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Trends in internal medicine

Moringa Oleifera and Mitochondria – A Short Literature Review

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Abstract

Mitochondrial dysfunction is a critical factor in the pathology of numerous diseases, impacting cellular energy production and metabolic processes. This review explores the potential of Moringa oleifera (MO), a well-established medicinal plant, in mitigating mitochondrial dysfunction. Highlighting its phytochemical components such as flavonoids, isothiocyanates and glycosides, this paper discusses their roles in reducing oxidative stress, combating inflammation and improving cellular health. Evidence from recent studies supports MO's capacity to restore mitochondrial functions, alleviate muscle atrophy and counteract neurodegenerative diseases. While promising, gaps in clinical research necessitate advanced trials to validate these findings and develop MO-based therapeutic interventions.

Keywords: Moringa oleifera, Mitochondrial Dysfunction, phytochemical constituents, neuroprotection, oxidative stress.

Introduction

Background

The nature of mitochondria is what interests many researchers today for its function in the human body. They are dynamic organelles that exist to maintain cellular metabolism alongside stress responses. These are among its primary activities but mitochondria has many roles to play. A high number of biochemical procedures take place with mitochondria being the one and only site. Procedures such as the synthesis of fatty acid and oxidative phosphorylation (OXPHOS) along with thermogenesis occur in mitochondria. The mitochondria is responsible for generating the signal intermediates at the time of metabolism. As a

result, the cellular functions fall into regulation as well as the phenotype.

Energy in the human body is produced on the basis of its metabolic demands alongside the efficiency it has during regular activities. Mitochondria is at the center of energy production and is capable of handling cellular homeostasis. When there is resting condition of the body, carbohydrates along with fatty acids get moved into the mitochondria. Once they are inside, they undergo oxidizing to Acetyl-CoA. It is a necessary part of the posterior oxidation maintained within the Kreb cycle as well as electron transport chain (ETC) [1].

In mitochondria, there are a number of processes that happen in non-stop order like, mitophagy, fusion as well as fission and transport cycles. These cycles help in determining mitochondria's morphology and distribution across cells. Furthermore, the above mentioned activities are the key to maintaining mitochondrial functions [2]. Given the level of involvement of mitochondrial function in energy production, it is elemental to know that malfunctions can create havoc in human body.

Role of Moringa Oleifera as Supplementary Medicine

Moringa oleifera (MO) is known for a long while as a medicinal plant. Originally found in India, it has been cultivated in other parts of the world for quite some time. As is the case for medicinal plants, every part of MO can be used for medicinal purposes. The parts that are most widely used are seeds, leaves and bark as well as roots. At the same time, one may also use the flowers and immature pods if they are looking for a source of phytoconstituents [3]. It has been stated by several experts in their studies that these parts of MO come with high safety levels. In short, there should be no adverse effect on the human body.

There are phytochemicals present in the leaves of MO, for instance, sterols, flavonoids, alkaloids, tannins etc. Minerals like calcium and potassium can also be found in them alongside zinc, iron and magnesium. More importantly, the plant consists of anti-oxidative as well as anti-inflammatory agents, for instance, isothiocyanates, glucosinolate to name a few. It is also made up of agents like glycosides as well as glycerol-1-9 octadecanoate which have anti-inflammatory characteristics [4]. For the malnourished people, MO can be used in ways to provide a source of protein. There are a high number of amino acids in the plant's extracts much like a primary protein source. The leaf extracts constitute amino acids like cystine, methionine, caline, lysine along with isoleucine [5].

Moringa oleifera is known for its anti-oxidative characteristics which has already been stated above. There is a radical scavenger-like property in the extracts. The extracts will highlight antioxidant activities quite strongly if they are fighting against free radicals. In addition, the leaf extracts can provide preventive measure against oxidative damage by simply enriching the polyphenols [6].

There are chlorogenic acid, quercetin glucoside and rutin that can be found in the leaves. In some experiments, researchers found that MO is capable of restoring glutathione (GSH). At the same time, it increases the activities of glutathione-S transferase (GST) along with glutathione reductase (GR) [7]. When the GSH activity rises to a new level, it leads to a higher degree of detoxification of the molecules. It takes place through the conjugation with that of the GSH. Moringa oleifera's leaf ex-

tract has many other activities to show. MO is shown to induce synthesis for the enzymes which play a key role in the regeneration of GSH levels.

As previously mentioned, MO contains anti-inflammatory properties which allows it to act against the related disorders. In order to provide an inflammatory response, it is vital to possess the transcription factor known as NF-kB. There are target genes in Nf-kB such as, TNFα, iNOS and IL-1β that will act as a mediator for the inflammation [8].

