterans (NCT01804049)	Prediabetes	Drug: metformin 850 mg/day for 1 month	Alteration in total lean mass from baseline, in physical performance - 400 m walk speed along with muscle characteristics	Preliminary data suggests older individuals who have diabetes experience a faster decline in muscle mass and gait speed unless they are undergoing treatment with metformin. Moreover, older adults with prediabetes exhibit a more significant reduction in muscle mass and a higher likelihood of experiencing disability.	Inimical sequelae may include chest pain, nausea, diarrhea, weight loss, along with memory loss.

Taking into Account Mitophagy one size is not Applicable to All

Impairment of mitophagy is involved in the pathophysiology of a myriad of age-related disorders inclusive of Alzheimer's disease, Parkinson's diseases, cardiovascular disease (CVD) as well as sarcopenia [74]. Thereby escalating mitophagy is an attractive approach for the treatment of such diseases in the coming future [75]. Nevertheless, situations are existent where mitophagy might be inimical. For instance, functional mitophagy apparently is imperative for the propagation of tumors. Tumors that commence from Oncogenic KRAS mutations, malignancy is escalated by mitophagy [76]. Actually, selectively hampering autophagy /mitophagy by liensinine, which portrays a natural alkaloid, escalate the cell demise

actions of doxorubicin via dynamin-related/-like protein 1 (DMN1L, also known as DRP1), based mitochondrial fission thus sensitizes, breast cancer cells to chemotherapy through mediated mitochondrial fission [77]. Akin to that mdivi, a DRP1 manipulating hampering agent, sensitizes hepatic cancer cells to cisplatin as well as escalate cell demise [78].

Besides cancer, the different pathogenic viruses inclusive of human papilloma virus (HPV), human immunodeficiency virus (HIV), CSFV, MeV) possess the capacity of activation of mitophagy for avoidance of the cell demise, thus facilitating the infectivity of viruses. For example, measles virus vaccines strain EdmonstonB (MV- Edm) resulting in liberation of somatic cytochrome-c(CYCS). Sequentially, apoptotic cell demise gets hampered in non-small lung cancer cells (NSCLC) [79]. Therefore, drawing conclusions that at the time of use of small molecule pharmacological agents, which possessed the capacity of activation of mitophagy yielded attractive therapeutic options, such strategy needs to be taken into account for plethora of parts of mitophagy in reference to cellular health in addition to disease.

Mitochondrial Biogenesis: The Converse Aspect of Same Coin

The manner previously stated selective depletion of mitochondrial components that have got injured is imperative for the natural actions of mitochondrial network. Nevertheless, it is imperative that such step gets correlated with newer mitochondrial getting supplied in an event referred to as mitochondrial biogenesis [200]. Actually, a good synchrony amongst mitophagy as well as mitochondrial biogenesis is essential for the cells to accommodate to variation of metabolic status along with stress situations in addition to absence of coordinated effort is intricately correlated with variable pathophysiological situations (for instance PD) [80].

In view of event of mitochondrial biogenesis is not topic getting detailed, here our concentration is simply on a point correlated with this topic. That point is mitochondrial biogenesis activation takes place by same molecules that result in activation of mitophagy in addition to shared signaling pathways/ molecules.

A Resveratrol

Resveratrol results in mitochondrial biogenesis variable kinds of cells inclusive of brain cells [81]. Furthermore, it has been illustrated to be advantageous in different disease models inclusive of models correlated with aggravated ageing. For example, delivery of daily resveratrol at a dosage of 20mg -a day prior to peripheral blood obtaining resulted in avoidance of diminished AMP-activated protein kinase (AMPK) mediates activity dependent regulation of Peroxisome Proliferator Activated Receptor γ coactivator -1 α (PGC-1 α) in addition to nuclear respiratory factor1(NRF-1) expression in rat visual cortical neurons [82]. Furthermore, resveratrol at a dosage of 60 μ M (24hrs before treatment escalated mitochondrial biogenesis via the working of PGC-1 α as well as mitochondrial TF A in a disease models of PD(PC-12) [83]. Noticeably, NRF-1(along with NRF-2) as well as the estrogen correlated receptors (α , β along with γ) in addition to PGC-1 α represent crucial TF's which regulate mitochondrial biogenesis in mammalian cells [80]. Finally, resveratrol at a at a dosage of 160mg/kg daily for a minimum of 8 wks resulted in improvement of cognition in addition to mitochondrial in mouse models of aggravated ageing (Senescence accelerated mouse prone 8, [SAMP8]) who were fed high fat diet (HFD [84]. Intriguingly, resveratrol escalated the

quantities of mitochondrial respiratory ion of mitochondrial complexes without influencing the quantities of PGC-1 α as well as SIRT-1, nevertheless, escalated AMPK phosphorylation.

