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Review Article

Emerging Therapeutic Approaches for Amyotrophic Lateral Sclerosis (ALS)

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Abstract

Motor neuron disease (MND) is a collection of degenerative neurological disorders that impact the motor neurons responsible for controlling involuntary muscular movements. Amyotrophic lateral sclerosis (ALS) is the predominant variant, affecting both the upper and lower motor neurons in the brain and spinal cord. As the disease progresses, these neurons deteriorate, leading to muscle weakness, wasting, and inability to regulate voluntary motions. ALS can impair speech, swallowing, and breathing, causing significant impairment over time. Additional types of motor neuron disease (MND) encompass primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), and progressive bulbar palsy (PBP). These types exhibit variations in the location and severity of motor neuron involvement, but they all share the progressive degeneration of motor neurons. Treatment may involve medication, physical therapy, assistive equipment, and supportive care to manage symptoms and consequences over time. This review's primary aim is crucial for gaining a deeper understanding of the disease's fundamental causes and creating innovative therapies or interventions to enhance the outlook and quality of life for individuals suffering from MND.

Keywords: Motor neuron, Motor neuron disease (MND), Amyotrophic lateral sclerosis (ALS), Progressive muscular atrophy, Bulbar palsy.

1. Introduction

MND is also known as ALS or Lou Gehrig's disease. Neurodegenerative diseases are a group of conditions where specific motor neurons in the brain and spinal cord undergo deterioration. MND is characterized by a progressive nature, whereby signs gradually deteriorate over time. It can impact your gait, speech, ingestion, consumption, and respiration. Occasionally, it might also alter your cognitive processes and actions. The condition manifested consistently during the Middle Ages and is more prevalent in males [1]**.** Roughly 5-10% of instances can be traced back to family inheritance, whereas approximately 20% are caused by a mutation in the Superoxide dismutase (SOD) gene. Diagnosing MND can be challenging due to its rarity, as initial symptoms like clumsiness, weakness, or slight speech impairment might be attributed to other

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causes. It causes the respiratory, bulbar, and limb muscles to weaken gradually.

A majority of MND in families is autosomal dominant. About 20% of inherited MND is caused by mutations in Cu/Zn superoxide dismutase (SOD1), an anti-oxidant enzyme that is widely present. It is yet unknown how these mutations result in the death of motor neurons. It has now been determined that certain rare variations of MND have a genetic basis, and only recently has it been demonstrated that typical ALS is caused by mutations in two additional genes, TARDBP (TAR DNA-binding protein) and fused in sarcoma, or FUS. The two gene products are proteins that bind DNA and ribonucleic acid (RNA), most likely for use in RNA processing. Together, these two gene mutations cause an additional ~10% of family MND cases. Their presumed shared role illuminates a novel perspective on the disease's development, and a significant shift in MND research will probably occur.

1.1. Classification of Motor Neuron Diseases

Motor neuron diseases (MNDs) are categorized as inherited (genetic mutation) or sporadic (no family history) based on whether they affect upper motor neurons, lower motor neurons, or both. It is important to note that Amyotrophic lateral sclerosis (ALS) and Multiple sclerosis (MS) can have similar symptoms but are different conditions [2, 3]. Multiple Sclerosis is an autoimmune disease that damages the myelin sheaths in the brain and spinal cord, preventing them from sending signals to motor neurons. On the other hand, ALS causes the death of the motor neurons. Both conditions impair the brain and spinal cord's ability to control voluntary muscles. However, people with MS often live for 25-35 years after diagnosis, while the life expectancy for those with ALS is only 2-5 years. Motor neuron disorders are generally categorized into specific subtypes. **(Fig. 1).**

