



Potential role of nutraceuticals in Spinal Muscular Atrophy: Current evidence and future perspectives – A review

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Abstract

Spinal muscular atrophy (SMA) is a devastating neuromuscular disease that is manifested by degeneration of the motor neurons, leading to progressive muscle weakness and atrophy, which is primarily caused by the mutations of the survival motor neuron 1 (SMN1) gene. Patients with SMA often present with feeding difficulties, dysphagia, malnutrition, obesity, and metabolic abnormalities, in addition to the muscle atrophy and weakness. Despite the availability of disease-modifying treatments, the importance of nutritional management in the treatment of SMA is well established, and several studies have demonstrated the potential benefit of nutraceuticals, such as vitamins, minerals, essential fatty acids, amino acids, and other bioactive nutrients. The review discusses the potential of nutraceuticals in the management of patients with SMA, describing their possible mechanism of action, along with providing evidences for their use and limitations. Nutraceuticals may play an important role as adjunctive treatment for patients with SMA; however, there is a need for additional research to confirm their efficacy and safety.

Keywords: Spinal Muscular Atrophy (SMA), nutraceuticals; vitamin D, omega-3 fatty acids, vitamin E, coenzyme Q10, B vitamins, calcium, magnesium, amino acids, protein, antioxidants, oxidative stress, muscle health, nutritional management

Introduction

Spinal muscular atrophy (SMA) is a neuromuscular disease that is characterized by the degeneration of motor neurons, which leads to progressive muscle weakness and loss of mass. The most common type of SMA is 5q SMA, which is caused by the mutations in the survival motor neuron 1 (SMN1) gene that decrease the production of survival motor neuron (SMN) protein and subsequently impair motor neuron function. The manifestations of SMA vary greatly from one patient to another and can range from severe disability with feeding and respiratory difficulties to only mild manifestations and slow disease progression ^[1].

The loss of muscle mass and function in patients with SMA has significant implications for their nutritional status. The abnormalities in body composition, growth, and energy expenditure are common in these patients. Individuals with severe SMA may have feeding and swallowing difficulties, chewing problems, gastroesophageal reflux, and other complications that affect their oral intake and nutritional status. Therefore, the management of these patients requires a multidisciplinary approach that addresses their nutritional needs.

The nutritional management of individuals with SMA is challenging because both malnutrition and overfeeding can have adverse effects on their health status. The loss of muscle mass and motor function can reduce the energy expenditure of these patients, whereas the feeding and swallowing difficulties can impair their oral intake. The review by Moore *et al.* revealed that the abnormalities in body composition are common in patients with SMA, with feeding and swallowing problems being frequent in types I

and II. The researchers also found that the evidence on the nutritional management of these patients is limited, making it difficult to establish standardized nutritional interventions. Therefore, the review highlighted the importance of individualized nutritional management and the need for more interventional studies to determine the most appropriate nutritional approaches ^[2].

The availability of disease-modifying treatments for SMA, including nusinersen, risdiplam, and onasemnogene APOB acceptor variant, has improved the prognosis of patients with SMA. However, the management of these patients still requires a comprehensive multidisciplinary approach because the disease-modifying treatments cannot address all the aspects of the disease. The review by van der Hulst *et al.* aimed to assess the nutritional status of patients with SMA who received disease-modifying treatments. It analyzed the anthropometric data, feeding methods, swallowing function, oral intake, biochemical, and metabolic status, gastrointestinal problems, and energy expenditure in these patients. The review also noted the heterogeneity of the findings and the need to consider nutrition as an outcome of interest in future studies ^[3].

Nutraceuticals represent a class of bioactive food compounds and nutrients that can improve health and functionality beyond their nutritional value. Many of these compounds have been shown to have beneficial effects on the body, including anti-inflammatory, antioxidant, mitochondrial-enhancing, and neuroprotective effects. They can also help to maintain bone and muscle mass. Therefore, it is possible that some nutraceuticals can improve the health status of patients with SMA by addressing the various

impairments that are caused by the disease. However, there is a need to conduct more studies to determine the potential benefits of these compounds for individuals with SMA [4]. The review of the literature on nutraceuticals and SMA revealed that most of the existing studies focused on the overall nutritional status of these patients, their feeding abilities, body composition, energy expenditure, and the effects of disease-modifying treatments on their nutritional status. However, there are limited studies that examine the potential effects of individual nutraceuticals and their mechanisms of action in patients with SMA. Therefore, a focused review of the literature is needed to highlight the potential benefits of nutraceuticals for patients with SMA. This review will discuss the potential role of nutraceuticals in the management of patients with SMA, including their mechanisms of action, the evidence for their therapeutic potential, and the limitations of the existing studies. It will also highlight the future directions in the use of these compounds to address the nutritional and health needs of patients with SMA [2].

Definition and Genetic Basis

Spinal muscular atrophy is an inherited neuromuscular disorder that primarily involves degeneration and loss of lower motor neurons in the spinal cord and brainstem, resulting in symptoms such as progressive muscle weakness and muscle atrophy which occur symmetrically. This disorder often manifests at different ages and with different levels of severity. The most common form of SMA is 5q SMA, which is caused by the mutation of the survival motor neuron 1 (SMN1) gene located on chromosome 5q13.2, leading to decreased production of SMN proteins [5]. The SMN2 gene, which encodes for survival motor neuron proteins, plays a significant role in modifying the condition. Since most SMN2 transcripts lack exon 7, they generate less functional protein compared to SMN1. Thus, a higher copy number of the SMN2 gene often corresponds to milder symptoms in SMA ## patients, although the manifestation of the disease depends on several other modifying factors [6].