Scope and Objective

Given the anti-oxidative and anti-inflammatory characteristics found in Moringa oleifera plant's extracts, there has to be a link between that and mitochondria dysfunction. The link that is being established here is to reduce the side-effects of mitochondrial dysfunction through the use of MO. Now, there are a number of parts of the plant with medicinal benefits. It is imperative to found out exactly which part can be used for treating mitochondrial dysfunction. The aim of this review is to find the connection between MO and mitochondrial dysfunction which can make it more treatable.

In clinical terms, muscle atrophy refers to tissue loss. The process is about an imbalance of the protein degradation which outgrows the rate of synthesis. There are multiple reasons associated with muscle atrophy. Primary reasons are high-fat, obesity and Alzheimer's disease (AD). Some studies in recent times have demonstrated the connection between mitochondrial dysfunction and muscle atrophy in patients suffering from Type-1 diabetes mellitus. This review article will further look into the possible connection between the two. In addition, there is need to understand how well Moringa oleifera leaf extracts respond to oxidative stress and managing mitochondrial dysfunction as well as muscle atrophy [9].

Furthermore, the fusion and fission process of mitochondria has been seen to impact the onset and progression of Alzheimer's disease (AD), Parkinson's disease (PD) along with Huntington's disease (HD). There is a burning need to understand the cause behind the changes of mitochondrial trafficking and the fusion-fission dynamics [10]. By understanding the causes, it should be possible to provide a clearer picture of mitochondria's involvement in the neurodegenerative disorders. This review article will also aim to go over existing research into the matter and provide insights.

Mitochondrial Functions and Their Importance

Overview of Mitochondrial Physiology

Mitochondria is known for having to perform various roles. One of these roles is a power station that serves eukaryotic cells. There is a connection between being the power station and playing the anchor role to metabolize lipids as well as saccharides. Due to this function of metabolize both, mitochondria can assist in energy production, taking the form of ATP. Beyond that, mitochondria takes part in so many different cellular activities as well that it is called as the powerhouse. For instance, mitochondria has a hand in activities like the urea cycles, signal transductions, cell proliferation as well as iron metabolism. In addition, mitochondria is one of the agents responsible for the maintenance of a cellular redox state. Mitochondria achieves that by creating a balance of reactive oxygen species (ROS) productions and then eliminates it through an antioxidant defense system. More than 4/5th of ATP generation is achieved due to OXPHOS. For a short period of time in the mito-

chondrial matrix, there are energy substrates that make their way inside the tricarboxylic acid cycle. As a result, electron carriers are produced and make their way past the electron transport chain. The movement is enough to prompt the available protons to leave the matrix for the intermembrane space. It results in the formation of a mitochondrial transmembrane potential [11].

As mentioned above, mitochondria actively works to balance out the production of ROS. The source material of the ROS within the living cells are highlighted by the physiological enzymatic mechanisms. Metabolic situation is generally under control as part of the ROS. If under any circumstance, the metabolic situation goes out of control then the ROS production goes into overdrive. The same may also happen in terms of ROS production with the appearance of xenobiotic compounds. Oxidative stress is the outcome of ROS production becoming uncontrollable.

The mitochondrial structures are hosts to ROS as they are the major producer of it. So, it is natural that the mitochondrial structures will need to bear the brunt of the attack when oxidative stress occurs. The damage which oxidative stress causes to mitochondrial components comprise of protein oxidation as well as lipid peroxidation. In addition, it is also at the root of mtDNA mutation. On the inner part of the mitochondrial membrane, there exists cardiolipin. Cardiolipin may be easily affected when lipid peroxidation occurs.

Meanwhile, oxidative stress results in the formation of protein oxidation which affects the enzymes in respiratory chain. Moreover, the protein oxidation is directly responsible for damages to the transhydrogenase along with adenine nucleotide translocator. When all of these damages are occurring, there is a particular damage to Complex I that needs to be mentioned strongly. Due to this oxidative damage, Complex I has limited activity within Parkinson's disease [12]. So, it is clear that mitochondrial functions are essential for the welfare of many activities.

Mechanisms of Mitochondrial Quality Control

Fusion and Fission Dynamics

Two adjacent mitochondria combine to form a fusion. On the other hand, fission is the process of a singular mitochondria breaking into two. In a way, the two processes counterbalance one another for as long as the host lives. If even one of them becomes inactive then there is nothing to oppose the other process. Naturally, there will be an imbalance that takes charge of the entire mitochondrial structure.