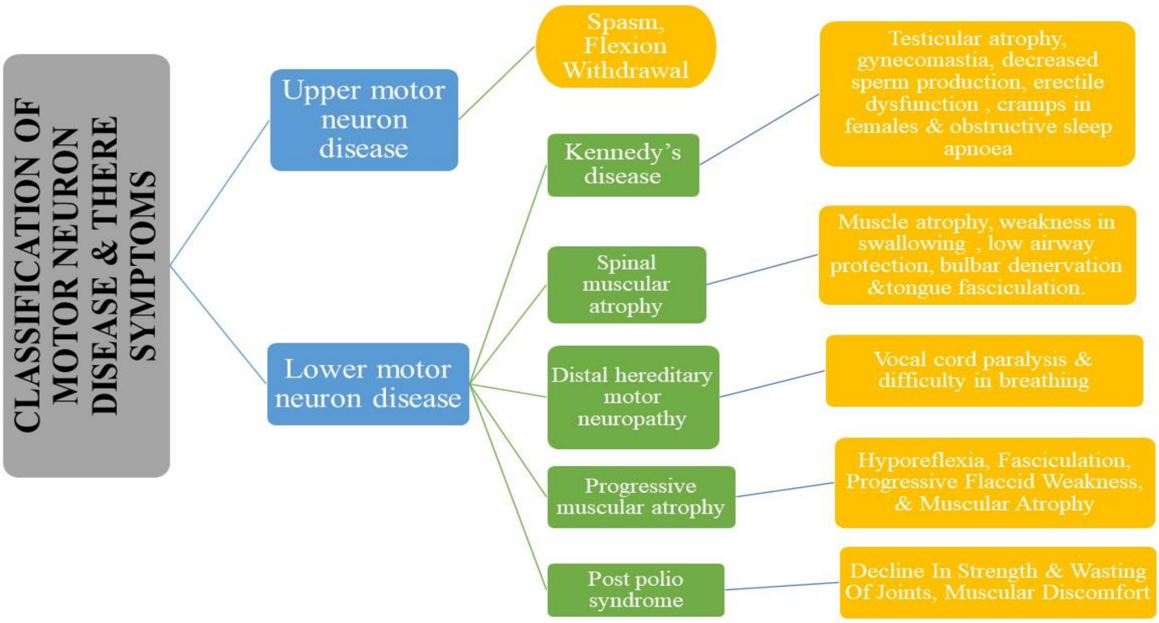

Figure 1. Classification of Various types of Motor neuron disease and their symptoms.

A) Upper Motor Neuron disease (UMND)

In the instance of UMND, the sufferer exhibits increased vulnerability to stretching. Furthermore, they exhibit spasm, flexion retraction, and various other indications [4, 5]. The UMN (Upper Motor Neuron) lesion mostly affects the lower limb's extensor muscles and the upper limb's flexor muscles.

It also increases reflexes in the tensor muscles and other related symptoms.

B) Lower Motor Neuron disease (LMND)

LMN (Lower Motor Neuron) lesions lack muscular contraction, causing weakness and decreased muscle tonicity. Subsequently, the deterioration of muscle tissue and the disruption of normal electrical activity lead to fibrillation, which may be seen using an electromyogram. Muscular atrophy is the final result [6]. LMND is categorized into various sub-categories:

a. Spinal and Bulbar Muscular atrophy (Kennedy's Disease)

b. Spinal Muscular Atrophy

c. Distal Hereditary Motor Neuropathy (dHMN)

d. Progressive muscular Atrophy (PMA)

e. Post-polio Syndrome (PPS)

a. Spinal and Bulbar Muscular atrophy (Kennedy's Disease):

Kennedy's illness, scientifically called spinal and bulbar muscular atrophy (SBMA), impacts individuals in their third to fifth decades of life. The condition predominantly affects males, while a minority of carriers and asymptomatic females are women [7]. This phenomenon occurs due to the limited presence of androgens in the bloodstream and the activation of androgen receptors in females. The trinucleotide repeat mutation in the androgen receptor (AR) gene is responsible for reduced androgen levels. The condition is thought to be caused by an elongated trinucleotide repeat of more than 37 glutamine proteins. Androgen-sensitive symptoms in males with SBMA include testicular shrinkage, gynecomastia, reduced sperm production, erectile dysfunction, and decreased sperm count. Females who carry the genetic trait have reported feeling cramps and other symptoms. Patients with SBMA frequently experience obstructive sleep apnea.

b. Spinal Muscular Atrophy:

A collection of hereditary illnesses that cause the degeneration of anterior horn cells, resulting in muscle wasting and weakening. The clinical manifestations encompass muscle atrophy, weakness during the acts of swallowing and sucking, diminished airway protection, bulbar denervation, and tongue fasciculation.

c. Distal Hereditary Motor Neuropathy (dHMN):

Distal hereditary motor neuropathy, type II, is a progressive disorder that affects nerve cells in the spinal cord, leading to muscle weakness and movement problems, primarily in the legs. It can start from the teenage years through mid-adulthood, with initial symptoms including muscle cramps or weakness in the big toe and the entire foot. Over 5 to 10 years, individuals with this disorder may experience a gradual loss of muscle tissue in the lower legs, leading to difficulty in walking and running and possibly complete paralysis of the lower legs. Some people may also experience weakening of the muscles in their hands and forearms, though it is usually less severe and does not usually result in paralysis.

d. Progressive muscular Atrophy (PMA):

This rare disease typically starts in adulthood and causes the deterioration of specific types of nerve cells called lower motor neurons. These nerve cells are found in the anterior horn cells and brainstem motor nuclei. The patient has hyporeflexia, fasciculation, increasing flaccid weakness, and muscle atrophy. Weakness and muscle wasting typically commence in the distal limbs unevenly, following a neuropathic pattern, and gradually worsen over months to years. Patients with bulbar weakness are at a higher risk of experiencing progression of ALS. Although there is a correlation with UMN participation, no data indicates cognitive impairment. ALS patients experience executive dysfunction due to impaired activation in the prefrontal cortex.

e. Post-polio Syndrome (PPS):

It is a condition characterized by the development of lower motor neuron (LMN) symptoms that arise several years after experiencing bouts of poliomyelitis. The onset of symptoms often manifests 30 to 40 years following the first poliovirus infection. It is predominantly observed in females [8]. The condition is characterized by a gradual decline in strength and wasting of joints, accompanied by muscular discomfort. Post-polio syndrome affects a significant proportion, ranging from 15% to 80%, of individuals who have previously experienced paralytic polio. The size of motor unit areas in the spinal cord significantly increases due to the collateral sprouting of neighboring motor neurons. The motor unit area is said to have a 20-fold increase, eventually hitting a limit where further reinnervation is impossible. Unremunerated denervation results in muscular weakening and the deterioration of muscle fibers. The exact cause of denervation remains obscure.

