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Epigenetic Nutraceuticals in Sarcopenia Prevention

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Abstract:
The loss of skeletal muscle mass and function associated with aging, known as sarcopenia, presents notable health hazards. The field of nutrigenomics, which investigates the interaction between genes and diet, provides valuable information on personalized nutrition approaches. This analysis delves into the nutrigenomic underpinnings of sarcopenia and assesses the effectiveness of nutraceuticals in averting or managing muscle deterioration.

Keywords: Sarcopenia, Epigenetic, Nutraceuticals, Gene expression, DNA Methylation, Histone modification, Epigenetic Biomarkers, Genetic Editting technology,

Introduction:
Sarcopenia, which comes from the Greek words "sarx" (flesh) and "penia" (loss), is the age-related decrease in skeletal muscle mass, strength, and function (1). This syndrome is defined by a decrease of muscle mass, quality, and function, which causes frailty, mobility impairment, and an increased risk of falls, fractures, and death (2).
Sarcopenia prevalence varies widely, and it affects: 5–13% of those aged 60–70 years (3), Approximately 50% of those over the age of 80(4), An estimated 50 million people in the United States, with yearly healthcare costs exceeding $50 billion (5).

Pathophysiology of sarcopenia:
Sarcopenia's complex etiology involves Hormonal changes such as decreased testosterone, growth hormone (6) Inflammaging of chronic, low-grade inflammation (7).Mitochondrial dysfunction and oxidative stress (8). Muscle fiber type shifting and neuromuscular junction degeneration (9) Sarcopenia's etiology also includes epigenetic modifications and genetic predisposition (10)

Overview of nutrigenomics:
Nutrigenomics, or the study of gene-diet interactions, investigates how genetic differences affect an individual's reaction to dietary components (11). This field has developed as a major component of personalized nutrition, allowing for customized dietary recommendations to improve health outcomes (12).
Relevance of nutrigenomics to muscle health is critical in understanding muscle health and genetic variables that affect muscle growth, maintenance, and responsiveness to nutrition and exercise (13). Gene-diet interactions that influence muscle protein production and breakdown (14). Epigenetic changes that control muscle gene expression (15). Nutrigenomic-based dietary recommendations for muscle health and performance(16).

Genetic factors in Sarcopenia:

1. Myostatin (MSTN): Variants in the MSTN gene have been linked to sarcopenia (17).
2. ACE (Angiotensin-Converting Enzyme): ACE gene polymorphisms have been associated with muscle strength and sarcopenia (18).
3. ACTN3 (Alpha-Actinin 3): Variants in the ACTN3 gene, which regulates muscle fiber type, have been linked to sarcopenia and muscle function (19).
4. Vitamin D Receptor (VDR): Variants in the VDR gene have been associated to muscular strength and sarcopenia (20).
5. Inflammatory genes: Variants in inflammatory genes such as TNF-a and IL-6 have been linked to sarcopenia (21).

Epigenetic Modifications:

Sarcopenia is also caused by epigenetic alterations that regulate muscle gene expression, such as DNA methylation and histone modification (22). Gene Variants and Sarcopenia Risk Several genetic variations have been linked to an increased incidence of sarcopenia, including: APOE ε4: The APOE 4 allele is associated with an increased risk of sarcopenia (23) and MSTN rs1805086: The TT genotype of the MSTN rs1805086 variation is related with an increased incidence of sarcopenia (24).

Epigenetic Targets for Sarcopenia Prevention:

1. Inhibiting DNA methyltransferases(DNMTS) prevents muscle-specific gene silencing [25].
2. Histone Deacetylases (HDACs): HDAC inhibitors increase muscle gene expression and growth [26].
3. MicroRNAs(miRNAs):Certain miRNAs control muscle development and differentiation [27]
4. Chromosome Remodeling Complexes: Modulating chromatin structure affects muscle gene expression [28].
5. Epigenetic Enzymes: Targeting enzymes such as SIRT1, SIRT6, and KDM6A alters muscle metabolism and function [29].