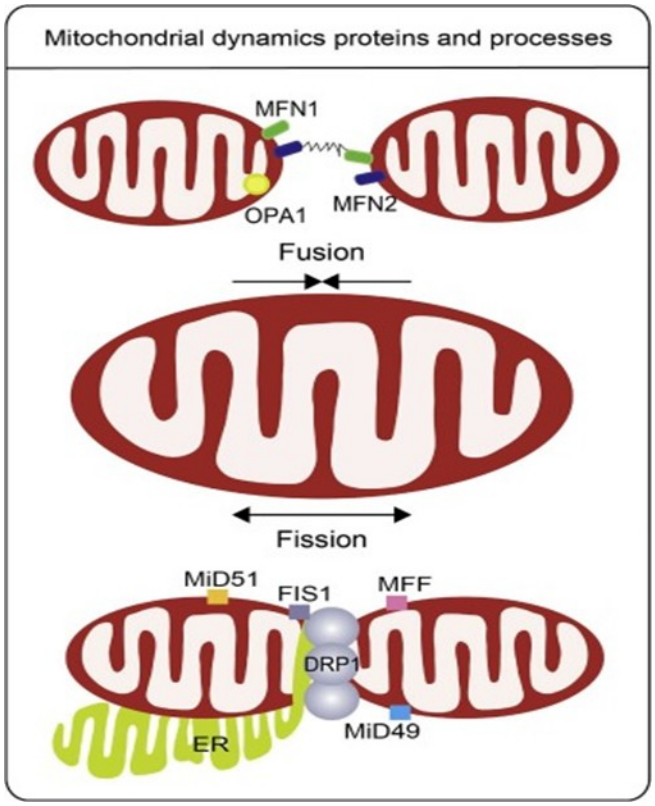

Figure 1: Fusion and Fission dynamics, image sourced from MDPI.com

The image above demonstrates a simple model of the fusion and fission dynamics. Fusion occurs in

mammalian cells and becomes harmonized with help from OMM-located mitofusin (MFN) 1, along with MFN2 as well as optic atrophy 1 (OPA1). The location of all three is in the IMM and there are separable sequential events for them. Synthesis of mitofusin occurs and transcriptional mechanism alongside a post-transcriptional one regulates it. Fusion proteins are necessary for the normal mitochondrial function. So, when there is a loss of these fusion proteins, that kick starts mitochondrial fragmentation [13].

Fission in the mitochondrial outer membrane (MOM) requires multiple steps in the same process. At the end of the process, the mitochondrion will break into a couple of smaller mitochondria. All of the steps rely on a huge cytoplasmic GTPase dynamin-1-like protein (DNM1L). This protein will translocate to a MOM when there are cellular as well as mitochondrial signals. By the time the DNM1L protein becomes a part of the MOM, it is ready to form a structure similar to a ring. The ring-like structure surrounds the mitochondria with the MOM becoming constricted. When fission occurs, mitochondria becomes redistributed. There is a lot of value in this process as smaller mitochondria can be redistributed to regions that need constant energy.

Imbalance may occur with fission at any point in time due to impaired fusion. This will lead to mitochondrial fragmentation. When there is unbalanced fusion, it may be a byproduct of defective fission that allows mitochondria to become elongated. There exist pathogenic variants inside the genes coding proteins which are tasked with mediating of fusion and fission. As a result, the equilibrium is disrupted and does not allow for proper mitochondrial energy to be produced. Without mitochondrial fission, issues are likely to rise in the homeostasis process [14].

One of the basic necessities for cells to provide optimal performance is the existence of cellular homeostasis. Inside eukaryotic cells, homeostasis occurs and is referred to as autophagy. Autophagy separates cellular components as well as affected organelles from cells as a maintenance activity for intracellular homeostasis. Some of the components that autophagy separates are accumulated proteins. Since autophagy is seen as a degradation pathway, it can create a balance for biosynthesis. Moreover, autophagy balances out the macromolecules so that the organisms are protected against a number of pathologies. The most notable pathologies to occur are cancer, aging as well as neurodegeneration. In order for cell physiology to remain at normal level, it is imperative to keep mitochondrial function unchanged. Mitochondria remains the primary producer of adenosine triphosphate (ATP).

Mitophagy is partially responsible for determining the amount of mitochondria. The other half of this activity is performed by mitochondrial genesis. One of them is not like the other and yet they hold the key for regulating the quality of mitochondria as well as mitochondrial turnover. Each time that a mitochondrion becomes damaged, it is not possible to replace them straight away. When the damage occurs, the affected mitochondria will corrupt the healthy ones with the assist from ROS-induced ROS release (RIRR). The best way to describe RIRR is to compare it with that of a downward spiral that amplifies the ROS signaling. In return, cells undergo irreversible damage.

One of the many jobs of mitophagy is the selective removal of damaged mitochondria. The removal of

the damaged ones balances out the physiological activities. Damage to the mitochondria can be an early sign of inflammation as well as aging. When there is stress, mitophagy works to eliminate the damaged mitochondria. In short, mitophagy is needed in the human body for the normal mitochondrial functions to be maintained at all times [15].