1.2. Clinical manifestation

MND encompasses various types with similar symptoms and progresses through three stages: early, middle, and advanced. The speed and severity of the diseases can vary. In the early stage, symptoms develop gradually and may resemble those of other health conditions. They typically begin in the arms, legs, mouth, and respiratory system. The early symptoms become more pronounced as the condition advances into the middle stage. Individuals may also experience muscle shrinkage, difficulty moving, joint pain, drooling due to swallowing issues, uncontrollable yawning, changes in personality and emotional states, and difficulty breathing. In the advanced stage, individuals with advanced ALS may require assistance with movement, eating, breathing, or a combination of these. The disease can become life-threatening, with breathing problems being the most common cause of death. The clinical manifestations depend on the type of MND and the specific body area it affects. These details are outlined in **Table 1**.

2. Pathophysiology

The exact cause of MND is not fully understood, but it is believed to involve a combination of genetic and environmental factors. The pathophysiology of MND involves several key mechanisms presented in **(Fig. 2).**

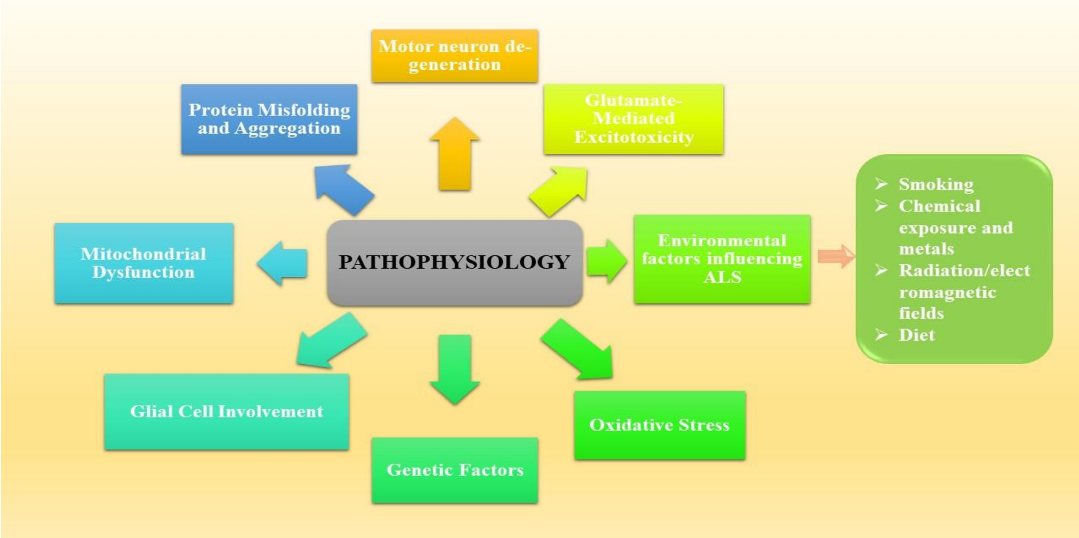

Figure 2. Pathophysiology of Motor Neuron Disease (MND).

The defining characteristic of Motor Neuron Disease (MND) is the gradual deterioration and death of motor neurons. Motor neurons are a type of dedicated nerve cells that have the specific function of delivering information from the brain to the muscles. This allows for the execution of voluntary muscular movements [18]. Both the lower motor neurons, which are found in the brainstem and spinal cord, and the upper motor neurons, located in the cerebral cortex, are affected by MND.

2.1. Glutamate-Mediated Excitotoxicity

Glutamate is generated within the presynaptic terminal. Enhancing glutamate uptake into synaptic vesicles is a function of vesicular glutamate transporters [19]. In the usual procedure of neurotransmission, glutamate is released into the synaptic cleft, which stimulates post-synaptic receptors. Once the vesicle is released, the synaptic cleft is cleared of glutamate by various transporter proteins in both glial and neuronal cells, including excitatory amino acid transporters (EAATs) [20]. Understanding the intricate process of glutamate synthesis and elimination is vital for maintaining a delicate balance in the concentration gradient and safeguarding neurons from potential harm caused by excitotoxicity [21, 22]. ALS patients and transgenic SOD1 mice models have decreased astroglial glutamate transporter EAAT2 in the motor cortex and spinal cord. This reduction increases extracellular glutamate levels, leading to excessive activation of glutamate receptors and subsequent neuronal death caused by excitotoxicity [23, 24]. In addition, this leads to an abundance of calcium, an excessive activation of motor neurons, and the onset of numerous harmful metabolic processes within the cell. These pathways play a crucial role in both hereditary and non-hereditary forms of ALS, according to research [25, 26]. Glutamate excitotoxicity has a role in neurodegeneration by either stimulating Ca2+-dependent enzymatic pathways through an increased entry of Na+ and Ca2+ ions or by generating free radicals [27- 29].

