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REVIEW ARTICLE

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Tissue and metabolic regeneration in the light of stem cells, gut microbiota, microRNAs, and exosomes: a systematic review

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Abstract

Introduction: In the regenerative nutrology scenario, nutrients and energy balance stand out as triggers for the balanced functions (maintenance of quiescence) of adult tissue stem cells for tissue and metabolic regeneration. **Objective:** It was to develop a systematic review of clinical studies to explore the main nutrients and diets to favor tissue and metabolic regeneration, as well as to understand the functions of mesenchymal stem cells, gut microbiota, microRNAs, and exosomes in this process**. Methods:** The systematic review rules of the PRISMA Platform were followed. The search was carried out from February to April 2025 in the Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** 133 articles were found. A total of 35 articles were evaluated in full and 23 were included and developed in the present systematic review study. Considering the Cochrane risk of bias tool, the overall assessment resulted in 26 studies with a high risk of bias and 21 studies that did not meet GRADE and AMASTAR-2. Most studies showed homogeneity in their results, with X^2=81.2%>50%. It was concluded that signaling pathways, including mTORC, AMPK, MAPK, and others, are all sensitive to changes in nutrient levels. A healthy plant-based diet can reduce skin inflammation and improve overall skin health. Intermittent fasting regimens can inhibit hair follicle regeneration. Despite this, fasting-stimulated autophagy degrades unwanted components and plays a key role in muscle regeneration. Omega-3 fatty acids, magnesium, zinc, vitamins A, C, D, and resveratrol, together with probiotics, positively improve ulcer healing. Milk

contains exosomes (extracellular vesicles) and microRNAs that influence the gut microbiota and aid in tissue regeneration. Supplementation with beta-hydroxy-beta-methylbutyrate, arginine, and glutamine promotes wound regeneration. Finally, studies have shown that patients with ulcers have deficient levels of vitamin C.

Keywords: Tissue regeneration. Metabolism. Epigenetics. Nutrients.

Introduction

In the regenerative nutrology scenario, nutrients and energy balance stand out as triggers for the balanced functions (maintenance of quiescence) of adult tissue stem cells for tissue and metabolic regeneration. Metabolic byproducts and substrates regulate epigenetic and signaling pathways in the regulation of cell fate decisions **[1-3]**.

Also, metabolism encompasses the interactions between diet, gut microbiota, and cellular enzymatic processes for the maintenance of life **[4-6]**. Endogenous metabolites and dietary nutrients can directly influence epigenetic enzymes. Epigenetic modifications in DNA and histone proteins alter cell fate, controlling chromatin accessibility and downstream gene expression patterns. Nutrological health acts directly on the human gut microbiota, impacting metabolism and the immune system for tissue regeneration **[5,6]**. Epigenetic factors also regulate transcription factors, cytokines, extracellular matrix proteins, and glycosaminoglycans. Nutrition provides an epigenetic signal that can actively influence each step of the wound-healing process **[7]**. Wound healing requires dietary amino acids, vitamins, and minerals **[8,9]**.

In this regard, adequate amounts of nutrients are required for the synthesis of nucleic acids (DNA and RNA), proteins, and other factors involved in functional tissue maturation and differentiation **[10,11]**. Malnutrition is widely associated with delayed or failed wound healing, but nutritional intervention can mitigate malnutrition and improve wound healing, mainly by increasing collagen deposition after trauma **[10]**.

Therefore, the present study developed a systematic review of clinical studies to explore the main nutrients and diets to favor tissue and metabolic regeneration, as well as to understand the roles of mesenchymal stem cells, gut microbiota, microRNAs, and exosomes in this process.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 02/21/2025. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 02/21/2025.

Search Strategy and Sources

The search strategies for this systematic review were based on the following keywords (DeCS/MeSH Terms): *"Tissue regeneration. Metabolism. Epigenetics. Nutrients".* The search was conducted from February to April 2025 in the Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar databases. Scientific articles from the last 15 years were selected. In addition, a combination of the keywords with the Boolean operators "OR", "AND" and the "NOT" operator was used to target the scientific articles of interest.