DNA Methylation:

DNA methylation is an important epigenetic mechanism that regulates gene expression. Sarcopenia induces changes in DNA methylation patterns, which affects muscle gene expression. Sarcopenia is connected with higher DNA methylation of muscle-specific genes including MyoD and Myf5. DNA methyltransferase (DNMT) activity increases with aging, promoting muscle methylation (30). Dietary factors such as folate and vitamin B12 influence DNA methylation (31).

Histone Modifications:

Histone Modifications, such as acetylation and methylation, also control gene expression. Histone acetylation diminishes with aging, resulting in lower muscle gene expression (32). Histone deacetylase (HDAC) inhibitors, such as butyrate, increase muscle growth (33). Histone methylation controls muscle stem cell self-renewal and differentiation (34).

The relationship between DNA methylation and histone modification are DNA methylation and histone modification work together to regulate gene expression (35) and DNA methylation and histone modification changes are linked to sarcopenia (36).

Noncoding RNAs in Sarcopenia:

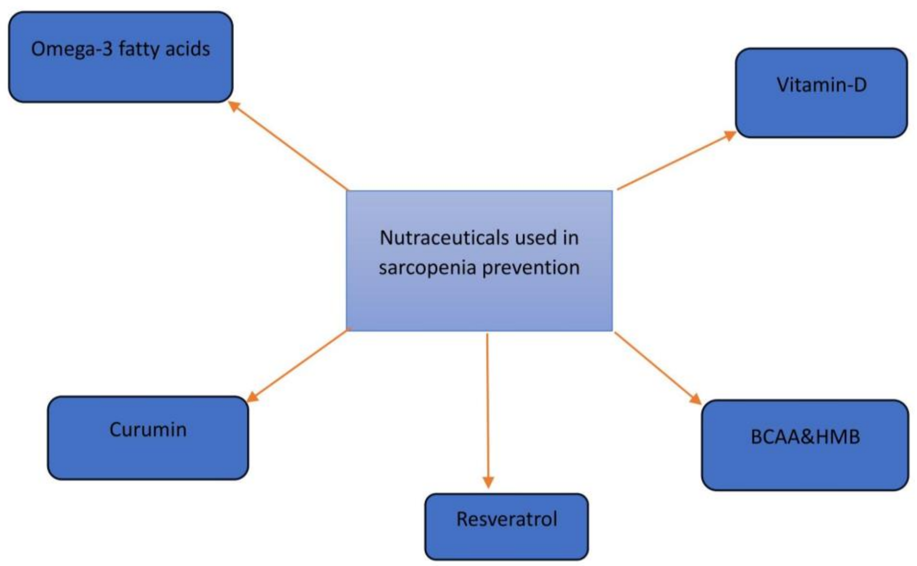
ncRNAs, which include microRNAs (miRNAs), long non-coding RNAs (IncRNAs), and circular RNAs (circRNAs), are critical regulators of muscle gene expression. MicroRNAs, or miRNAs, are miR-21, miR-29, and miR-206 all influence muscle growth and differentiation (37), Sarcopenia is associated with reduced levels of miR-1, miR-133, and miR-206 (38) and MiRNA-21 suppression stimulates muscle regeneration (39).

Long noncoding RNAs (IncRNAs): The lncRNA MALAT1 affects muscle differentiation and proliferation (40), LncRNA-H19 stimulates muscle development while inhibiting atrophy (41) and LncRNA-XIST controls muscle stem cell self-renewal (42).
Circular RNAs (cirRNAs): CircumRNA-ITCH controls muscle differentiation and proliferation (43) and CircRNA-MYLK stimulates muscle development while inhibiting atrophy (44).