2.2. Oxidative Stress

Free radicals, also known as reactive oxygen species (ROS), are released into the environment as an unavoidable consequence of the regular oxygen metabolism [30]. The accumulation of reactive oxygen species (ROS) causes severe damage to the structures of the cells as they accumulate. Oxidative stress is caused by an imbalance between the creation of reactive oxygen species (ROS) and the cell's capacity to neutralize them through anti-oxidant defences [31]. Cell death occurs when the capacity to neutralize hazardous reactive intermediates is lost. Oxidative damage is higher in biopsies from ALS cases, and changes in redox processes were among the initial hypotheses of how mutant SOD1 may lead to cell toxicity [32]. The SOD1 protein plays a crucial role in anti-oxidant defense. Hence, any alteration in this gene might lead to cellular toxicity. CSF (Cerebrospinal Fluid), serum, and urine samples from ALS patients exhibited elevated levels of free radicals and enhanced oxidative damage [33, 34]. Furthermore, mutant SOD1 rodent models and human CNS biopsies exhibited oxidative damage to RNA species [35]. Oxidative damage threatens several cellular constituents, such as proteins, lipids, and DNA, leading to the deterioration of motor neurons [36].

2.3. Protein Misfolding and Aggregation

Anomalous protein accumulations are frequently observed in the brains and spinal cords of individuals with Motor Neuron Disease (MND) [37]. TDP-43 (TAR DNA-binding protein 43) and FUS (Fused in Sarcoma) are the primary proteins implicated in this process. These proteins undergo misfolding and aggregation, resulting in the formation of intracellular inclusions. These inclusions interfere with cellular function and contribute to the degeneration of motor neurons.

2.4. Mitochondrial Dysfunction

Aside from glutamate excitotoxicity, mitochondrial dysfunction also significantly contributes to the degeneration of motor neurons. Mitochondria are organelles enclosed by a membrane that play a crucial role in essential biological activities, including intracellular energy generation, cellular respiration, regulation of calcium levels, and apoptosis control [38]. Recent research suggests that abnormalities in the structure and chemical processes of mitochondria may contribute to the progression of ALS. Patients with ALS exhibited effective problems and changes in mitochondrial structure in their skeletal muscle and spinal motor neurons. These alterations included a fragmented system, swelling, and increased cristae [39-44]. In ALS patients, the mutant SOD1 can be found within the cytoplasmic side of the outer membrane and matrix of mitochondria in the spinal cords [45, 46]. Spinal cord mitochondria are greatly affected by the build-up of misfolded mutant SOD1, leading to significant mitochondrial dysfunction. This dysfunction manifests as a decrease in ATP production, disturbances in calcium levels, hindered transport of mitochondria along axons, and the triggering of apoptosis [47, 48]. Mitochondria play a vital role in generating energy for cells by converting it into ATP, which is essential for cellular metabolism. ALS patients' skeletal muscle biopsies have revealed disruptions in energy balance and ATP deficiencies [49].

2.5. Glial Cell Involvement

Glial cells, specifically astrocytes and microglia, support and safeguard nervous system neurons. In the case of MND, glial cells activate and produce inflammatory chemicals, exacerbating the neurodegeneration and neuroinflammation [50].

2.6. Genetic Factors

Certain Motor Neuron Disease (MND) instances have a hereditary or genetic element. Genetic mutations in many genes, including superoxide dismutase 1 (SOD1), have been linked to the hereditary type of motor neuron disease (MND). ALS is not caused by the loss of SOD1 function due to mutations in this gene. Instead, these mutations make the protein more likely to form aggregates, which disrupts several crucial cellular processes [51] C9orf72, TARDBP, and FUS [52]. Genetic mutations can potentially interfere with cellular processes and heighten the vulnerability to motor neuron degeneration.

2.7. Environmental factors influencing ALS

Prior epidemiological research has indicated that individuals with ALS may have encountered environmental pollutants [53]. The study investigated the correlation between amyotrophic lateral sclerosis (ALS) and factors such as exposure to agricultural pesticides, heavy metals, solvents, electromagnetic fields, dietary patterns, airborne particles, and physical activity [54].

2.7.1. Smoking

Studies have demonstrated that cigarette smoke can increase the risk of developing ALS as a result of the presence of inflammatory conditions, oxidative stress, and neurological damage induced by the inclusion of heavy metals in cigarettes. Individuals who begin smoking at a younger age have the highest chance of developing ALS among those who smoke regularly. However, it is not linked to the length or severity of smoking practices. In addition, the exhaled smoke from cigarettes includes formaldehyde, a substance that is linked to increased mortality rates in people with ALS [55-58]. Cigarette smoking is widely believed to be the most reliable non-genetic risk factor for ALS.

2.7.2. Chemical exposure and metals

ALS has been linked to the exposure of agricultural chemicals, including pesticides, fertilizers, herbicides, insecticides, and formaldehyde. Prospective research revealed that individuals who reported being exposed to pesticides/herbicides for a duration of 4 or more years may have a higher likelihood of developing ALS. However, no correlation was seen between the death rate and the level of exposure. Additionally, this study revealed that individuals who had prolonged exposure to formaldehyde had a mortality rate from ALS that was more than double compared to those who were not exposed [59]. Lead exposure has been widely studied concerning ALS amongst all the heavy metals. This is likely because individuals who are exposed to elevated amounts of lead frequently experience symptoms that are comparable to those of ALS. Further inquiries have established a correlation between being exposed to lead and the development of ALS. Professions that include exposure to lead, such as welding, have shown a strong correlation with the development of ALS [60- 63].