Study Quality and Risk of Bias

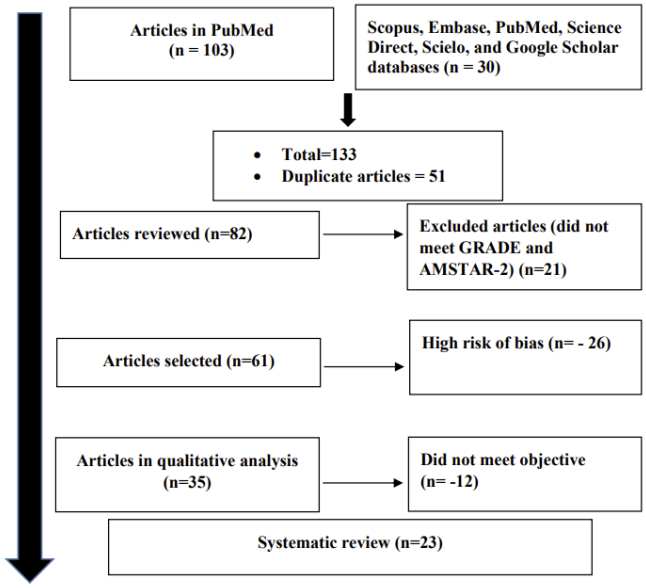
The quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane tool by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Findings

A total of 133 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing the articles that did not include the theme of this article, resulting in 82 articles. A total of 35 articles were evaluated in full and 23 articles were included and developed in the present systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 26 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2. According to the GRADE tool, most studies presented homogeneity in their results, with X^2=81.2%>50%.

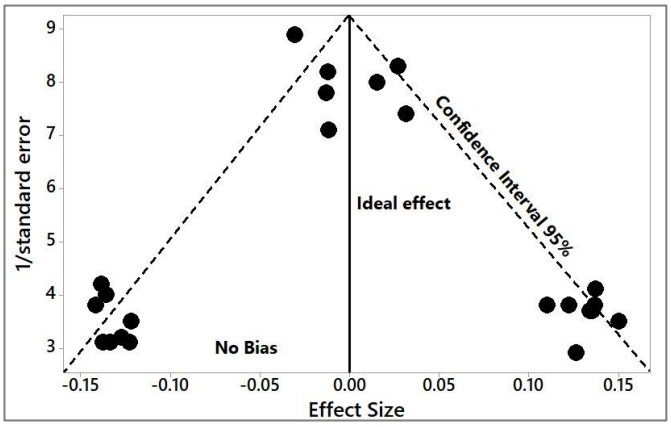
Figure 1. Flowchart showing the article selection process.



Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are presented at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n=23 studies).



Source: Own Authorship.

Significance and Main Clinical Approaches of Regenerative Processes and Nutrology

Authors Chen et al. (2025) **[12]** reported that intermittent fasting regimens can inhibit hair follicle regeneration by selectively inducing apoptosis in activated hair follicle stem cells. This effect is independent of caloric reduction, circadian rhythm alterations, or the cellular nutrient sensing mechanism via the mTORC1 pathway. Fasting can activate cross-talk between the adrenal glands and dermal adipocytes in the skin, triggering the rapid release of free fatty acids into the niche, which in turn disrupts the normal metabolism of activated hair follicle stem cells and elevates cellular reactive oxygen species levels, causing oxidative damage and apoptosis. Despite this, fastingstimulated autophagy maintains the stability of eukaryotic cells by degrading unwanted components and recycling nutrients and plays a key role in muscle regeneration by regulating the quiescence, activation, and differentiation of satellite cells. Effective muscle regeneration is vital for maintaining muscle health and homeostasis. However, in certain pathological conditions, such as aging, muscle regeneration may fail due to dysfunctional satellite cells. Dysregulated autophagy may limit satellite cell self-renewal, impair differentiation, and increase susceptibility to apoptosis, thus preventing muscle regeneration **[13]**.

Diet is a major determinant of the composition and function of the gut microbiota. Authors Borrego-Ruiz and Borrego (2024) **[14]** analyzed the mechanisms underlying the relationship between nutritional factors, gut microbiota, and certain skin diseases, such as acne vulgaris, alopecia, and atopic dermatitis. Thus, these authors demonstrated that adequate intake of certain foods can promote a balanced gut microbiota, potentially reducing skin inflammation and improving overall skin health, while inadequate dietary choices can lead to worse outcomes by disrupting intestinal homeostasis. In this sense, diets rich in antioxidants, fiber, and phytonutrients appear to be beneficial for improving skin health and preventing associated comorbidities. In addition, the administration of probiotics, synbiotics, and postbiotics in the treatment of skin diseases has been shown to restore skin homeostasis and improve the symptoms of the skin conditions analyzed.

