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Review

Calcium Hydroxyapatite in Its Different Forms in Skin Tissue Repair: A Literature Review

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Abstract: The skin is crucial for homeostasis and body defense, requiring quick healing to maintain internal balance. Initially used for bone repair, calcium hydroxyapatite (HAp) is now being studied for soft tissue engineering. This literature review investigated HAp's role in tissue repair through searches on PubMed, Scopus (Elsevier), Science Direct, Springer Link, and Google Scholar databases without time restrictions, using keywords "hydroxyapatite AND skin AND wound" and "hydroxyapatite AND skin repair". Inclusion criteria encompassed in vivo studies in humans and animals, English publications, full access, and sufficient data on HAp's role in tissue repair. Exclusions included duplicates, unrelated articles, editor letters, reviews, comments, conference abstracts, dissertations, and theses. Out of the 472 articles initially identified, 139 met the inclusion criteria, with 21 focusing on HAp for tissue repair. Findings indicate that HAp and nano-HAp in skin regeneration are promising, especially when combined with other biomaterials, offering antimicrobial and anti-inflammatory benefits and stimulating angiogenesis. This suggests their potential application in dermatology, surgery, and dentistry, extending HAp's versatility from hard tissues to enhancing critical properties for soft tissue repair and accelerating healing.

Keywords: hydroxyapatite; nanomaterials; tissue repair; wound healing; skin tissue; scaffolds; regenerative medicine; dermatology; surgery

Citation: Cruel, P.T.E.; dos Santos, C.P.C.; Cueto, T.M.; Avila, L.P.V.; Buchaim, D.V.; Buchaim, R.L. Calcium Hydroxyapatite in Its Different Forms in Skin Tissue Repair: A Literature Review. *Surgeries* **2024**, *5*, 640–659. https://doi.org/10.3390/surgeries5030051

Academic Editor: Derek H. Rosenzweig

Received: 23 May 2024
Revised: 2 August 2024
Accepted: 8 August 2024
Published: 9 August 2024

1. Introduction

As the largest and most important organ of the human body, the skin plays a fundamental role in maintaining homeostasis, preventing microbial and chemical invasion and serving as the body's first line of defense against injuries, infections, and dehydration [1–3]. When the skin loses its integrity, the body's natural response is to initiate a complex healing process characterized by three main stages: inflammation, proliferation, and remodeling.

In the initial inflammation stage, an inflammatory response is triggered, evidenced by up to five signs: redness, heat, rubor, edema, and functional limitation. This stage is responsible for clearing debris and pathogens in the area and preparing the site for the next phase. Soon after, the proliferation stage begins, where the body starts repairing the damaged tissue through the formation of new blood vessels (angiogenesis) and specialized cells like fibroblasts and endothelial cells, promoting the creation of granulation tissue to fill the wound. The proper functioning of this stage is crucial for restoring skin integrity. Finally, remodeling,

the final phase of the process, involves the reorganization of collagen, maturation of the newly formed tissue, and deposition of the extracellular matrix (ECM) [3,4], followed by a cascade of events that lead to tissue repair. Throughout this cascade, any interruption or complication can lead to persistent infections, undesirable scars, and even complete failure of wound healing [5].

When damaged, the skin loses its protective function, facilitating the invasion of microorganisms and leading to severe infections [6–8]. Various conditions, such as diabetes, burns, and senile diseases, can cause significant skin defects [9–12]. Prolonged inflammation, with continuous secretion of pro-inflammatory mediators, impairs and delays healing [13,14]. Therefore, the repair and regeneration of soft tissues are growing areas of study due to their importance for human survival [11,13].

In tissue engineering, the need for the use of natural and synthetic substitutes that meet criteria of biocompatibility, biodegradability, and adequate mechanical strength has emerged [14–17]. Calcium hydroxyapatite is a bioactive ceramic based on calcium phosphate [18] that fits these criteria to become a good tissue substitute, as it helps in the attachment, proliferation, and differentiation of cells [19]. Additionally, it releases calcium and reduces wound size by inducing blood clotting, as calcium ions are mediators of wound healing and tissue regeneration [20].

Calcium hydroxyapatite nanoparticles have been shown to be excellent nanomaterials due to their modern properties of bioactivity, non-toxicity, and biocompatibility [21]. Moreover, hydroxyapatite is non-toxic and has seamless structures that promote accelerated cell proliferation, spreading, rapid bioabsorption, and regeneration in a short period of time [2]. There are several studies on its medical use in various fields, such as cartilage regeneration, as a coating for implants due to its hard tissue structure, and mainly for bone repair [22].