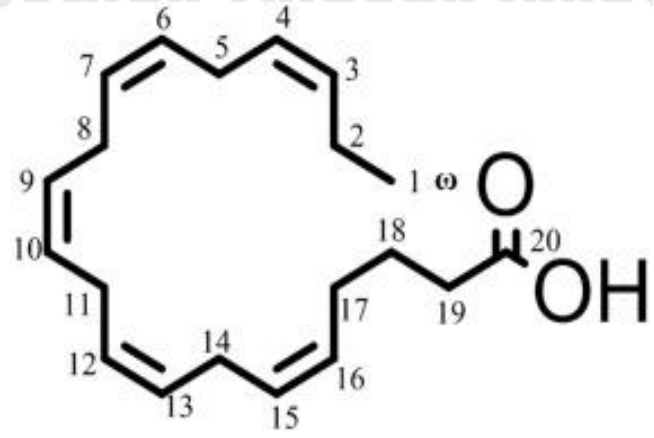
Inflammation

Prolonged low-grade inflammation accelerates muscle loss (sarcopenia) due to(45) the Main Contributors which are : Pro-inflammatory molecules such as TNF-a, IL-6, IL-1B etc (46) and Activated NF-KB signaling pathway (47).
Effective Strategies to Reduce Inflammation:
1. Regular Exercise such as aerobic and strength training (48, 49).
2. Anti-inflammatory nutrients such as : Omega-3 fatty acids, Curcumin and Polyphenols (50, 51)
3. Targeted Pharmacological Interventions: Nonsteroidal anti-inflammatory drugs (NSAIDs) and Corticosteroids (52)

Nutraceuticals with Epigenetic Effects:



Omega 3 Fatty acids:



Alpha-linolenic acid (ALA; 18:3n-3), eicosapentaenoic acid (EPA; 20:5n-3), and docosahexaenoic acid (DHA; 22:6n-3) are the three primary dietary forms of omega-3 fatty acids, sometimes referred to as n-3 fatty acids. These polyunsaturated fatty acids have numerous potential health benefits. ALA, which is present in nuts, seeds, canola oil, and other foods, is regarded as an essential fatty acid as the body is unable to produce it. Fish oil is the primary source of EPA and DHA.

Mechanism:

Endoplasmic reticulum stress (ERS) and autophagy are triggered during the inflammatory phase of skeletal muscle atrophy, which results in tissue reorganization and cell death (53, 54). By reducing the rise in PERK and ATG14 expression, EPA and DHA may both reduce ERS and autophagy in skeletal muscles that are atrophying (55). Furthermore, by inducing intermediate oxidative stress and preventing proteasomal breakdown of muscle proteins (56), DHA delays muscle atrophy and stimulates mitochondrial biogenesis and skeletal muscle fiber rebuilding (57).

Related Studies:

According to data demonstrating markedly elevated levels of IL-6 and TNFα in older Chinese individuals with sarcopenia, it has been suggested that elevated plasma levels of proinflammatory cytokines impact muscle catabolic and anabolic signaling pathways and may therefore be crucial in the onset and progression of sarcopenia (58). As a result, lowering aging-related chronic inflammation is becoming a viable therapeutic target for sarcopenia. However, because of the significant risk of side effects associated with NSAID use in older people, NSAIDs may not be advised for the treatment of sarcopenia.There is growing evidence that omega-3 polyunsaturated fatty acids, especially eicosapentaenoic acid, docosahexaenoic acid, and alpha-linolenic acid, have anti-inflammatory properties and lower the expression of inflammatory genes (59). Omega-3 fatty acid supplementation has been shown to increase lean body mass, skeletal muscle mass, and isometric contraction maximum muscle strength in the quadriceps, according to a systematic review and meta-analysis (60).

Vitamin D:

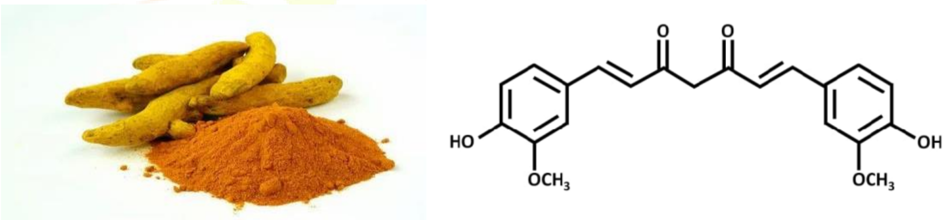
Mechanism:

Proteolysis, mitochondrial activity, cellular senescence, and obesity are among the molecular processes essential to sarcopenic muscle atrophy that are regulated by the vitamin D/VDR axis (61). First, a lack of vitamin D seems to cause autophagy, increased AMPK and renin-angiotensin system members, and enhanced muscle protein breakdown through the ubiquitin-proteasomal pathway (UPP) (62, 63). Second, it has been demonstrated that the vitamin D/VDR axis has regulatory control over senescence, a crucial aging event that involves permanent exit from the cell cycle (64). Third, active 1,25(OH)2D3 can enhance oxygen consumption rates and fission/fusion dynamics (65, 66), while low vitamin D conditions may result in compromised mitochondrial activity (67).

Clinical Studies:

Clinical research 90% of vitamin D, a fat-soluble vitamin produced in the skin, is obtained by UV exposure, with the remaining 10% coming from diet. Nowadays, vitamin D deficiency is regarded as a worldwide public health issue. Chronic renal insufficiency, decreased sun exposure, and poor intestine absorption put older people at higher risk for vitamin D deficiency. It is believed that lower 25-(OH)-VD levels are linked to negative alterations in muscle mass and bodily function (68). In order to assess the degree of skeletal muscle atrophy, Yang et al. (69) immobilized mice after feeding them a diet low in vitamin D for 24 weeks.Consequently, the loss of grip strength, muscle fiber cross-sectional area, and gastrocnemius muscle mass was hastened by vitamin D insufficiency; on the other hand, the loss of grip strength was prevented by vitamin D supplementation. Linear regression analysis revealed that physical activity and serum 25 hydroxyvitamin D were directly related and interacted with timed running time and grip strength. The researchers also conducted a cross-sectional examination of 4,139 older persons. But in another trial, where the intervention group received 800 IU of vitamin D orally daily and the control group took a placebo daily, there were no differences in lean body mass, function, or leg push-up strength after a year (70).Vitamin D administration by itself did not increase muscle strength or SPPB scores, but rather markedly reduced them, according to systematic reviews and meta-analyses (71). Even in the absence of physical exercise, vitamin D, whey protein, and leucine can effectively increase the muscle mass of sarcopenia patients' limbs. When combined with physical exercise, this combination not only increases muscle mass but also improves muscle strength and performance (72). However, because protein and amino acids are present, we cannot be certain that vitamin D supplements alone will be beneficial.In conclusion, because of the great variability of research and the contradictory findings of RCTs, the precise function of vitamin D supplementation in the prevention and treatment of sarcopenia is still unknown.

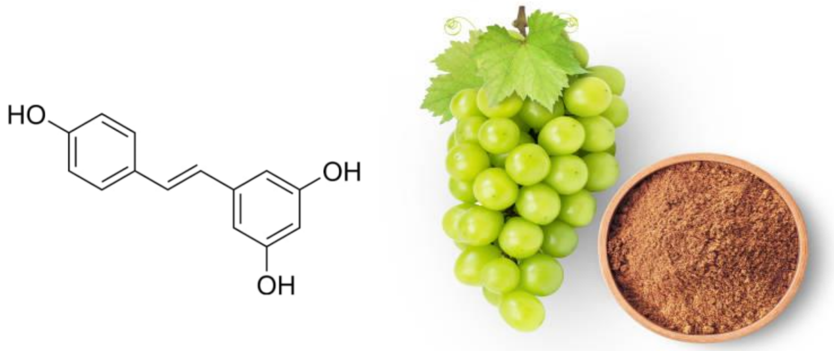
Curcumin:



Curcumin is a polyphenolic molecule derived from turmeric (Curcuma longa), a spice popular in Indian and Middle Eastern cuisine. A component of the spice turmeric (Curcuma longa) phytocomplex, curcumin (diferuloylmethane) has been used in traditional Asian medicine. As an epigenetic modulator, curcumin also affects histone acetylation/deacetylation, microRNAs, and DNA methyltransferases (DNMT) [73]. In processes pertaining to muscular exhaustion, muscle mass loss, muscle soreness, and post-exercise recovery, curcumin may be helpful as an antioxidant and anti-inflammatory [74].Reactive oxygen species (ROS) generation and an inflammatory response are linked to delayed onset muscle soreness (DOMS) brought on by eccentric muscle exercise. Although this inflammatory state is required to carry out muscle repair mechanisms, it might worsen muscle degeneration and catabolism over time, particularly in older subjects [75]. Curcumin appears to be a promising chemical to reduce inflammation and oxidative stress-induced muscle injury during prolonged eccentric exercise.According to additional data, oral curcumin probably lessens DOMS pain and improves muscle performance recovery [76, 77]. Curcumin's effects on muscle strength and exhaustion during exercise have been characterized by preliminary in vivo findings.

Epigenetic Effects: Histone modification (78), DNA methylation (79), Chromatin remodeling (80) and MicroRNA regulation (81)

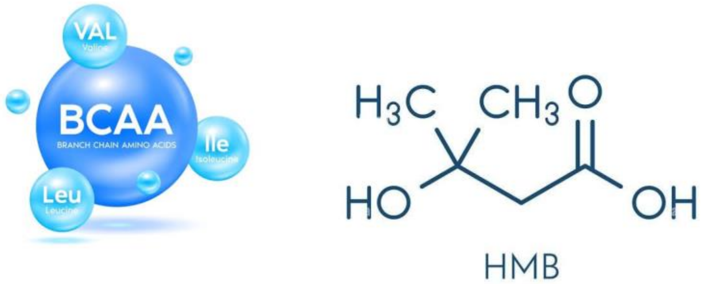
Resveratrol:



Resveratrol (RSV), a naturally occurring polyphenol found in many plant species, has a wide range of health advantages, including antioxidant, anti-inflammatory, anticancer, and antiobesity effects [82]. In recent years, the anti-aging effect of RSV has sparked widespread interest [83]. Because skeletal muscle plays important roles in the systemic regulation of aging and age-related disorders [84], RSV's effects on an organism's lifespan and overall aging may be directly tied to the polyphenol's effects on skeletal muscle. RSV has been shown to prevent muscle atrophy in a variety of catabolic situations, including cancer, diabetes, chronic renal disease, and inactivity (85, 86). Furthermore, earlier studies have shown that RSV reduces aging-induced oxidative damage in skeletal muscle [87], and we previously discovered that RSV inhibits HFD-induced hepatic steatosis via activating the PKA/AMPK signaling pathway [88]. These findings lead us to propose that RSV could protect against sarcopenic obesity by reducing mitochondrial dysfunction and oxidative stress via the PKA/LKB1/AMPK pathway. To test this idea, we looked at the effects of RSV on HFD-induced sarcopenic obesity in elderly rats and palmitate acid (PA)-induced muscle atrophy in myotubes. The changes in mitochondrial function and oxidative stress, as well as the possible participation of the PKA/LKB1/AMPK signaling pathway, were also studied.

Resveratrol administration helped maintain muscle mass and prevent metabolic dysfunction in a rat muscle unloading paradigm (Momken et al., 2011). Polyphenols may prevent atrophy caused by inflammation-related causes, according to growing research. In vitro studies by (Wang et al. 2014) found that combining resveratrol with TNF-α resulted in much less muscle atrophy compared to TNF-α alone. The study found that resveratrol regulates the Akt/mTOR/FoxO1 signaling pathway, which helps reduce TNF-α-induced atrophy. Long-term dietary supplementation with resveratrol did not prevent age-related sarcopenia in rats, suggesting that alternative polyphenols may be more effective therapies for aging (Jackson et al., 2011).