2.7.3. Radiation/electromagnetic fields

Controlled experimental investigations have demonstrated that when cells are exposed to exceedingly low-frequency electromagnetic waves, there is an observed rise in the creation of reactive oxygen species. When a live creature is exposed to something, it causes oxidative stress and reduces the anti-oxidant capacity of its cells. Oxidative damage plays a role in the progression of ALS, as oxidative stress is implicated in the development of ALS. Empirical research has substantiated that electromagnetic fields induce the fragmentation of DNA strands within brain cells, resulting in cellular demise through apoptosis and necrosis. This comment aims to elucidate the correlation between electromagnetic fields and the likelihood of developing ALS [64- 65]. The consumption of glutamate and fat in excessive levels has been demonstrated in previous research to be detrimental to patients who have amyotrophic lateral sclerosis (ALS).

On the other hand, it has been discovered that protective effects can be attributed to omega-3 fatty acids, vitamin E, and fiber. Previous studies have shown that an excessive amount of glutamate receptor activation results in an increase in the amount of calcium that is delivered to the intracellular space. The elevation in calcium levels can initiate the targeted demise of neurons, akin to the mechanism identified in ALS. The amino acid glutamate can be found in foods high in protein, such as cheese, milk, mushrooms, and tomatoes. It is usually impossible for glutamate to get across the BBB; therefore, whether glutamate from the diet affects neural communication levels is not known.

Moreover, areas of the brain referred to as circumventricular organs are susceptible to variations in plasma glutamate concentration. Omega-3 fatty acids are known to possess anti-inflammatory characteristics, which could potentially reduce inflammation caused by the loss of neurons [66-68]. It has been demonstrated that combining omega-3 fatty acids with vitamin E can reduce the risk of getting amyotrophic lateral sclerosis by as much as sixty percent. These nutrients seem to have a cumulative effect when combined.

3. Diagnosis

An in-depth analysis of the individual's health history, a comprehensive bodily investigation, and a battery of tests designed to rule out other probable disorders that share similar symptoms are often required to arrive at a diagnosis of motor neuron disease (MND) [69]. Here are some steps typically involved in the diagnosis process:

3.1. Medical History

Before initiating the examination, the physician will gather comprehensive medical information, encompassing symptoms, their duration, and any pertinent familial history of neurological disorders.

3.2. Physical investigation

A comprehensive physical investigation will evaluate muscular strength, reflexes, coordination, and other neurological processes.

3.3. Electromyography (EMG)

It is a diagnostic procedure that assesses the electrical signals muscles produce. Abnormal muscular activity patterns can be identified in individuals with MND.

3.4. Nerve Conduction Studies (NCS)

It can be conducted in conjunction with EMG to evaluate the functionality of peripheral nerves.

3.5. *Magnetic resonance imaging (MRI)* is used to rule out other illnesses and determine whether or not there are any signs of motor neuron disease (MND)Requesting an MRI examination of the brain and spinal cord is possible.

3.6. Lumbar Puncture (Spinal Tap)

On rare occasions, a puncture of the lumbar region may be performed in order to examine the cerebrospinal fluid for any abnormalities that may be present. Blood tests are beneficial in determining the presence of certain signs associated with Motor Neuron Disease (MND) and removing alternative reasons that may contribute to your muscular weakness.

3.7. *Clinical Assessment*

The doctor will regularly observe the development of symptoms and conduct routine clinical evaluations to determine alterations in muscular strength and neurological function [70].

4. Treatment for MND

Interdisciplinary healthcare medical management of individuals with motor neuron disease (MND) has positively affected several aspects, including enhancing quality of life, reducing complications and hospitalizations, extending longevity, and lowering death rates. Based on the symptoms and course of the condition, the health and social care team may explore the following therapies **(Fig. 3).**

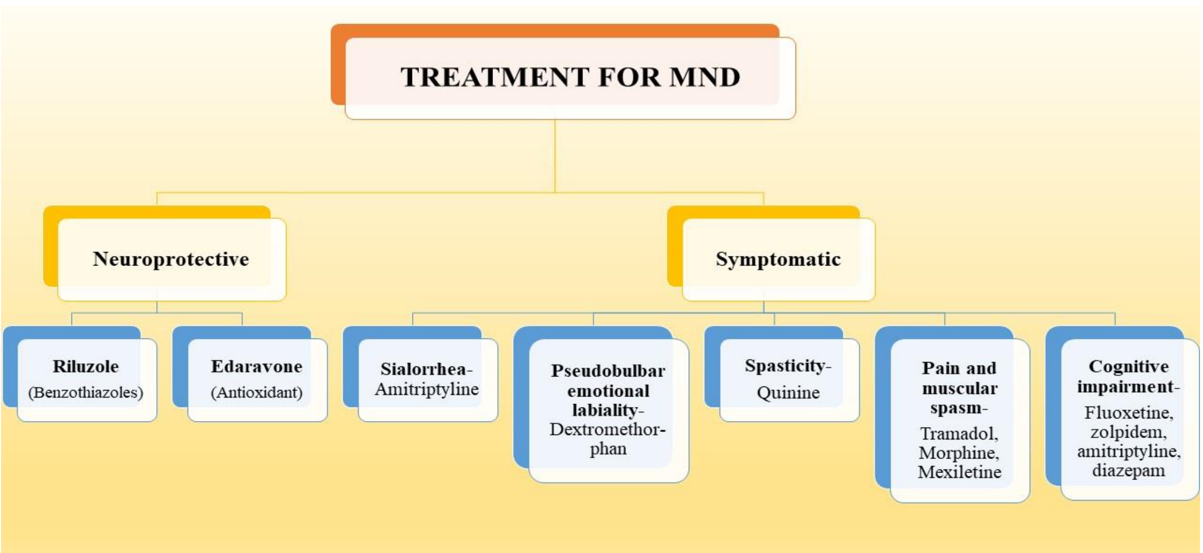

Figure 3. Several Aspects for the Treatment of Motor Neuron Disease.