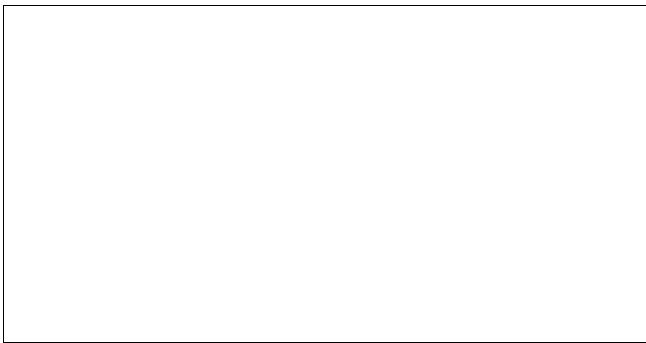


Fig 1:

Epidemiology of Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a rare, inherited degenerative disease of the central nervous system. The prevalence of the disease varies among different studies, since they are based on clinical and genetic findings in relatively small populations. For 5q SMA, the incidence is about 1 per 10,000 births, and the prevalence is about 1-2 per 100,000 people [1]. About 60% of cases of SMA are type I, and about 30% each are types II and III. The disease has an autosomal recessive mode of inheritance, and the number of unaffected carriers

of mutation of the SMN1 gene is relatively high in the general population. The true prevalence and incidence of SMA are difficult to estimate due to different methodologies in various studies. As genetic and neonatal screening tests become more common, a more precise understanding of the incidence and prevalence of SMA will emerge [7].

Classification and Types of Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is traditionally classified into five clinical types (0–IV) according to the age at disease onset and the level of motor function. However, the clinical presentation of SMA is a continuum, and the distinction between the types is sometimes blurred [1].

- **Type 0:** This is the most severe but rarest type and occurs during the prenatal period. This type is characterized by decreased fetal movements and extreme hypotonia, which leads to respiratory insufficiency and, in many cases, congenital deformities [8].
- **Type I:** This type usually manifests before six months and is characterized by profound muscle weakness, decreased hypotonia, and feeding or swallowing difficulties. Patients with this type are unable to sit unsupported [9].
- **Type II:** This type usually manifests between six and eighteen months. Children with this type can usually sit unsupported but are unable to walk independently. These patients usually present with proximal muscle weakness and progressive loss of motor skills [10].
- **Type III:** This type usually manifests after the age of 18 months. Although these patients can walk independently, they may present with progressive proximal muscle weakness, fatigue, and loss of motor function [11].
- **Type IV:** This is the mildest type of SMA and manifests in adulthood. The major symptom is proximal muscle weakness and fatigue, while ambulation is not affected [12].

The number of SMN2 gene copies determines the severity of SMA; therefore, patients with a higher number of gene copies present with milder forms of the disease. However, the clinical outcome of SMA cannot be predicted reliably based on the number of SMN2 copies [13].

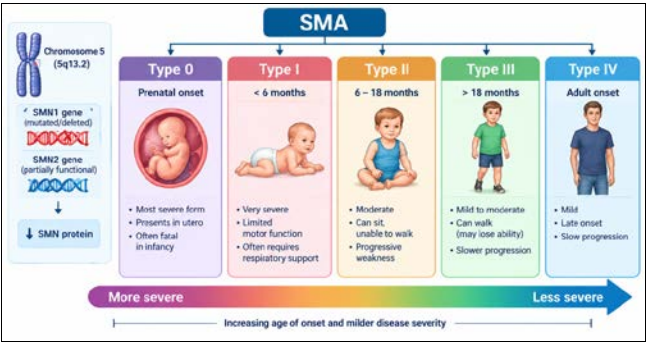


Fig 2:

Causes and Genetics of Spinal Muscular Atrophy Essay

Spinal muscular atrophy (SMA) is caused by pathogenic variant in both copies of the SMN1 gene located on chromosome 5q13.2. A loss of SMN1 function leads to motor neuron loss resulting in SMA.

The inheritance pattern of SMA is autosomal recessive. The majority of SMA cases are due to large deletions or other variants within SMN1 gene causing reduced or absent SMN protein [14].

SMN2 gene is closely related to SMN1 and plays an important role in determining SMA severity. The SMN2 genes mostly make messenger RNA instructions that do not contain exon 7, hence production of less SMN protein. An increase in the number of SMN2 gene copies usually leads to milder SMA with later symptom onset. However, the number of SMN2 copies cannot predict SMA severity due to the contribution of other genetic and non-genetic factors. Conclusively, loss of SMN1 function is the major cause of SMA while SMN2 copy number influences the severity of SMA symptoms [15].

Clinical Features of Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) has a range of clinical features that depend on the age at which the condition begins and its severity. The defining characteristic of SMA is the development of progressive, symmetrical and predominantly proximal muscle weakness as a result of the degeneration of lower motor neurons. Muscle atrophy, hypotonia and diminished or absent tendon reflexes are also common [16].

Individuals with more severe early-onset SMA may experience difficulties with head control, sitting, sucking, swallowing and feeding. Involvement of bulbar muscles can lead to aspiration and poor growth. Weakening of the respiratory muscles may result in ineffective coughing, frequent lung infections and progressive respiratory insufficiency, especially in severe forms of SMA [17].

As SMA manifests later in life, Thus, SMA can affect not only motor function, but also potentially respiratory, feeding, gastrointestinal, nutritional and musculoskeletal health. These complications emphasize the importance of comprehensive and individualized support measures, including proper nutritional care [16].

Pathophysiology of Spinal Muscular Atrophy

Spinal muscular atrophy is caused by the loss or mutation of the survival motor neuron 1 (SMN1) gene, leading to decreased levels of the Survival Motor Neuron (SMN) protein. The SMN protein plays a critical role in the formation of small nuclear ribonucleoproteins (snRNPs), which are essential for RNA splicing and processing. Its deficiency can disrupt cellular functions and specifically targeting lower motor neurons results in degeneration and loss [6].

The survival motor neuron 2 (SMN2) gene can partly compensate for the loss of SMN1; however, transcription of SMN2 is often lacking in exon 7, resulting in production of unstable protein. Therefore, an increase in the number of SMN2 copies often correlates with increased production of SMN and a milder form of the disease [18].