BCAA and HMB:



BCAA's effects, however, are primarily (or completely) due to leucine, a powerful activator of skeletal muscle protein synthesis (MPS) (89,90) and suppressor of muscle protein breakdown (MPB)(91). HMB is a metabolite of leucine. The International Society of Sports Nutrition believes that HMB can reduce exercise-induced skeletal muscle damage and is most effective when consumed for two weeks prior to exercise, so athletes should take 38 mg per kg of body weight per day to promote skeletal muscle growth and strength (92). The manufacturer normally suggests taking 3 g of HMB per day (93), which is similar to consuming 60 g of leucine (94).However, if 60 g of leucine is taken directly, the oxidation of branched-chain amino acids and the activity of rate-limiting enzymes for catabolism increase. This can result in the loss of valine and isoleucine in bodily fluids and ultimately in an imbalance in the concentration of branched-chain amino acids, which may have a detrimental effect on protein metabolism (95).The findings derived from published research on the impact of HMB supplementation on muscle health and athletic performance, however, vary greatly. According to supporting research, older persons who use HMB have stronger upper and lower extremity muscles (96). People over 65 benefit most from taking 3 g of HMB supplements to improve their strength and body composition, especially if they are bed-rested and not trained (97). Through a rigorous examination and meta-analysis, Phillips et al. (98) in the opposing study concluded that there is now inadequate data to evaluate the effects of HMB supplementation on muscular function because the evidence is inconsistent and supports little. The leucine metabolites alpha-hydroxyisocaproic acid (α-HICA) and β-hydroxy-β-methylbutyric acid (HMB) were given to the intervention group in a randomized controlled trial that involved 40 young adult men (99); consequently, supplementing with leucine metabolites did not improve the changes in muscle thickness brought on by resistance training when compared to a placebo (100). In conclusion, the current evidence does not currently offer clear support for suggesting HMB supplementation to treat sarcopenia, and further high-quality primary investigations are required in the future to examine the effects of HMB in patients with sarcopenia.

Clinical Trials and Evidence:

Although clinical trials and evidence on epigenetic nutraceuticals in sarcopenia prevention are scarce, research has shown that diet is important in preventing this widespread skeletal muscle condition.

Clinical trials: The International Clinical Practice Guidelines for Sarcopenia (ICFSR) include resistance exercise training and conditional dietary treatments to boost protein intake, The Global Leadership Initiative on Malnutrition (GLIM) suggests using low skeletal muscle mass as a criterion for malnutrition diagnosis(101).

Evidence: There is little data on how variations in the diet of specific foods throughout younger adulthood may affect muscle growth and function as people age. Overall, there are conflicting and inconsistent findings about the possible preventive advantages of foods compared to diet quality. However, the collinearity of foods in the diet presents a unique challenge in interpreting the observational data on individual foods. This means that a high intake of one food may indicate a lower or higher intake of other foods, rather than specific foods being causally linked to differences in muscle outcomes. For statistical models to comprehend independent effects, these must be modified.For instance, the Whitehall ll study's findings highlight the significance of habitually consuming little fruits and vegetables, and they may convey a crucial message about the buildup of risk over a longer period of time in mid-adulthood [102]. It's also feasible, though, that a low intake of fruits and vegetables serves as a sign of variations in the larger eating pattern, which may include a high intake of other foods that are detrimental to muscle. The influence of highly processed foods may be especially significant in this context, since low quality diets also tend to have lower intakes of fruits and vegetables and higher intakes of these items. Recently, Zhanget al. [103] analyzed data from the Tianjin Chronic Low-grade Systemic Inflammation and Health research and found that high proved that a higher annual loss in grip strength (median follow-up 3.0 years) was linked to excessive consumption of ultra-processed foods (UPF) in mid-adulthood (5409 males and females; median age 48.3 years). Subgroup and sensitivity analyses showed that the link held true even after controlling for a number of variables, such as baseline grip strength and other dietary characteristics. This new discovery implies that UPF directly affects muscle function, either by influencing low-grade inflammation [104] or by increasing exposure to ingredients associated with food processing, like advanced glycation end products [105].