4.1. Neuroprotective Treatment

Neuroprotective therapies aim to preserve the health and function of nerve cells in the face of conditions that can cause neurodegeneration. These therapies are crucial for conditions like Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Multiple Sclerosis (MS), and other related ailments. ALS is a degenerative disorder that affects the motor neurons, leading to their gradual deterioration. Currently, there is no known cure for ALS. Nevertheless, certain treatments and strategies exist aimed at slowing down the progression of the disease and relieving its symptoms. Riluzole and Edaravone are the most effective neuroprotective agents used in the treatment of ALS.

4.1.1. Riluzole

The initial medication demonstrated certain advantages in individuals with ALS and received FDA approval in 1995. The precise action method is poorly understood; however, it has been seen to regulate glutamate's effects by suppressing its release and altering post-synaptic glutamate receptor signaling. Riluzole, taken at a dose of 50mg twice a day, is believed to decrease the harmful effects of excessive glutamate activity in the brain. It is the only medication shown to increase the chances of life in general (74% compared to 58% with placebo after 12 months) and survival without needing a tracheostomy (57% compared to 50% after 18 months) in two large-scale randomized studies [71-73]. Riluzole is also reported to have neuroprotective effects. The treatment decelerates the advancement of the illness. It extends the lifespan by a minimum of 3 months, as demonstrated in two extensive trials that included a control group receiving a placebo. The recommended daily dosage of 100mg is considered safe. However, it may lead to elevated liver enzymes, asthenia, dizziness, and gastrointestinal discomfort, which are the most often seen adverse effects. All patients diagnosed with MND/ALS should be provided with Riluzole. Patients often exhibit a high tolerance to riluzole, with minimal side effects such as tiredness and nausea.

Regular evaluation of liver function is crucial, and medication should be discontinued if liver enzymes surpass five times the greater limit of typical or if the individual develops neutropenia. Substances that decrease the activity of CYP1A2, such as coffee and theophylline, can impact the elimination of riluzole **(Fig. 4)** [74]. Administering additional nutritional supplements, such as vitamins and anti-oxidants, alongside riluzole benefits people with MND. Riluzole extended the duration of tracheostomy-free survival by 3-6 months in individuals diagnosed with ALS. However, the potential long-term harmful effects of riluzole need to be assessed specifically for cancer patients, taking into account their higher life expectancy [75-79]**.**

4.1.2. Edaravone

A free radical scavenger has been discovered, which is believed to decrease oxidative stress and has demonstrated benefits in a specific group of patients with early-stage conditions [80]. Edaravone, initially authorized in Japan in 2015 for the management of ALS, subsequently received FDA clearance in 2017. Edaravone is administered intravenously in cycles, with daily doses given for two weeks, followed by a 2-week hiatus without the medication [81]. Exercise caution while administering Edaravone to individuals with asthma since it has the potential to induce severe asthmatic responses in around 5% of cases [82].

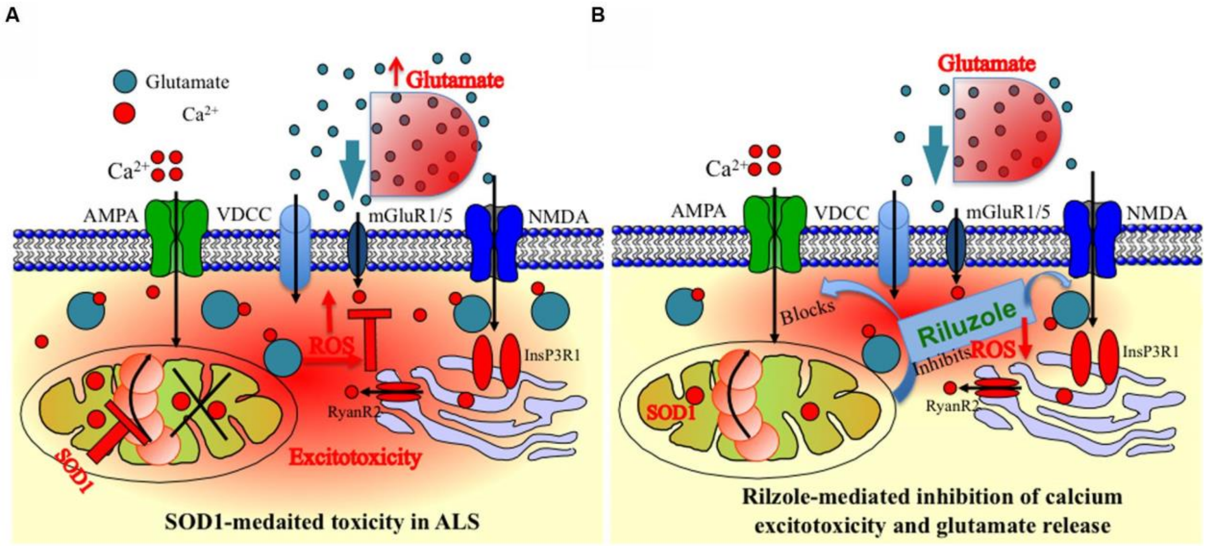

Figure 4. The diagram illustrates how Riluzole inhibits sodium-azide-generated excitotoxicity in ALS through the mitochondria.