It is believed that the calcium particles released by hydroxyapatite trigger an inflammatory response already in the initial stage of healing, accelerating wound healing and promoting the migration and proliferation of fibroblasts and keratinocytes, the second stage of the wound regeneration cascade, essential for the formation of new epithelial tissue [19]. Additionally, HAp can modulate the inflammatory response, reducing pro-inflammatory cytokines and creating an environment conducive to tissue regeneration [23]. Recent studies show that HAp can also stimulate angiogenesis, providing nutrients and oxygen to damaged areas [24]. Therefore, through all these mechanisms, calcium hydroxyapatite can significantly accelerate skin wound healing.

Furthermore, when used in orofacial harmonization, calcium hydroxyapatite promotes the regeneration of collagen I and III, elastin, and proteoglycans, in addition to stimulating the formation of new tissue and vasculature. Clinically, this translates into firmer, brighter, more flexible, elastic, and hydrated skin with fewer wrinkles [25]. These effects can result in a younger and more aesthetic appearance, without leaving scar marks or resulting in thinner scars after complete healing. The authors of this study aim to fill any gaps that may exist in the available literature on the use of calcium hydroxyapatite and its role in skin tissue repair, presenting evidence, practical aspects, and applications of this substance. It is hoped that the knowledge gained from this literature review will contribute to the use of this material in skin healing.

2. Materials and Methods

We accessed and selected manuscripts from five databases, PubMed, Scopus (Elsevier), Science Direct, Springer Link, and Google Scholar, without temporal restrictions regarding the year of publication and using the following keywords: “hydroxyapatite AND skin AND wound”, “hydroxyapatite AND skin repair”, and “hydroxyapatite and/or burn wound treatment”. Through the intersection of these keywords, we conducted a detailed analysis of the results, considering the title and abstract of each scientific article as important criteria for selection. Each manuscript was analyzed to ensure the relevance of both the title and abstract. Subsequently, the manuscripts were classified as included or not included according to the established eligibility criteria. In selecting studies for a detailed analysis,

two independent reviewers evaluated the manuscripts, considering the selection criteria to minimize bias.

The inclusion criteria consisted of studies conducted in humans and animals, in vivo/in vitro studies, and publications in English that allowed access to the full text and provided sufficient data to understand the role of calcium hydroxyapatite in tissue repair. We excluded duplicate articles, those not directly related to the objective of this review, cases where calcium hydroxyapatite was not used for tissue repair or was not the focus of the study, as well as articles, letters to the editor, reviews, commentaries, conference abstracts, dissertations, and theses from repositories.

Studies with titles and abstracts related to the chosen topic were initially selected according to the focus of this review: the use of calcium hydroxyapatite in the tissue repair process. The next step involved excluding duplicate articles in the consulted databases and removing studies that did not meet the eligibility criteria through a careful reading of the texts. Special attention was given to the methodology used in the study, ensuring that the procedures were effectively related to the proposed theme. The article selection scheme is presented in Figure 1.