Human studies on Epigenetic nutraceuticals for sarcopenia: Human research on epigenetic nutraceuticals for sarcopenia is still in its early phases, but researchers have found some promising findings.

Dietary Patterns and Sarcopenia Risk: Research suggests that eating a higher-quality, nutrient-dense diet may help maintain muscular mass and function in old age.

Protein Intake and Muscle Mass: According to research, older people require more protein to maintain muscle mass and function, especially when combined with exercise training.

Vitamin D Insufficiency and Sarcopenia: Vitamin D deficiency may increase the risk of sarcopenia, possibly through anti-inflammatory effects.

Some of the epigenetic nutraceuticals under investigation for their potential in preventing or curing sarcopenia include: Omega-3 fatty acids Anti-inflammatory fatty acids have been demonstrated to improve muscular health while decreasing inflammation. Antioxidants, such as vitamins C and E and polyphenols, may assist to minimize oxidative stress and muscle damage. Probiotics are beneficial bacteria in The gut microbiota has an important influence in muscle function and general health(106).

Mechanism of Action:

Signaling pathways and gene expression regulation:

Signaling Pathways:

1. mTOR (Mechanistic Target of Rapamycin): Regulates protein synthesis, muscle growth, and the process of autophagy (107). Its activation is influenced by the availability of nutrients, such as amino acids and glucose (108). The activity of mTOR can be suppressed by rapamycin and various other pharmacological agents (109).
2. AMPK (AMP-activated Protein Kinase): Regulates energy metabolism, mitochondrial biogenesis, and muscular function (110). Activated by energy stress, exercise, and nutrients, such as berberine (111). Inhibited by high-energy states and chemicals, such as glucose (112).

Gene Expression Regulation:

Transcription Factors such as MyoD, Myf5, and MRF4 control muscle cell differentiation (113). NF-KB controls inflammation and muscle injury (114).Nutraceutical-Induced Mechanisms are Omega-3 Fatty Acids in which inhibit NF-κB, activate AMPK, and enhance muscle protein synthesis (164); reduce inflammation and improve muscular function (115)

Epigenetic Biomarkers for sarcopenia diagnosis and monitoring:

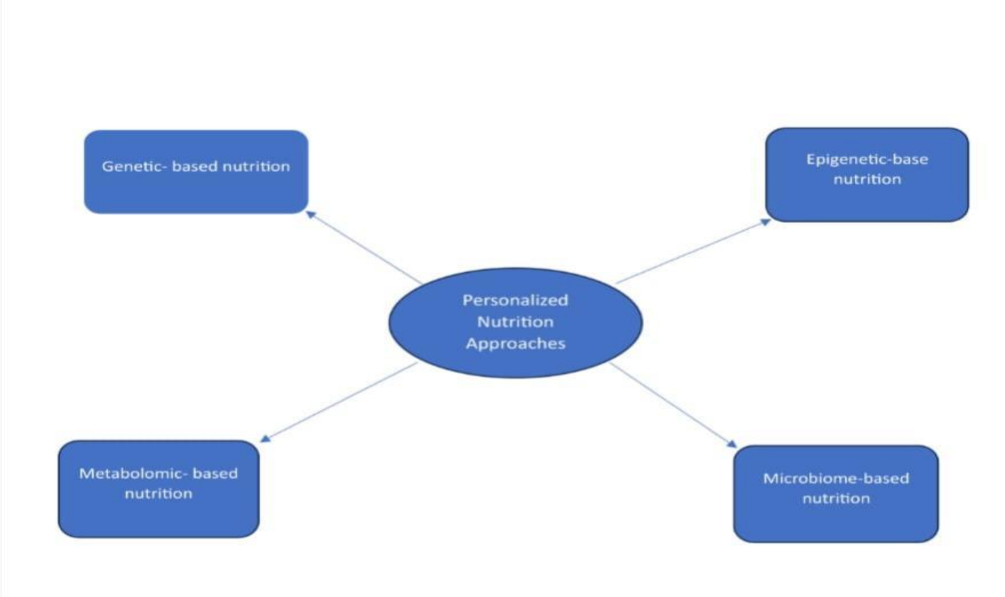
DNA methylation biomarkers: DNA methyltransferase 3B, which is important in muscle cell development, is downregulated in sarcopenia (116). MSTN which is Myostatin, a muscle growth inhibitor, is hypermethylated in sarcopenia, resulting in decreased expression (117). IGF1 which is Insulin-like growth factor 1, which is required for muscle growth, is hypomethylated in sarcopenia, resulting in increased expression (118).