4.2. Symptomatic Treatment

Given the limited impact of medications on extending the lifespan of individuals with MND, the management of MND heavily relies on symptomatic therapy.

Efficient management has the potential to optimize functionality, enhance the quality of life, and promote more self-reliance. Most medications utilized for symptomatic therapy are from limited investigations or expertise gained in other neurological conditions [83].

4.2.1. Pulmonary complications in individuals diagnosed with motor neuron disease

The primary cause of respiratory insufficiency in individuals with MND is the weakening of respiratory or bulbar muscles. This condition can be worsened by the inhalation of foreign substances and the development of bronchopneumonia. Additionally, respiratory insufficiency is the leading cause of mortality in the majority of MND patients. Timely identification of dyspnoea and hypoventilation is crucial, as prompt initiation of mechanical ventilation has been demonstrated to extend the lifespan of individuals with motor neuron disease (MND). A spirometer is often preferred over conducting a pulmonary function evaluation when assessing respiratory symptoms in their early stages. It is incredibly simple and easy to execute [84]. Forced vital capacity is a key metric for evaluating individuals with neuromuscular disease, and research has demonstrated its reliability as a predictor of survival in MND. Respiratory symptoms can be linked to a significant reduction in vital capacity, dropping to just half of the expected value. Hypoventilation is characterized by increased levels of carbon dioxide and bicarbonate in the blood, resulting from respiratory acidosis.

Nevertheless, these insights are typically discovered belatedly. Sleep studies that involve overnight oximetry can identify instances of nocturnal desaturation. For certain situations, it may be necessary to conduct thorough polysomnography to differentiate between obstructive sleep apnea and hypoventilation as the potential reasons for desaturation. If a patient encounters respiratory challenges, many treatments and remedies assist. Request a referral from the patient's health and social care team to visit with a respiratory specialist for guidance. This will encompass deliberation over utilizing mechanical assistance for respiration, commonly called ventilation. The gradual deterioration of the muscles responsible for chewing and swallowing leads to a condition called dysphagia. The initial approach to managing this condition involves changing the individual's diet. It is important to focus on consuming foods high in calories and using nutritious drinks, especially during the first two years following diagnosis, as weight loss is linked to a poorer outcome, which improves prognosis [85].

Nutritional concerns in individuals diagnosed with motor neuron disease If a patient experiences difficulties with swallowing, it is advisable to get guidance on the patient's nutritional needs. This will assist you in managing your nutritional intake, hydration, and medication requirements and guide safe and comfortable swallowing. This may encompass options such as easily digestible meals, therapeutic interventions, dietary supplements, fortified food products, or exploring other methods of food and beverage consumption. Request a referral from your health and social care team to consult with a dietician and a speech and language therapist for advice. There will be a rise in dysarthria, and eventually, communication will become impossible. Given the limited efficacy of speech therapy, patients may find it irritating. Therefore, patients should choose alternate communication methods such as writing, alphabet boards, or electronic assistive devices. The user's text is incomplete and does not provide any information [86].

4.2.2. Sialorrhea

Sialorrhea is a condition that hampers social interactions and also raises the risk of inhaling saliva owing to difficulties in managing it. Typically, it can be effectively treated. Amitriptyline is often prescribed; nevertheless, patients should be closely watched for potential anticholinergic adverse reactions. Taking oral dosages of no more than 50 mg two to three times per day is recommended. Botulinum toxin type A can be administered through injections into the salivary glands, providing an additional anticholinergic effect. Its mechanism of action involves diminishing saliva production.

Nevertheless, the impact diminishes within a few months, necessitating additional injections. Additionally, there is a concern regarding the drug's potential to damage further the swallowing and breathing abilities of a patient who already has poor function in these areas. Amitriptyline and botulinum toxin were shown to have equivalent efficacy in a single experiment. If conventional treatments have proven ineffective in alleviating sialorrhea, a potential option is to administer low-dose palliative radiation therapy to the parotid and submandibular glands. The goal of this treatment is to decrease the production of saliva. It is worth mentioning that this approach can result in some side effects, including redness, a sore throat, and feeling nauseous [87].

4.2.3. Pseudobulbar emotional labiality

The manifestation of pseudobulbar affect in motor neuron disease includes uncontrollable episodes of laughter, sobbing, and an involuntary dysfunction of emotional expression. Approximately 20 to 50% of people with Motor Neuron Disease (MND), particularly those with pseudobulbar palsy, are believed to be affected by this condition. The administration of a specific dosage of a combination of dextromethorphan and quinine is the sole pharmacological treatment that has demonstrated efficacy in diminishing the intensity and scope of laughter and sobbing [88].