A deeper understanding of the disease pathophysiology is essential in exploring potential avenues for nutraceutical

intervention, including therapies targeting antioxidant, anti-inflammatory or mitochondrial pathways [19].

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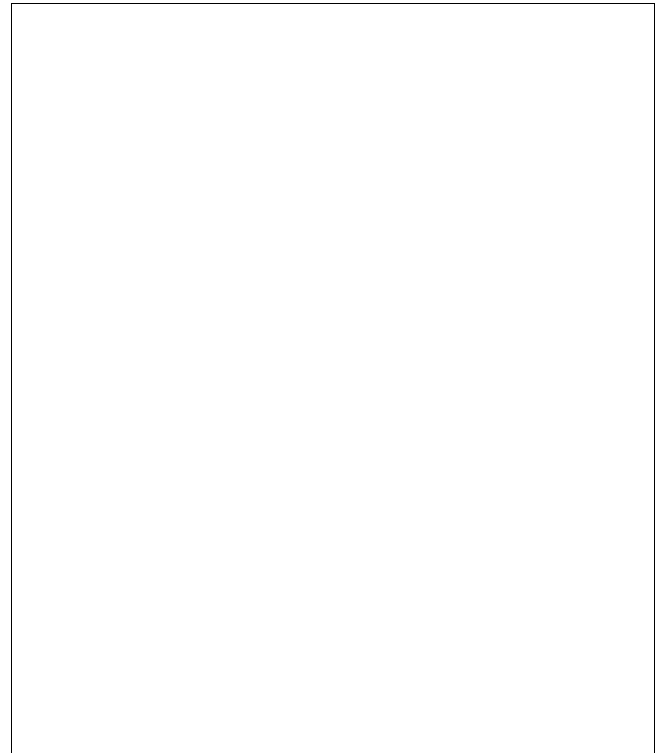


Fig 3

Nutritional and Metabolic Abnormalities in Spinal Muscular Atrophy

The most common nutritional and metabolic abnormalities that develop in patients with spinal muscular atrophy (SMA) are associated with the progressive loss of body mass due to muscular degeneration, insufficient motor activity, and altered energy expenditure. Moreover, the swallowing and feeding difficulties that are frequent in the advanced stages of the disease negatively impact the patients' oral intake of food and the normal functioning of the gastrointestinal tract [2].

Due to the extensive muscular atrophy and immobility that occurs in SMA, the energy expenditure of the affected individuals is significantly decreased. Thus, the nutritional requirements in SMA patients are inconsistent with their energy needs. In addition, decreased energy intake may lead to malnutrition, while overeating can cause metabolic complications such as obesity and diabetes mellitus. The observed nutritional and metabolic abnormalities emphasize the importance of carefully assessing the feeding process and individual caloric requirements in people with SMA. Furthermore, the data provide a strong foundation for exploring the potential benefits of specific nutrients and nutraceuticals in the management of SMA [21].



Fig 4

Role of Nutraceuticals in Spinal Muscular Atrophy Essay

Nutraceuticals are nutrients or supplements derived from food that may provide health benefits beyond the essential nutrients they contain. They may include vitamins, minerals, fatty and amino acids, coenzymes and other active substances. However, the term nutraceutical does not have a scientifically or officially recognized definition ^[22].

Progressive muscle weakness, loss of muscle mass, reduced physical activity, problems with feeding and energy metabolism changes that occur in spinal muscular atrophy (SMA) can lead to nutritional and metabolic imbalances. Thus, nutritional status and proper nutrient intake are essential components of care for SMA patients ^[21].

Nutraceuticals may play an important role by providing antioxidant, anti-inflammatory, mitochondrial, metabolic and muscle support functions. In addition, certain nutrients can provide the body with the necessary elements and substances for the maintenance of normal muscle and

cellular function in the case of a deficiency. Nevertheless, clinical evidence of the effectiveness of nutraceuticals in SMA is currently limited, and they cannot replace the disease-modifying treatment of this disease.

Therefore, based on the potential areas of impact, the nutraceuticals of interest in SMA include vitamins, omega-3 fatty acids, coenzymes, minerals and amino acids. The role of the above substances and their mechanisms of action are discussed further in this article ^[23].

Examples of nutraceuticals

- Vitamin D
- Omega-3 fatty acids
- Vitamin E
- Coenzymes Q10
- B vitamins
- Calcium & Magnesium
- Amino acids & Proteins
- Other antioxidant nutraceuticals

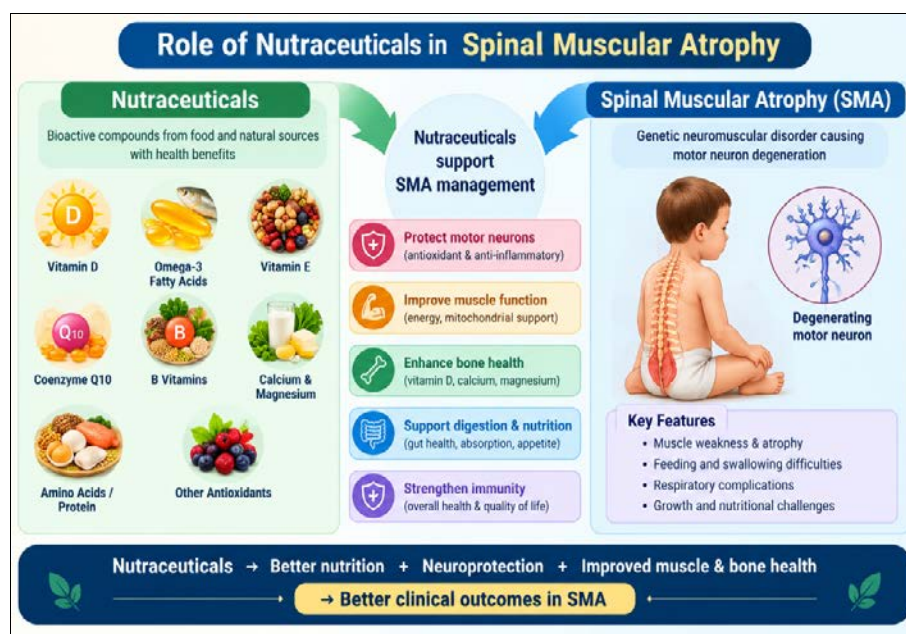


Fig 5:

Vitamin D

Definition:

The vitamin D is a fat-soluble vitamin that is essential for the proper body functioning. It plays a critical role in balancing the levels of calcium and phosphate, normalizing the bone structure and muscle function. The 1,25-dihydroxyvitamin D, which is the hormone form of vitamin D, primarily acts on the vitamin D receptors (VDR), and its signaling pathways are involved in skeletal muscle functioning [24].



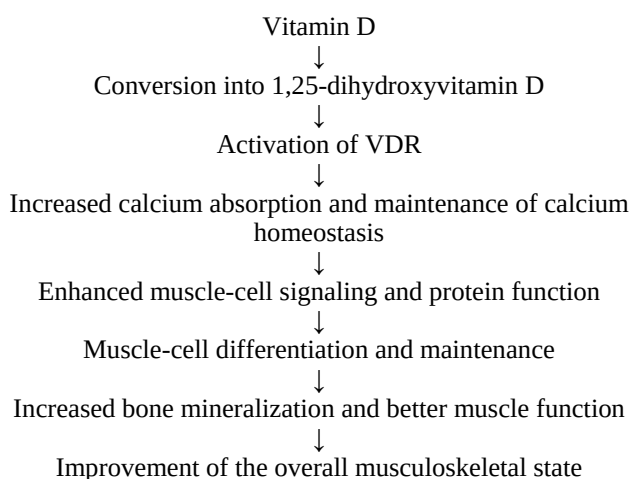
Fig 6:

Benefits / Potential Role in SMA:

- Promotes the overall health of the bones.
- Ensuring the normal bone structure and level of calcium and phosphate in the body.
- Contributing to normal muscle function.
- Normalizing the calcium-phosphate balance.
- Preventing the development of the disease by supporting the normal cell function via VDR.
- Correction of vitamin D deficits in patients with SMA may be key to maintaining overall bone health.

According to the findings of a clinical study conducted among children with SMA type I, 75% of patients were found to have vitamin D deficiency, while an association was demonstrated between vitamin D intake and bone mineral density. Thus, although vitamin D supplementation may improve the overall health status of the patient, it is not a causal treatment of SMA [25].

Proposed Mechanism:



Evidence in SMA:

There is a limited amount of evidence in the SMA field for vitamin D's role in disease progression. Therefore, the current level of research allows to suggest the possible beneficial effect of vitamin D on musculoskeletal structures in patients with SMA. At the same time, the data do not prove the causal role of the vitamin in disease development, which must be the focus of future studies [26].

Omega-3 Fatty Acids:

Definition

Omega-3 fatty acids are essential polyunsaturated fatty acids that are involved in cell-membrane structure, lipid metabolism and cellular signalling. The major dietary omega-3 fatty acids include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are primarily obtained from fatty fish and fish oils, whereas ALA is present in plant sources, such as flaxseeds, chia seeds and walnuts [27].

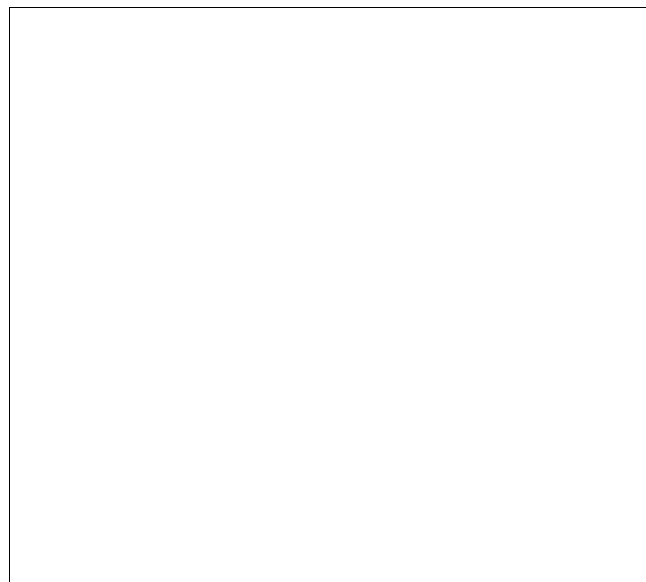


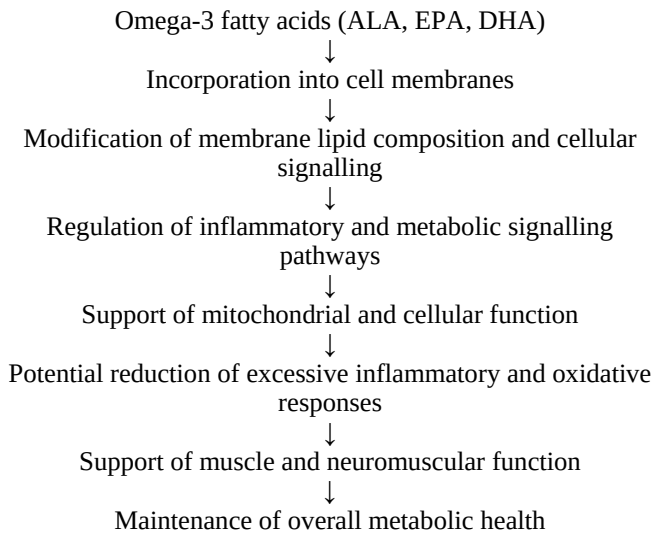
Fig 7:

Benefits / Potential Role in SMA:

- May support normal cell-membrane structure and function
- May contribute to regulation of inflammatory responses
- May support lipid and fatty-acid metabolism
- EPA and DHA may provide neuroprotective and cellularly supporting effects
- May support muscle and neuromuscular function
- May help maintain overall nutritional and metabolic health

Altered fatty-acid metabolism and body composition have been reported in SMA. Thus, omega-3 fatty acids are under investigation as a potential nutritional intervention in the disease. However, there is currently no firm evidence that omega-3 supplementation improves SMA disease outcomes [2].