Histone modification biomarkers: H3K27me3: Sarcopenia muscle exhibits elevated trimethylation of histone 3 lysine 27, which is related with gene silence (119).

2. H3K4me3: Sarcopenia muscle has lower levels of histone 3 lysine 4 trimethylation, which is related with gene activation (120).

Future Directions and Research Gaps:

Personalised nutrition approaches:



Integration with pharmaceutical interventions:

Hormonal therapies:

1. Testosterone Replacement Therapy(TRT):

- Snyder et al. (2016): The effects of testosterone replacement therapy on muscular mass and strength in older men. Journal of Clinical Endocrinology and Metabolism, 101(11), 4219–4228. [121]

2. Growth Hormone (GH) Therapy: Nass et al. (2017) discuss growth hormone and muscle function in elderly persons. Journal of Gerontology: Medical Sciences, 72(9):1221-1228. [122]

Protein Synthesis Stimulants :

1) Leucine: - Verhoeven et al. (2015): The effects of leucine supplementation on muscle mass and strength. Nutrients, 7(10): 9033–9045. [123]

2. O'Connor et al. (2018) investigated the effects of HMB (β-Hydroxy ß-Methylbutyrate) supplementation on muscular function. Journal of Strength and Conditioning Research, 32(5), 1315–1325. (124)

Epigenetic editing technology:

1.CRISPR-Cas9:

CRISPR-Cas9 is a modified bacterial adaptive immune system used for genome editing. It employs a guide RNA to target specific DNA sequences, enabling precise epigenetic alterations.

Mechanism: Double-stranded break creation, repair via non-homologous end joining, or homologous recombination. Applications include gene knockout, activation, silencing, and epigenetic alteration(125)

2. Base Editing and Precision:

Base editing is a unique method for directly and irreversibly converting one DNA base to another without causing double-stranded breaks. Mechanism: Base conversion by cytidine deaminase or adenine deaminase. Precision: High specificity and minimal off-target impacts(126).

3. Epigenome-Editing Enzymes (TALEs and ZFNs): TALEs and ZFNs are designed enzymes that target specific DNA sequences for epigenetic alteration. Mechanism: DNA-binding domain connected to the epigenetic effector domain. Applications include gene regulation and epigenetic modification(127).

4. RNA: Targeting Epigenetic Editors (Cas13)

Cas13 is an RNA-targeting CRISPR system that regulates gene expression. mechanism: Cas13-mediated medium RNA fractionation and procedures. Gene silencing and RNA degradation(128)

5. Delivery Styles for Epigenetic Editing Tools:

Epigenetic editing tools can be delivered using viral vectors, nanoparticles, or electroporation. Challenges: cellular and towel walls, off-target goods(129).

Conclusion:

Sarcopenia, a crippling disorder marked by increasing muscle loss and weakness, offers serious health hazards to older persons. Emerging research suggests that epigenetic nutraceuticals, such as omega-3 fatty acids, vitamin D, curcumin, resveratrol, and other polyphenols, have the potential to prevent or treat sarcopenia. These bioactive substances improve muscle health and function by modulating epigenetic mechanisms such as gene expression, DNA methylation, and histone modification. By targeting epigenetic pathways, these bioactive substances can reduce muscle mass loss, improve muscular function, and promote healthy aging. While further research is needed to completely understand their effects, current evidence supports the use of epigenetic nutraceuticals as adjuvant therapy for sarcopenia management. Future research should focus on translational research, standardized dose, and long-term efficacy in order to integrate these revolutionary approaches into clinical practice.

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