4.2.4. Spasticity and cramps

MND can induce discomfort and hinder functionality in sufferers. Presently, the available treatment choices include stretching exercises, undergoing hydrotherapy in heated pools, and utilizing medication in the form of oral baclofen. However, it has been shown that gabapentin, vitamins, and riluzole do not provide good results. Quinine is a widely used medication for the treatment of muscle cramps [89].

Pain is a prevalent symptom among individuals with Motor Neuron Disease (MND), and it is often managed with non-specific analgesic medications. The treatment often begins with basic analgesics, progressing to mild opioids (such as tramadol) and, if necessary, strong opioids (like morphine). It is important to consider the potential side effects of opioids, such as constipation. Mexiletine is an effective treatment for frequent and severe muscular spasms. It is well-tolerated and has shown a positive clinical response when taken at 150 mg twice a day. Additional alternatives include levetiracetam, which is less effective, and gabapentin, baclofen, and tizanidine [90]. When oral medication proves ineffective or poorly tolerated, the utilization of botulinum toxin injections directly into the spastic muscles might be beneficial, and it is important to offer patients various assistive devices such as canes, orthoses, crutches, and, eventually, wheelchairs to address the inevitable progression of weakness and functional decline. Patients with neck weakness may benefit from removable headrests. Additionally, specialized utensils and holders can be provided. As the condition worsens, it becomes necessary to use a pressure-relieving mattress and frequently reposition the patient to prevent the development of pressure ulcers [91].

4.2.5. Cognitive and behavioral impairment

Among individuals who have been diagnosed with motor neuron disease, There has not been any research conducted to assess the effectiveness of therapy for depression in Motor Neuron Disease. Depression medications that are frequently prescribed include tricyclics such as amitriptyline, as well as SSRIs like fluoxetine. Typically prescribed for the treatment of insomnia are amitriptyline and zolpidem, which are the main drugs used in this case [92]. Benzodiazepines, such as diazepam and lorazepam, are frequently prescribed anxiolytic medications for individuals with anxiety who have MND.

4.2.6. Multidisciplinary management of motor neuron disease

It is widely recognized that comprehensive care units that cater to the physical, emotional, relational, and spiritual needs are beneficial for individuals with Motor Neuron Disease (MND). A comprehensive approach to care often involves a team of experts from various disciplines, including medical specialists, therapists, and psychologists. This collaborative effort ensures that patients receive the best possible care and support for their needs.

4. Conclusion

A comprehensive molecular docking study of phytochemicals derived from *S. album* that inhibit AQP3 yielded promising results, as detailed through various computational analyses. This research integrated structural modeling, virtual screening, physicochemical property evaluation, biological activity prediction, ADME/T analysis, molecular dynamic simulations, and interaction analysis to identify potential therapeutic candidates. The structural modeling of AQP3 using SWISSMODEL, coupled with validation metrics such as the GMQE score, MolProbity score, QMEAN Z-score, and Ramachandran analysis, ensured the reliability and quality of the modeled AQP3 structure. This provided a robust foundation for subsequent molecular docking studies. Virtual screening of phytochemicals involved meticulous protein and compound preparation, followed by blind docking using AutoDock Vina. The assessment of docking scores facilitated the identification of compounds with potential therapeutic efficacy against AQP3, focusing on those exhibiting docking scores of -7 or less. Using SWISS ADME to evaluate physiochemical properties and drug-likeness highlighted compounds with favorable solubility, permeability, and gastrointestinal absorption. Lipinski's rule of five aided in selecting compounds suitable for oral administration. The PASS webserver's Biological activity prediction revealed the potential dermatologic and antineoplastic activities of selected phytochemicals. Compounds such as alpha-bergamotenol, lupeol, himachalol, sclareol, and levomenol exhibited significant probabilities of both activities, suggesting their multifunctional therapeutic potential. Subsequent analysis of ADME/T properties using the ADMET Lab 2.0 server provided insights into the compounds' pharmacokinetic characteristics and safety profiles. Compounds such as alpha-bergamotenol, sclareol, levomenol, and lupeol demonstrated favorable properties, including intestinal absorption potential and no toxicity, while himachalol exhibited respiratory toxicity. Molecular dynamic simulations allowed exploration of the dynamic interactions between the receptor and ligands over time. RMSD, Rg, RMSF, and SASA analyses provided valuable insights into the receptor-ligand complexes' stability, compactness, and flexibility. Compounds such as sclareol and levomenol exhibited stable interactions with AQP3, suggesting their potential as potent inhibitors. Finally, visualization and interaction analysis of the best-docked poses provided a detailed understanding of the binding mechanisms of the phytochemicals with AQP3. Compounds such as sclareol and levomenol displayed hydrogen bonding and alkyl interactions with key residues, indicating their potential for stable complex formation. This comprehensive computational study identified phytochemicals levomenol and sclareol from *S. album* as promising inhibitors of AQP3, with potential therapeutic implications in dermatologic conditions and melanoma treatment. Further experimental validation is warranted to confirm the efficacy and safety of these compounds for clinical application.

Conflict of interest

The authors declare to have no conflict of interest.

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