Proposed Mechanism:



Evidence in SMA:

There is insufficient evidence evaluating the benefit of omega-3 supplementation in SMA. Research in SMA has demonstrated abnormalities in fatty-acid metabolism and body composition, suggesting that lipid metabolism may be relevant to the disease biology. These findings, however, do not support omega-3 supplementation as an effective treatment for SMA. Further controlled clinical studies are required to determine this supplement's potential benefits, optimal dosage and long-term safety [28].

Vitamin E

Definition:

Vitamin E is a fat-soluble vitamin and an essential antioxidant that protects cell membranes against oxidative damage. Alpha-tocopherol is the primary form of vitamin E that is stored in the body. Vitamin E is naturally present in a number of foods. This includes nuts, seeds and vegetable oils.



Fig 8:

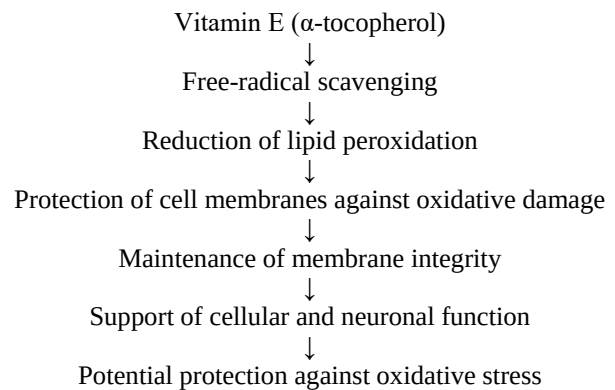
Benefits / Potential Role in SMA:

- Protects cell membranes against oxidative damage.
- Acts as a lipid-soluble antioxidant.
- May help reduce lipid peroxidation that is induced by free radicals.
- May help support cellular and neuronal function.

- May help maintain membrane integrity.
- Its antioxidant properties may offer a theoretical supportive role for cellular health.

It is established that oxidative stress plays a part in a number of neurodegenerative diseases. This includes SMA. Vitamin E has antioxidant properties that may help protect biological membranes against oxidative damage. However, these properties do not establish vitamin E as a therapy option for SMA [29].

Proposed Mechanism:



Evidence in SMA:

Evidence on vitamin E specifically in SMA is limited. An earlier study that looked at children and adults with SMA found that serum vitamin E levels and vitamin E-to-lipid ratios were normal in all participants. The authors concluded that vitamin E nutritional status appeared to be normal in individuals with SMA and that routine vitamin E therapy was not indicated.

Therefore, despite the fact that vitamin E has biologically relevant antioxidant properties, there is currently insufficient evidence to establish vitamin E supplementation as a disease-modifying treatment for SMA [30].

Coenzyme Q10 (CoQ10):

Definition:

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a naturally occurring fat-soluble compound present in cell membranes, particularly in mitochondria. It plays an important role in the mitochondrial electron transport chain and acts as an antioxidant. CoQ10 aids in transferring electrons during mitochondrial respiration and supports cellular energy production.



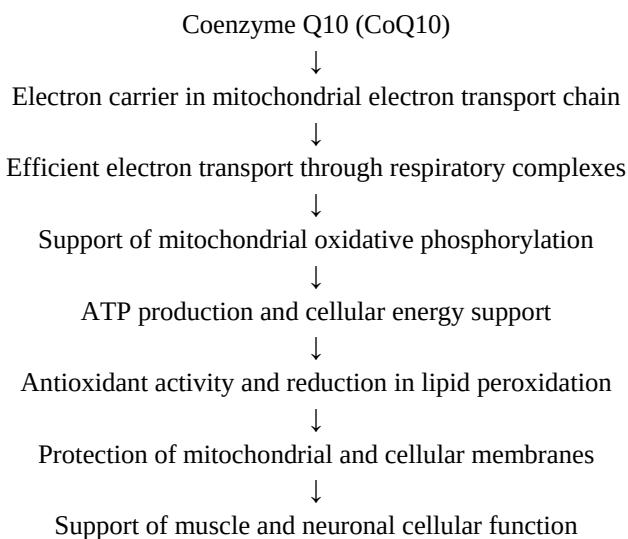
Fig 9:

Benefits / Potential Role in SMA:

- Mitochondrial electron transport support.
- Cellular energy (ATP) production support.
- Lipid-soluble antioxidant.
- Protection from oxidative damage to cell membranes.
- Mitochondrial and cellular support.
- Potential relevance to muscle and neuronal health.

Mitochondrial abnormalities and altered mitochondrial function have been implicated in SMA models and are considered potential contributors to disease progression. Therefore, CoQ10 is an interesting candidate as a supportive nutraceutical, however, there is currently no evidence directly supporting the use of CoQ10 supplementation in SMA [31].

Proposed Mechanism:



Evidence in SMA:

Evidence specifically relating to CoQ10 supplementation in SMA is limited. It has been established that mitochondrial dysfunction contributes to motor neuron abnormalities and skeletal muscle weakness in SMA. However, there is currently no evidence to suggest that CoQ10 supplementation has a beneficial effect on motor function, muscle strength or disease progression in individuals with SMA. Therefore, CoQ10 should be considered a potential supportive nutraceutical rather than a proven treatment for SMA [32].