Consequences of Mitochondrial Dysfunction

When there are disruptions in the normal functions of mitochondria, it is a strong indicator for programmed cell death. Disruptions caused within the mitochondria consist of redox potential alongside altered membrane potential. These two are vital characteristics of a functional mitochondrion. Calcium is stored in the internal membrane potential and also takes charge of regulating the generation of ROS. In addition, the membrane takes care of ATP synthesis with the process of oxidative phosphorylation.

With the mitochondrial membrane getting depolarized, this is a telltale sign of dysfunction. Experts state that the depolarization may be a consequence of the toxicity related to drugs. Changes will occur in the membrane's potential. One of these changes is a reduction in the ADP/ATP ratio. At the same time, the matrix levels for calcium undergo changes as does oxidative stress. Nowadays, there are fluorescent-based assays to assist with viewing the changed functioning of mitochondria [16].

Mitochondrial dysfunction plays a pivotal role in skeletal muscle wasting. There have been three ways noted so far in which it contributes to skeletal muscle wasting. These three ways are:

- Damage to mitochondria leading to reduction in the manufacturing of ATP
- Proapoptotic factors release of the mitochondria
- Increase in mitochondrial production for ROS

Studies confirm the fact that longer durations of skeletal muscle inactivity leads to an increase emissions of mitochondrial ROS [17]. Oxidative stress can contribute to muscle wasting. When oxidative stress occurs, it activates each of the proteolytic system. To be precise, it is responsible for elevating proteolysis. There are three independent ways in which it does that. Moreover, oxidative stress is responsible for muscle wasting as it depresses the protein synthesis which is a part of the skeletal muscle fibers [18].

Moringa oleifera: A Medicinal Powerhouse

Ethnobotanical and Historical Uses

Moringa is known to experts as a fine source of nutritional components. There is a lot of calcium in the leaves that equates to four times of the amount found in milk. By tradition, MO has its use as an antispasmodic and a stimulant among other things. The fresh roots of the plant are known for being acrid. On an internal basis, the plant has its use as diuretic while the bark is antifungal. On the whole, MO is being considered as this cardiac circulatory tonic. Historically, the decoction of MO plant has been used for gurgling as it can cure sore throat. As every part of the plant can be used for medicinal purpose, the fried pods have been used in some countries to treat diabetes. Meanwhile, the root juice has been in use as an antiepileptic [19]. It is important to note that, Moringa is easy to cultivate even within adverse environment.

Nutritional and Phytochemical Components

MO is known to contain high amount of valuable phytochemicals. There are many reports which state the plant is responsible for curing or preventing in excess of 300 diseases. As mentioned above, there are many historic uses of the entire plant. In order

to specifically understand about the phytochemical components, it is vital to look deeper into the leaves. The leaves are known to contain the highest amount of phytomedicinal properties. Leaves of MO can be used for treating diseases like paralysis, malaria, joint pain and even HIV infections.

When it comes down to the pharmacological properties, Moringa oleifera exhibits analgesic, antidiabetic and antioxidant properties. Furthermore, the leaves have been used in experiments to yield positive result when going up against high-altitude hypoxia. This has been achieved through a modification of monoamines which can be found in the brain. Here is a table to highlight the bioactive components of MO:

Table 1: Bioactive Component available in MO with effects on certain chronic ailments:

Compounds	**Postulated Function**	**Model**	**Protection Against**	**References**
Flavonoids	Quercetin Hypolipidemic and anti-diabetic characteristics Decrease of expression of DGAT	Zucker rat Rabbits In vitro study	Diabetes Atherosclerosis Cardiovascular ailments as well as diabetes	Vergara-Jimenez, et al. (2017). Fatoumata et al. (2020) Almatrafi, M. (2017)
Chlorogenic Acid	Impacts lowering of glucose level Lowers cholesterol effects in plasma as well as liver Anti-obesity characteristics	Diabetic rats Zucker rat High-fat induced obesity rats	Diabetes Cardiovascular ailments Obesity	Villarruel-López et al. (2018) Ocheleka et al. (2020) Redha, et al. (2020)
Alkaloids	Cardioprotection	Cardiotoxic-induced rats	Cardiovascular ailments	Hugar, et al. (2018)

The table was compiled with high level of assistance from Kumar, et al (2024).

Key Bioactivities

The concept of free radicals dictate that they carry a singular unpaired electron as they exist as independent molecules. As it takes place in their orbital, it results in the body experiencing oxidative reactions. The outcome of those reactions is ageing and the aftermath of old age. In a healthy human body, balance exists between the amount of antioxidants and free radicals generated. Imbalance occurs when the amount of free radicals increase, which creates oxidative stress [20]. Oxidative stress is at the core of a number of problematic and life-threating diseases. The list of diseases comprise of coronary artery diseases, emphysema and arthritis among others.