It is also found that nutritional therapy is an important adjuvant to improve the clinical picture and healing of chronic lower limb ulcers. In this sense, a systematic review study found 1,184 articles on antioxidant nutrients associated with the most common causes of chronic lower limb ulcers. A total of 14 articles showed that omega-3 fatty acids, magnesium, zinc, vitamins A, C, D, and resveratrol, together with probiotics, positively improved ulcer healing. These effects were more significant when there was an initial deficiency of the respective supplemented nutrients **[15]**. Furthermore, it is noteworthy that milk contains exosomes (extracellular vesicles) and microRNAs that

influence the gut microbiota, promoting the integrity of the intestinal barrier, aiding in tissue repair and regeneration, and modulating immune responses for the treatment of conditions such as inflammatory bowel disease (IBD) and colorectal cancer **[16]**. Furthermore, the potential of collagen in bone regeneration is highlighted, reinforcing its promising potential as a treatment option with significant clinical implications, paving the way for innovative and effective therapeutic strategies in this field **[17]**.

Based on the nutritional functions mentioned in the previous paragraphs, metabolism involves interactions between diet, gut microbiota, and cellular enzymes in the processes that generate the chemical pathways necessary to sustain life. Endogenous metabolites and nutrients derived mainly from the diet can directly influence epigenetic enzymes, promoting modifications in DNA and histones that control chromatin accessibility and downstream gene expression **[18]**.

The majority of substrates and cofactors for chromatin-modifying enzymes are derived from metabolic pathways involving the tricarboxylic acid (TCA) cycle, the methionine cycle, the folate cycle, glycolysis, β-oxidation, and the hexosamine pathway **[19]**. These complex and interconnected networks generate intermediates that coactivate epigenetic enzymes and/or serve as direct substrates for modifications, including acetyl-CoA, alpha-ketoglutarate (α-KG), succinate, fumarate, S-adenosyl methionine (SAM), UDP-GlcNAc, ketone bodies, lactate, and the reducing equivalents NADH and FADH2 **[20,21]**.

In addition, dietary nutrients such as ascorbic acid (vitamin C) and sodium butyrate regulate the activity of chromatin-modifying proteins and DNA. Nutrients can impact the cellular state by modulating the activity of the mechanistic target of the rapamycin (mTOR) signaling pathway and in particular the mTOR complex 1 (mTORC1), which regulates cell growth only when nutrients and growth factors are present **[22]**. In this regard, depletion of specific nutrients, such as arginine, leucine, and SAM, prevents growth factor-induced mTORC1 activation by blocking mTORC1 recruitment **[23]**. Furthermore, nutrients impact the cellular state through AMP-activated protein kinase (AMPK), which at low cellular ATP levels phosphorylates substrates to restore the cell's energy balance, regulating cell growth and autophagy **[5,24]**.

Transcription factors can be directly regulated by metabolites. Tryptophan kynurenine is an endogenous agonist for the aryl hydrocarbon and alpha-ketoglutarate (αKG) receptor that binds to and activates IKKβ and initiates NF-κβ signaling **[5]**. Dietary and metabolite manipulations can affect tissue stem cells and direct cell fate decisions, as highlighted in the small intestine (intestinal stem cells), hematopoietic system, liver, muscle (muscle stem cells/satellite stem cells, and hair follicle stem cells **[25]**.

Hematopoietic stem cell self-renewal and differentiation can be regulated by manipulating vitamin C, A, or D levels. Hematopoietic stem cell self-renewal is also impaired by valine restriction. A methionine-rich diet, which increases plasma homocysteine levels, impairs liver regeneration after partial hepatectomy **[5]**.

Also, the intestinal epithelium is the fastest renewing tissue and has great flexibility to adapt. Lgr5+ crypt basal cells act as stem cells during homeostasis and are essential during regeneration. Nutritional status and inflammation have recently been identified as regulators of stem cell activity in the human intestine **[26]**. One study demonstrated that the expression of the enzyme Hmgcs2, which regulates the rate-limiting step in ketone body synthesis, is enriched in intestinal stem cells and LGR5+. Loss of Hmgcs2 impairs intestinal stem cell regeneration and promotes differentiation toward the Paneth cell lineage. The ketone body β-hydroxybutyrate inhibits class I histone deacetylases to enhance transcriptional activation of Notch signaling and maintain stem cell self-renewal **[27,28]**.