B Vitamins

Definition:

B vitamins are a group of water-soluble vitamins, including thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folate (B9) and cobalamin (B12). They mainly play the role of coenzymes in different metabolic reactions involved in energy production, amino-acid metabolism, DNA synthesis and cellular function.



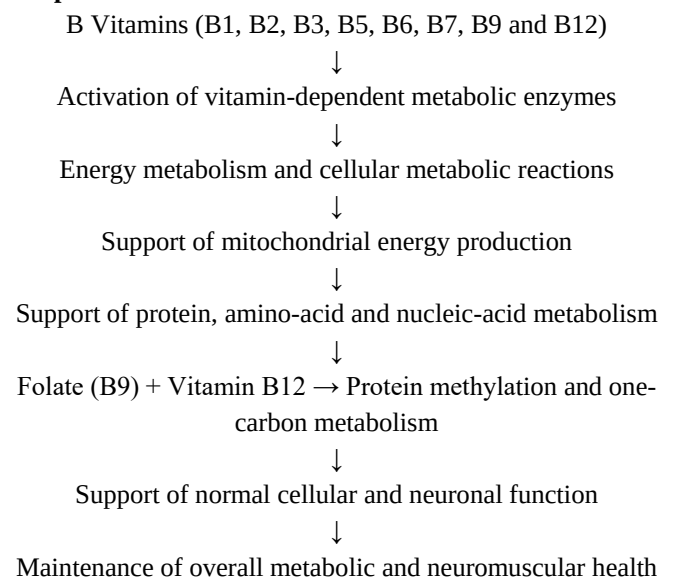
Fig 10

Benefits / Potential Role in SMA:

- Support energy metabolism and cellular energy production
- Support normal protein and amino-acid metabolism
- Contribute to DNA and RNA synthesis and cellular maintenance
- B6, B9 and B12 contribute to normal nervous-system function
- Folate (B9) and vitamin B12 are involved in protein methylation, which may be relevant to SMN protein-related processes
- Adequate B-vitamin intake may help maintain overall nutritional and metabolic health in individuals with SMA

In SMA, folic acid and vitamin B12 have particular biological interest as they are involved in protein methylation. Inadequate intake may contribute to hypomethylation and could potentially impact on SMN-related processes, but this does not establish B-vitamin supplementation as a treatment for SMA.

Proposed Mechanism:



Evidence in SMA:

Evidence specifically evaluating B-vitamin supplementation in SMA is limited. A review of metabolic and nutritional abnormalities in SMA reported that folic acid and vitamin B12 are involved in protein methylation and suggested that inadequate intake could lead to protein hypomethylation, but clinical evidence demonstrating that B-vitamin supplementation improves motor function or disease progression in SMA is currently insufficient [33].

Calcium and Magnesium

Definition:

Calcium and magnesium are essential minerals needed by the human body for normal bone, muscle and cellular function. Calcium plays an important role in bone mineralization, muscle contraction and cellular signalling, while magnesium acts as a cofactor for numerous enzymes and is involved in energy metabolism.



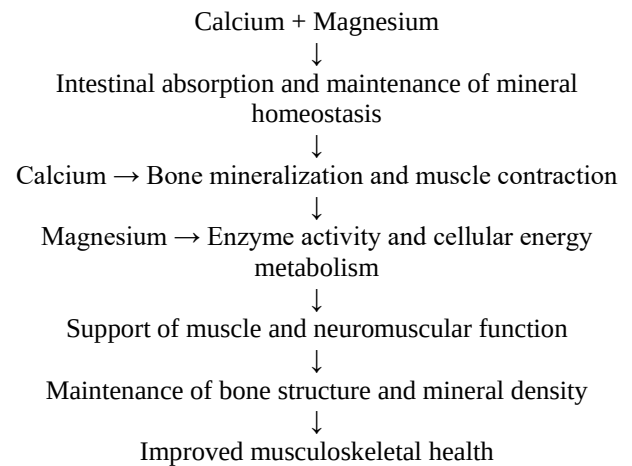
Fig 11

Benefits / Potential Role in SMA:

- Support bone mineralization and skeletal health.
- Help maintain normal muscle function.
- Calcium contributes to muscle contraction and cellular signalling.
- Magnesium supports energy metabolism and neuromuscular function.
- Help maintain calcium-magnesium homeostasis required for normal cellular function.
- Adequate intake may help reduce nutritional risk associated with low bone mineral density in SMA.

Individuals with SMA may have suboptimal intake of calcium and magnesium due to reduced food intake and nutritional difficulties. Studies have reported a positive association between vitamin D, calcium and magnesium intake and bone mineral density in SMA [34].

Proposed Mechanism:



Evidence in SMA:

Evidence specifically evaluating calcium or magnesium supplementation as a treatment for SMA is limited. Nutritional studies suggest that calcium and magnesium intake may be below recommended levels in some individuals with SMA, while adequate calcium and vitamin D intake is considered important for maintaining bone health. Low bone mineral density and increased fracture risk are recognized concerns in SMA.

However, there is insufficient evidence to conclude that calcium or magnesium supplementation directly improves motor function or alters the progression of SMA. Their primary relevance is currently nutritional and supportive, for maintaining bone and musculoskeletal health [35].

Amino Acids and Proteins

Definition:

Proteins are essential macronutrients comprising amino acids and indispensable for muscle structure, growth, repair and normal cellular functions. These macromolecules play dual roles in supporting the energy metabolism and participating in numerous biochemical processes. In addition, an adequate protein intake is critical for the maintenance of lean body mass.