In order to fend off oxidative stress, the body relies on molecules known as antioxidants. The antioxidants protect the body through a reaction with free radicals. Antioxidants also protect by increasing the activities of enzymes such as, catalase along with SOD. Both of these enzymes are known for producing antioxidants. Of all the antioxidants, flavonoids, vitamin E as well as polyphenols are most well-known. Moringa oleifera's leaves consists of substances which will suppress COX-2 while also suppressing pro-inflammatory cytokines [21].

The Intersection of Mitochondrial Dysfunction and Disease

Mitochondrial Acquired Disorders

Involvement of Mitochondrial Dysfunction in Skeletal Muscle Atrophy

Mitochondria plays the anchor role in many activities within the human body. As such, it has direct involvement in the vital metabolic pathways and is the site that allows ATP production. When there is any defect in the mitochondria, the aftermath is always bad. A strong case can be made about this aftermath due to mitochondria's role in activities such as, cytopathological mechanisms for cancer, aging as well as neurodegenerative diseases [22].

When muscle atrophy begins, there is mitochondrial degradation which has an influential role to play in reducing mitochondrial quantity. At the same time, it will reduce the mitochondrial quality which under the control of mitochondrial autophagy alongside the fusion and fission kinetics of mitochondria [23]. All of them make up the quality-controlling system for the mitochondria. As part of the various activities of mitochondria, this system is responsible for maintaining the skeletal muscle mass. The muscle mass is managed by making corrections to mitochondrial dysfunction.

Mitochondrial dysfunction plays the catalyst role for catabolic signaling pathways. With that underway, the nucleus receives the feed to engage in the expression of the genes of muscle atrophy. While the particular molecular mechanisms are yet to be specified, mitochondrial dysfunction is known for playing a role in skeletal muscle atrophy [24].

Mitochondrial Dysfunction's role in Neurodegenerative Disorders

Mitochondria's function can be linked to a number of neurological activities. Oxidative phosphorylation is at the backbone of mitochondria as it relies on this mechanism along with a few other mechanisms. Through these mechanisms, mitochondria is able to achieve sustainability for the wellbeing of neurons. In the human body, there are a significant number of complex activities one of which are the cellular responses provide to stressors. Mitochondria acts as the regulatory hub for the responses. Through maintaining these functions, mitochondria ensures the overall neuronal welfare.

The work of mitochondria is diverse and it is connected to a number of cellular organelles. When these organelles work with mitochondria, it determines the body's response to the stressors. Now, the stressors can either be favorable or unfavorable. Over the years, there have been many studies to confirm the link between mitochondrial dysfunction and the neurodegenerative diseases.

There are quite a few age-related neurodegenerative

e disorders, one of which is Alzheimer's disease (AD). A probability exists for these neurodegenerative disorders to be connected to oxidative stress as well as mitochondrial dysfunction. When there is an increased level of oxidative damage coupled with the decrease in complex I activity, it may be a sign of Parkinson's disease (PD). In addition, impairment of the antioxidant defense enzyme functions can suggest the onset of PD [25].

Before linking mitochondrial dysfunction with skeletal muscle atrophy, it is vital to comprehend the signaling network which assists in developing the disease. Only then will it be possible to progress with therapeutic approaches. The production of ROS is tied with the onset and progression of the disease. At the same time, the decrease in mitochondrial biogenesis and impairment of mitochondrial dynamics have a hand to play. Muscle atrophy can be caused due to excess amount of ROS production as it can induce oxidation for myofibrillar proteins. With this oxidation, the proteins have heightened vulnerability towards proteolytic breakdown.

When protein synthesis occurs in the body, it is the responsibility of skeletal muscle to provide the necessary amino acids. Protein synthesis is crucial for muscle growth as well as repair work. There is a thin line maintaining the balance between degradation and protein synthesis. If for any reason, the protein degradation increases, then it results in muscle atrophy. One of the outcomes of muscle atrophy is the fall of muscle strength.

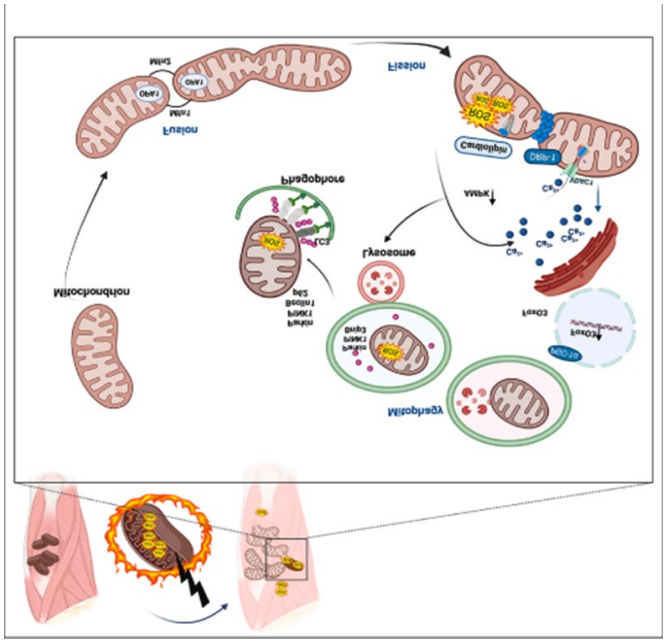

Figure 2: Mitochondrial dynamics with turnover for skeletal muscle atrophy, image sourced from ResearchGate