A multicenter, randomized, double-blind, controlled study investigated the potential of a high-protein, arginine, and micronutrient-enriched food, oral nutritional supplement (ONS), to improve pressure ulcer healing. The results demonstrated that ONS supplementation accelerated pressure ulcer healing, as indicated by a significantly faster decrease in ulcer size compared with control after eight weeks. The decrease in severity score (Pressure Ulcer Healing Scale) in the ONS group differed significantly from the control. Furthermore, blood vitamin C levels increased significantly in the ONS group compared with control **[29]**.

Another randomized clinical trial investigated the efficacy of a nutraceutical supplement (arginine 9 g, vitamin C 500 mg, zinc 30 mg) on pressure ulcer healing. A total of 17 patients with category II, III, or IV pressure ulcers were randomized to receive daily a standard hospital diet, a standard diet plus two high protein/energy supplements, or a standard diet plus two high protein/energy supplements containing the additional nutraceutical. The results showed that only patients receiving the additional nutraceutical supplement demonstrated clinically significant improvement in pressure ulcer healing **[30]**.

A study analyzed the effect of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine supplementation for four weeks on wound healing in 11 diabetic dialysis patients. After four weeks, according to the Bates-Jensen score, healing was observed in the

wound depth score of seven (63.6%) patients and the wound appearance score of eight (72.7%) patients. While the wound depth score of four (36.4%) patients and the wound appearance score of three (27.3%) patients remained the same, no deterioration was observed in any of the cases during the entire follow-up period. This supplementation may contribute positively to wound healing in diabetic dialysis patients. The beneficial effects of arginine on wound healing are related to the gene-mediated hormonal secretagogue actions of arginine (growth hormone, prolactin, insulin, and glucagon) **[31]**.

A randomized clinical study demonstrated the efficacy of supplementation with antioxidant micronutrients and glutamine in accelerating wound healing. A total of 20 patients with wound-healing disorders were included. Patients received antioxidant micronutrients (ascorbic acid, alpha-tocopherol, beta-carotene, zinc, selenium) and glutamine (verum) or isoenergetic amounts of maltodextrin (placebo) for 14 days. The results showed that serum levels of micronutrients were not modified, except for selenium, which increased in the verum group (1.1±0.2 versus 1.4±0.2 µmol/L; p=0.009). Glutamine levels decreased only in the placebo group (562±68 versus 526±55 µmol/l; p=0.047). The prevalence of hypovitaminosis and VEGF-A concentration remained unchanged. Considering microcirculation, only oxygen saturation decreased in the placebo group. Wound closure occurred more quickly in the verum than in the placebo group **[32]**.

Finally, high-dose vitamin C supplementation aids in the healing process of surgical wounds in healthy individuals and those with pressure ulcers. Vitamin C supplementation in doses of 500 mg, combined with at least 17 mg of zinc, and even in combination with arginine, is useful for wound healing by increasing collagen synthesis **[33]**. In addition, vitamin C is essential for the formation of cross-links between collagen fibers, fibroblast maturation, and angiogenesis. Some studies have shown that patients with ulcers have deficient levels of vitamin C **[33,34]**.

Conclusion

It was concluded that signaling pathways, including mTORC, AMPK, MAPK, and others, are all sensitive to changes in nutrient levels. Consuming a healthy plant-based diet can reduce skin inflammation and improve overall skin health. Intermittent fasting regimens can inhibit hair follicle regeneration. However, fasting-stimulated autophagy degrades unwanted components and plays a key role in muscle regeneration. Omega-3 fatty acids, magnesium, zinc, vitamins A, C, D, and resveratrol, along with probiotics, have been shown to positively improve ulcer healing. Milk contains exosomes (extracellular vesicles) and microRNAs that influence the gut microbiota and aid in tissue regeneration. Supplementation with beta-hydroxy-beta-methylbutyrate, arginine, and glutamine promotes wound regeneration. Finally, studies have shown that patients with ulcers have deficient levels of vitamin C.

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Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

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Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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