B Metformin

Metformin delivery of daily dosage of 2mM ameliorates human endothelial cells senescence by facilitating mitochondrial biogenesis via AMPK activation by escalating quantities of PGC-1 α as well as SIRT-3 [85]. Furthermore, metformin escalates the trimethylation of H3K79 (H3K79m3) in the SIRT-3 promoter area via an SIRT-3- DOT1-L (Deletion of the prorenin receptor in the ureteric bud that is known to hamper H3K79) signaling axis [87 & rev in ref 17]. In turn escalation of SIRT-3 expression takes place that results in escalated mitochondrial biogenesis [86]. Additionally, metformin at a dosage of 1700mg daily for a minimum of 1 year escalates the quantities of PGC-1 α in peripheral blood mononuclear cells (PBMC) obtained from type 2 diabetic patients [86], in addition to skeletal muscle along with liver [88,89].

C Molecular Expositions

Taking into account the molecular expositions AMPK activation works in the form of a juncture mitophagy along with mitochondrial biogenesis.

In particular activation of AMPK by PGC-1 α induces mitochondrial biogenesis, with simultaneous stimulation of autophagy /mitophagy via Unc 51 like autophagy activating kinase 1 as well as 2 (ULK1 & 2) [80]. Noticeably, activation of AMPK takes place by extrinsic in addition to intrinsic stimuli. For example, escalated Calcium (Ca^{2+}) quantities possess the capacity of, activating Ca^{2+} / calcium calmodulin dependent protein kinase (CaMK) that further activates Ca^{2+} -calcium calmodulin dependent protein kinase kinase β (CAMKK β), therefore activating AMPK [80,90]; with CaMK possessing the capacity of, directly activating PGC-1.

Although, there is considerable enrichment of information in reference to mitophagy along with mitochondrial biogenesis events, a substantial lack of garnering the interassociation; In particular in reference to regulation at the level of organism in addition to therapy with agents where combination of such events take place. Thereby its assessment of the combination of activation of mitophagy in addition to biogenesis might workout in a magnificent manner in acquisition of understanding in reference to prolongation of lifespan along with healthspan of different biological models.

CONCLUSIONS

Diminished cellular mitophagy aids in the injury in addition to generation of situations, for instance ALZHEIMER'S DISEASE, PARKINSON'S diseases as well as cancer. Thereby activation of mitophagy through different small molecule pharmacological agents isolated yielded a plausible manner of mitophagy stimulators inclusive of i) antioxidants ii) mitochondrial uncouplers iii) complex I hampering agents iv) redox manipulators v) metabolic manipulators vi) neuronal manipulators vii) autophagy manipulators viii) antibiotics along with anti fungal agents ix) reactive oxygen species (ROS) producers.

In plethora of individuals utilization of such agents get manipulated by TF's which harmonize cell's reaction to stresses for instance DAF-16/FOXO, HLH-30/ transcription factor EB (TFEB), PHA-4/FOXA, as well as SKN/NRF2. Nevertheless, in plethora of instances particular cellular

receptors that possess the capacity of binding such agents in addition to the manner such binding stimulates the prolongation of life- along with healthspan is by activation of specific mitophagy pathway, continue to be uncharted. One needs to gather insight on the mechanism of action of such events which has become imperative in reference to generation of greater safe as well as efficacious molecules for the treatment of age correlated diseases.

Clinical utility of mitophagy activating compounds (MAC) cocktail for the therapeutic reasoning apparently is an attractive approach in reference to escalating advantageous mitophagy actions. MAC cocktail might work in prolongation of life- along with healthspan plausibly by targeting variable constituents of same cellular event. Nevertheless, it is key to take into account probability of restriction in view of escalated mitophagy might result in inimical sequelae. Sustenance of idealization of mitophagy is key in orchestrating of mitochondrial actions in addition to ROS quantities, with overtaking such threshold might cause inimical sequelae. Thereby fashioning therapy MAC cocktail has to take into account such frail harmony of mitophagy guaranteeing it would not over take threshold, with the idea of maximization of therapeutic advantages.

Subsequent to aforementioned details, one has to be cautious at the time of utilizing small molecule pharmacological agents, for activating mitophagy is necessary in view of its actions are situations based. Implications of mitophagy in the propagation of tumors as well as infection by viruses have illustrated double kind of its influence on the cellular events with both advantageous along with inimical sequelae having been found. Thereby a therapeutic strategy meant for modulating mitophagy has the requirement of considerable precautions with total alteration in addition to exhaustively worked out for guaranteeing maximal result in variable disease situations.

Lastly, mitochondrial biogenesis leads to harmony amongst mitophagy for guaranteeing appropriate mitochondrial network homeostasis. Intriguingly, mitochondrial biogenesis activation might be caused by akin molecules stimulating mitophagy for instance, resveratrol in addition to metformin. Although remarkable work has been undertaken acquisition of insight regarding such events, plethora of information needs unraveling, specifically in the context of acquisition of insight of their interassociation at the level of organism along with evaluation of combination of such agents which target mitophagy as well as biogenesis. Future assessment such field might be unveiling the manner such combinations might be influencing lifespan along with healthspan in different biological models.

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