Autophagy serves as the backbone to numerous intracellular pathways while also controlling the survival for cells. So, it is crucial to find out its role and activities in patients suffering from neurodegeneration. Muscle atrophy occurs and spreads due to a combination of factors. These factors are: uptick of cell death as well as oxidative stress, collection of damaged mitochondria as well as autophagic protein ATG7 getting deleted from skeletal muscle [26].

In the mitochondria, fusion and fission are two nonstop procedures that need to be carried out with balance. The processes need to be continuous for them to maintain regular size and shape. Any error can cause a bulk load of problem for mitochondria. On

the other hand, ROS-mediated mitochondrial oxidative stress damage leads to apoptosis. There exists harmony in mitochondrial homeostasis. So, when that harmony is disrupted, it can create new problems. For instance, mitochondrial dysfunction occurring within dopamine neurons leads to oxidative stress. In return, neurotoxins are green lit for production and can be connected to PD. Protein fragments, namely, beta-amyloid (Aβ) along with phosphorylated Tau (pTau) accumulate inside human brains and has long been considered to be pathological attribute for AD. These fragments negatively impact the mitochondrial integrity to further ruffle mitochondrial dysfunction. Multiple studies confirm the existence of imbalance in mitochondrial homeostasis in patients suffering from AD and PD. Moreover, the mitochondrial fission in AD patients appear abnormal with a decrease in the expression for proteins of mitochondrial biogenesis. Through a regulation of the mitochondrial functions, the nuclear genomic DNA methylation creates an impact on PD development [27].

Genetic and Congenital Disorders

When the mitochondria get affected, the human body will be prone to many diseases. There certainly are repercussions for the development of mitochondrial dysfunction. A strong example of it is the level at which the immune cell functions become compromised. If that happens, then there is a weakened line of defense to fight off pathogens. Of all the mitochondrial disorders, MELAS syndrome is a typically complex one. Due to its complex nature, the clinical symptoms are also not simple, for instance, myopathy, and dementia and stroke-like episodes. Of course, there are a number of other signs but, these are the notable ones alongside recurrent headaches. When the mitochondria malfunction, it has a negative impact on key cell functions leading to these symptoms [28].

The pathogenesis was studied for the stroke-like episodes which reveals oxidative stress as a potential underlying factor. Patients who fell victim to MELAS syndrome were considered and their brain samples were obtained. Studies on the sample reveal that there was an increase in the amount of neurons consisting of 8-OHdG during a stroke-like episode. This is a strong indicator of the presence of oxidative stress within DNA [27]. In addition, infant patients suffering from Leigh syndrome reportedly have mitochondrial disease phenotype. These patients typically suffer due to encephalopathy, movement disorder as well as psychomotor delays [29].

Role of Moringa oleifera in Mitigating Mitochondrial Dysfunction

Antioxidative Mechanisms

Experiments conducted with Moringa oleifera leaf extracts were done to highlight the antioxidant effects. A recent study was conducted taking MO hot water extract (MOH) with Vero cells. There were no signs of cytotoxicity from MOH for the Vero cells to the level of 125 µg/mL. During the experiment, vitamin C was introduced for positive control. The primary objective of this study has been to investigate the presence of certain phenolic components. With this study, the presence of polyphenols were further confirmed alongside glucosinolates. In addition, these components are considered for having bioactive effects.

According to the studies of Young Chool Boo, phenolic compounds found in numerous plants decreases ROS levels within cells. At the same time, the compounds reportedly increase cellular antioxidant capacities. As such, it may be stated that

MOH contains antioxidant properties as there are many phenolic compounds available in them [30].

Anti-inflammatory pathways

In recent years, a number of anti-inflammatory drugs have been tested to observe their pharmacological actions. The outcome is that the drugs contain a mechanism for free radical scavenging. Experts suggest that the MO leaves' antioxidant characteristics can be cellular mechanism for the anti-inflammatory potential found within macrophages with LPS stimulation.