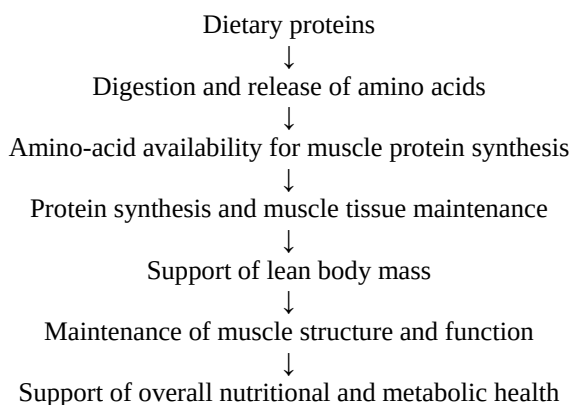
Fig 12:

Benefits / Potential Role in SMA:

- Support muscle protein synthesis and maintenance of muscle mass.
- Provide amino acids required for muscle growth and repair.
- Support maintenance of lean body mass.
- Contribute to energy and metabolic processes.
- Support normal cellular and neuromuscular functions.
- May help reduce the nutritional consequences associated with muscle wasting and inadequate dietary intake.

The nutritional studies on SMA reported inadequate protein intake in some of the affected individuals, whereas progressive muscle wasting and altered body composition are universal characteristics of the disease. Thus, an adequate protein and amino-acid nutrition may be critical as part of the individual nutritional management.

Proposed Mechanism:



Evidence in SMA:

There are limited data specifically evaluating the potential benefits of high-protein diets or individual amino-acid supplementation as a treatment for SMA. The current literature on SMA nutrition highlights the importance of individual assessment of energy and protein requirements due to the risks for under- and over nutrition. Therefore, the nutritional management should be tailored depending on age, disease severity, ability to feed, body composition and metabolic status.

Even though protein and amino acids are essential for the maintenance of muscle tissue, there is currently insufficient evidence to conclude that protein or amino-acid supplementation directly improves motor function or alters the disease progression in individuals with SMA [36].

Other Antioxidant Nutraceuticals

Definition:-

Other antioxidant nutraceuticals are nutritionally-derived substances that offer protection against oxidative damage by scavenging reactive oxygen species and aiding the antioxidant defence system. The most important representatives are curcumin, alpha-lipoic acid, and selenium.

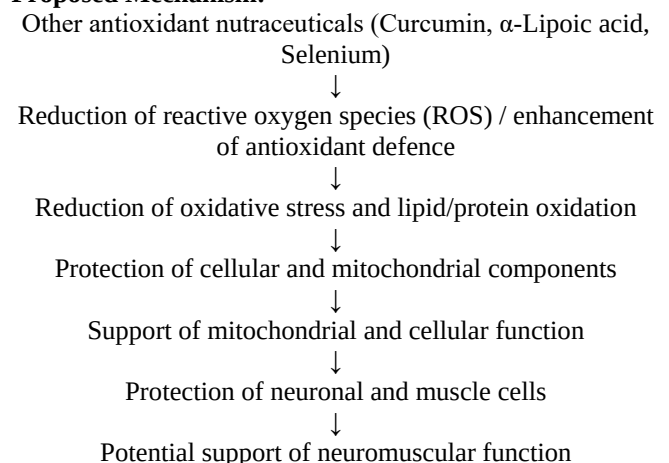


Fig 13

Benefits / Potential Role in SMA:

- Reduction of oxidative stress and reactive oxygen species (ROS)-mediated cellular damage
- Support of mitochondrial and cellular function
- Protection of neuronal and muscle cells from oxidative damage
- Support of endogenous antioxidant defence mechanisms
- Curcumin reduces oxidative stress and has shown protective effects in SMA cellular models
- Alpha-lipoic acid is an antioxidant and may support other antioxidant systems
- Selenium is an essential element and component of antioxidant enzymes such as glutathione peroxidases [37].

Proposed Mechanism:



Evidence in SMA:

Oxidative stress is one of the cellular abnormalities associated with SMA. Increased reactive oxygen species (ROS) and oxidative damage have been described in SMA models and patient-derived cells. Curcumin has been investigated in SMA cellular models and has shown potential to reduce oxidative stress. However, these findings are mostly based on preclinical studies and do not

demonstrate curcumin as an effective treatment for SMA. For alpha-lipoic acid and selenium, the antioxidant effects provide a biological basis for further investigation, but SMA-specific clinical evidence is lacking. Thus, these

substances cannot currently be considered disease-modifying treatments for SMA [38].

Potential benefits and overall summary:



Fig 14:

Clinical Studies and Current Evidence of Nutraceuticals in SMA:

Table 1:

Nutraceutical / Nutrient	Clinical Evidence in SMA	Potential Role	Major Limitation
Vitamin D	In children with SMA type I, inadequate vitamin D intake was found in 75% of individuals. Intake was positively associated with bone mineral density.	Supports bone health, calcium homeostasis, and muscle function.	No evidence of an effect on the underlying disease process.
Calcium	Calcium intake has been associated with bone mineral density in individuals with SMA.	Supports bone mineralization.	Supplementation has not been established to improve motor function or disease progression.
Magnesium	Magnesium intake shows a positive association with bone mineral density in SMA.	Supports bone mineralization.	SMA-specific supplementation trials are limited.
Protein and Amino Acids	Nutritional studies report inadequate protein/energy intake and body composition abnormalities in SMA individuals.	Supports muscle synthesis, maintenance, and lean body mass.	Optimal protein requirements and supplementation benefits are not well established.
Omega-3 Fatty Acids	Direct clinical studies of omega-3 supplementation in SMA are limited, though altered fatty acid metabolism has been reported.	May support lipid metabolism, inflammatory regulation, and cellular function.	Lack of SMA-specific randomized clinical trials.
Vitamin E	Earlier clinical research reported that vitamin E status was normal in individuals with SMA.	Provides antioxidants and membrane protection.	No established clinical benefit from supplementation.
Coenzyme Q10 (CoQ10)	Direct clinical evidence for CoQ10 supplementation in SMA is currently limited.	May support mitochondrial energy production and antioxidant defense.	Lack of adequate clinical trials in SMA.
B Vitamins	Clinical evidence specifically evaluating B-vitamin supplementation in SMA is limited.	Supports energy metabolism, cellular function, and nervous system health.	No established disease-modifying effect in SMA.
Curcumin & Other Antioxidants	Evidence is mainly from pre-clinical and general antioxidant research; human SMA clinical evidence is limited.	May reduce oxidative stress and support cellular defense.	Limited clinical evidence regarding efficacy and safety in SMA.