There is existence of pro-inflammatory cytokines in the form of TNF-α along with IL-6. These cytokines are being termed as the key inflammatory mediators that are byproducts of monocyte alongside macrophages. The production occurs during the inflammatory process. A big reason for their production is to respond to LPS by means of the NFkB activation. Of these two cytokines, the IL-6 is regarded as multifunctional which can regulate immune responses as well as inflammation. When the amount of IL-6 production increases, there has been a link between it and the appearance of diseases such as, osteoporosis, arthritis as well as psoriasis. A recent study was carried out with MO hydroethanolic bioactive leaves extracts. The extracts displayed remarkable inhibition in the production of TNF-α, IL-6 as well as IL-1 β when induced in LPS. During the study, the doses were carefully coordinated to reveal that Moringa oleifera possesses anti-inflammatory characteristics. So, they may be administered with care to treat anti-inflammatory disorders [31].

Protective Effects on Skeletal Muscle

The leaf extracts of Moringa oleifera are capable of increasing the energy metabolism for the muscle cells. Molecular mechanisms of the extracts showed favorable results for protein expression within SIRT1 as well as PPARα in one recent study. The skeletal muscle is a plastic tissue with unique characteristics such that it can adapt with physiological stimuli. There is adaptive response in the skeletal muscle from an aerobic exercise. As a part of the response, the study discovered a rise in the amount of mitochondria. In addition, there is increase in activities linked to oxidative metabolism-based enzymes. Hence, the muscle's capacity for sustaining aerobic metabolism increases. As a result, there is enhancement of muscle mass which can be linked to an increase of creatine kinase (CK) activities. It is important to note that CK is crucial for maintaining ATP homeostasis.

Moreover, the aqueous extracts of MO have shown anti-fatigue characteristics. In one experiment on rats, it has increased the mobilization for body fats to improve swimming performance. Based on that, it may be said that MO has its use as an alternative for nutritional exercise [32].

Neuroprotective Potential

It is not hard to look at Moringa oleifera as having neuroprotective potential. In fact, studies have been conducted in the past to investigate the neuroprotective impact on the neuroblastoma cell lines of humans. These extracts were taken in to test for cytotoxicity and as such, the Moringa oleifera extracts display a low value for cytotoxicity. There were more parts of the study with the focus shifting to neuroprotection activities.

When the extracts were optimized with H_2O_2 for the SHSY5Y cell line, they provided 44% neuroprotection. It is vital to note that the H_2O_2 concentration was made lethal on purpose for the study.

The extracts work their way in AD patients by enhancing the amount of superoxide dismutase (SOD) alongside catalase. Both of them are enzymes which may play a key role in improving the memory of AD patients. Moreover, the moringa oleifera leaf extracts can diminish the lipid peroxidase levels. As such, there is a chance that the antioxidant activities of the extracts can provide the necessary boost that improves cognitive functions [33].

A study was conducted in 2018 by Zhou et al., and it was on mice. The scope of this study was to examine the scopolamine related cognitive impairment. During the study, around 70% of the ethanolic extracts sourced from the seeds of the plant. The result was in favor of the neuroprotective characteristics [34].

Discussion

Integrative Insights

If oxidative stress levels increase then it causes functional losses for the electron transport chain (ETC). As it is closely related to the functionality of mitochondria, there is decline in mitochondrial Mn-SOD levels. Experts had belief that the leaf extracts of MO contain ameliorating effects. In order to prove it, they carried out experiments on mice to find the expression level for α-synuclein, PARP1, Tyrosine Hydroxylase (TH) as well as Bax. In addition, they checked the expression levels of cleaved caspase-3 within the tissue lysate for SNpc. The method used for the experiment is the western blot analysis. It was found that there was an enhancement in the expressions of both TH and Bcl-2 when compared to another group treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The outcome signifies the ameliorating effect of MO extracts.

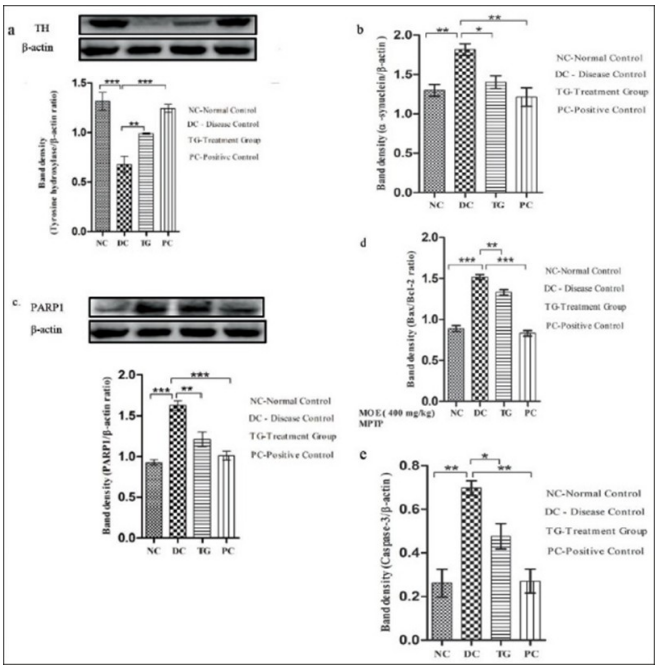

Figure 3: Evaluating the relative expressions of TH, α-synuclein, PARP1, Bax, and Caspase-3, image sourced from SageJournals.com

The study also displayed how MPTP intoxication was at the root of mitochondrial dysfunction in mice brains. With moringa oleifera leaf extracts, it is possible to decrease the ROS production. This allows the extracts to reduce the burden put on the entire mitochondrial antioxidative defense system. At the same time, these extracts are capable of enhancing activities related to the complexes of the ETC. All of this is made possible due to the high availability of antioxidants in the extracts [35].

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Research Gaps

Across the decades, there have been many studies on animals to validate the hypothesis regarding the medicinal benefits of Moringa oleifera. However, there is very little to go on in terms of application on the human body. Even now, the use of Moringa oleifera outside of South Asia is a rarity. It may well be due to a lack of awareness regarding its benefits and healing properties. So, there is need to do clinical studies which confirms the findings and spreads awareness.

Certain plants consist of synergistic effects. For one study, plants such as, *C. albicans*, *M. oleifera* along with fluconazole were used [36]. The combination was put against ethanol extraction and displayed a high level of synergy effect with that of mean zone for inhibition (mm) representing 37.33±0.57. It is a fact that many medicinal plants comprise of characteristics of antifungal agents and Moringa oleifera is no different. This is due in part of the resident phytochemical constituents [37].

Implications for Future Research

In the last two decades, there has been a collective growth in many countries regarding what Moringa oleifera can offer. As such, scientists from different countries have collaborated to conduct studies.

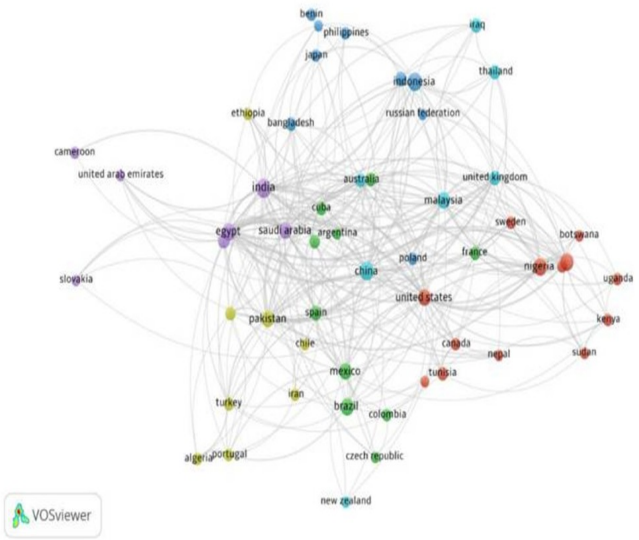

Figure 4: Visualizing the network of international collaborative research on Moringa oleifera, image sourced from PubMed Central

The image above is an indication of growing interests among countries to find the benefits of the plant. Given that the plant's extracts possess anti-cancer, anti-oxidant, anti-inflammatory and cardio-vascular activity among others, it is critical to conduct more research [38].

Furthermore, the plant displays its utilities in various contexts. There is economic value in cultivating the plant. Moringa oleifera can be used as a key source for nourishment and even as animal feed. It also comprises of properties which make it a natural coagulant. The health benefits of the leaf extracts alone are many. At the very least, the wound healing capabilities of *M. oleifera* can be put to great use [39]. Given how many cases of neuro-degenerative disorders are left unsolved, it is imperative to find an alternative. At the same time, the losses contributed by mitochondrial dysfunction is yet to be countered. The malfunction along with its side-effects spread fast throughout the body. Hence, a need exists for extensive research into ways to include Moringa oleifera into novel therapeutic applications against these disorders. There is always the possibility for some parts of the plant to emerge as beneficial addition towards naturally existing compounds exhibiting promise.

Conclusion

Mitochondrial health is pivotal to numerous physiological processes, and its dysfunction contributes to severe health issues such as neurodegenerative diseases, muscle atrophy, and metabolic disorders. Moringa oleifera, rich in antioxidant and anti-inflammatory phytochemicals, shows immense promise in addressing these challenges. By restor-

ing mitochondrial dynamics, reducing oxidative damage, and supporting energy metabolism, MO offers a natural and holistic approach to mitigating the effects of mitochondrial dysfunction. While preliminary findings are encouraging, comprehensive clinical studies are essential to confirm its efficacy and integrate MO into mainstream therapeutic regimens. Advancing research in this area could open new avenues for treating diseases linked to mitochondrial dysfunction.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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