[39].

Limitations and Research Gaps:

Although nutraceuticals may offer nutritional and metabolic support in spinal muscular atrophy, there are several limitations and research gaps that must be addressed before their use can be recommended.

Limited clinical evidence: The majority of studies to date have explored general aspects of nutritional status, dietary intake, bone mineral density, and body composition, with few addressing the therapeutic potential of specific nutraceutical agents.

The lack of RCTs: There is a need for well-designed randomized controlled clinical trials investigating the effects of selected nutraceutical agents.

Limited evidence of therapeutic potential: There is insufficient evidence linking nutraceutical administration with improvements in motor function, muscular strength, or disease progression.

Unclear optimal dose: Dosing regimens and formulations for many nutraceuticals have not been established.

Variability in patient characteristics: The severity, age distribution, nutritional status, ability to feed independently, mobility and body composition of patients with SMA vary widely and can be difficult to manage within standardized nutritional guidelines.

The impact on current therapies: Further research is needed to elucidate the potential for nutraceuticals to interact with disease-modifying therapies for SMA in a beneficial, neutral or detrimental manner.

Safety concerns: The long-term safety and tolerability of large-scale or combination nutraceutical supplementation has not been adequately assessed.

Need for mechanistic studies: Future work should aim to characterize oxidative stress, mitochondrial dysfunction, inflammatory pathways and metabolic biomarkers in relation to nutritional interventions.

Need for personalized approaches: Nutraceutical interventions for SMA may require individualized approaches based on patient-specific factors such as nutritional deficiencies, severity of disease, age and metabolic needs.

Overall, future work is needed to clarify the therapeutic potential of nutraceuticals for spinal muscular atrophy. These efforts should include large-scale clinical trials examining the effectiveness, safety and optimal dosing of specific nutraceutical agents ^[2].

Future Perspectives

The future role of nutraceuticals in the context of spinal muscular atrophy is an exciting area of research. While there is currently limited evidence to support their use, future research may help elucidate their potential supportive role in nutritional, metabolic and neuromuscular health.

- **More clinical trials:** Larger, well-designed randomized controlled trials are needed to evaluate individual agents for efficacy and safety in the context of spinal muscular atrophy.
- **Individualized nutrition:** Future nutritional interventions should be individualized based on age, the type of SMA, disease severity, feeding capacity, body composition and nutritional status.
- **Combination approaches:** The potential additive or synergistic effects of different combinations of nutraceuticals, such as antioxidant, vitamin, mineral and omega-3 formulations, should be investigated.

- **Interaction with disease-modifying therapies:** Future studies should assess the potential for nutraceuticals to augment established disease-modifying therapies for SMA and investigate potential interactions.
- **Biomarker research:** Oxidative stress, mitochondrial dysfunction, inflammation and metabolic biomarkers may help identify patient populations most likely to benefit from specific nutraceutical interventions.
- **Long-term studies:** Long-term studies are needed to assess the safety, tolerability and long-term benefits of nutraceutical supplementation.
- **Development of evidence-based guidelines:** As clinical evidence accumulates, standardized recommendations for nutritional assessment and appropriate nutraceutical use in the context of SMA may be developed.

Overall, future research should focus on establishing evidence-based, individualized and safe nutraceutical strategies that complement standard therapies for SMA. Nutraceuticals are likely to have a supportive rather than a substitutive role in the comprehensive management of SMA ^[1].

Conclusion

Spinal muscular atrophy (SMA) is a genetic degenerative neurological disease characterized by motor neuron loss, muscle weakness, muscle degradation, and significant nutritional and metabolic abnormalities. Disease-modifying treatments have radically changed the scenario of SMA therapy, offering unprecedented control over the natural history of the disease and improving patients' quality of life. Nevertheless, nutritional care still plays a leading role in SMA management due to the high risk of malnutrition, altered body composition, lean body mass reduction, bone health deterioration, and the peculiar energy needs of SMA patients.

Nutraceuticals have attracted considerable attention for the treatment of various components of SMA due to their metabolic and anti-inflammatory activity. Vitamins D, calcium, and magnesium are essential for normal bone and muscle tissue function. Additionally, proteins and amino acids contribute to the maintenance of muscle mass and weight. Omega-3 acids affect lipid and energy metabolism and reduce pro-inflammatory cytokines' effects, while vitamin E, coenzyme Q, and other antioxidants participate in mitochondrial functioning and protect against oxidative stress. Finally, B-complex vitamins are responsible for energy production and the normal functioning of the nervous system.

Despite the broad range of positive effects, the clinical utility of nutraceuticals in SMA remains unproven. Whereas some trials indicate that nutritional imbalances frequently accompany SMA, data on the role of nutraceuticals in the management of SMA are scarce. Thus, despite the overall beneficial impact of nutraceuticals on body functions and processes involved in SMA, there is currently no reliable clinical evidence for their effectiveness in treating or managing SMA. Therefore, nutraceuticals cannot replace disease-modifying treatments and should not be considered a valid alternative to established therapies. Nevertheless, nutraceuticals may have a place in SMA treatment and management by addressing patients' nutritional and energy needs.

Further studies and clinical examinations are required to assess the potential of nutraceuticals in SMA management. Particular attention should be paid to analyzing the effects of individual nutrients and developing personalized nutritional interventions to SMA patients' unique requirements. Moreover, well-designed interventional trials are needed to evaluate the impact of nutraceuticals on clinical outcomes and biomarkers related to SMA progression. Overall, additional research is required to fully understand the role of nutraceuticals in the treatment and management of SMA patients.

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