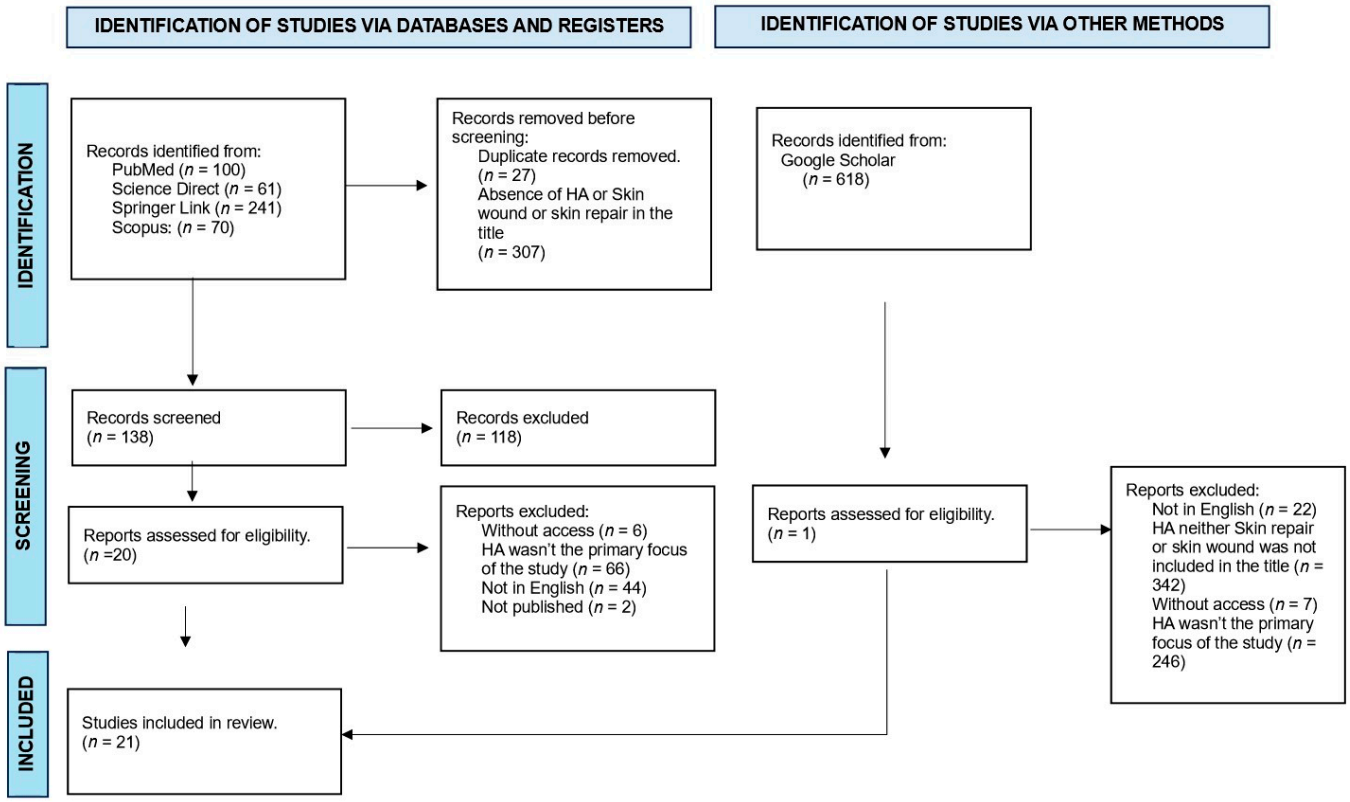

Figure 1. Flowchart of article selection for detailed analysis.

3. Results

We identified 472 articles in the literature on calcium hydroxyapatite (HA). After applying the inclusion and exclusion criteria outlined in this paper, 139 articles were retained in the context of the role of hydroxyapatite in regeneration, from which we selected 21 studies that specifically addressed the use of the calcium hydroxyapatite compound as a material directly to achieve tissue repair. The results of this detailed analysis are presented in a systematic manner below (Table 1).

Table 1. Articles selected by detailed analysis.

Reference	Objectives	Form of Calcium Hydroxyapatite	Calcium Hydroxyapatite Particle Size	Associated Material	Intervention	Outcomes
Majeed and Naimi, 2012 [26]	To evaluate the role of hydroxyapatite in the healing of experimentally induced dermal wounds in rabbits supported by clinical histopathologic evaluations.	Calcium hydroxyapatite powder (0.5 mg)	Not specified	None	Sample: Thirty adult native rabbits Defect: Dorsal defects Divided into two groups: a control group (n = 15) and a treatment group (n = 15) Time of histopathologic examination: Histopathologic examination was performed at 3, 5, 7, 14, and 21 days postoperatively	There was more calcification compared to the control group. Calcium hydroxyapatite induced angiogenesis and attracted more macrophages and fibroblasts to the area. HA-based materials promote wound healing and are promising in situations where rapid proliferation is required to optimize regeneration.
Kawai et al., 2012 [27]	To demonstrate the effect of hydrolyzed calcium on wounds and release calcium nanoparticles into the acidic environment to facilitate the repair process.	Nanoparticles with various experimental coating solutions	50–200 nm	None	Sample: 8-week-old female mice Defect: Dorsal cutaneous Divided: Control group (A) and treatment group (B) Time to histopathologic examination 0 h, 3 h, 24 h, 72 h, 7 days, and 10 days	The nanoparticles accelerated healing and were detected in the wound marked by fusion tag (FLAG). In other words, the material has the potential to reduce the size of open wounds through contracture by releasing ionized calcium into the wound. This study suggests therapeutic implications for the effective treatment of wounds with calcium nanoparticles.
Qianqian et al., 2021 [2]	To evaluate the mechanical and antibacterial properties of nano-hydroxyapatite/chitosan/tilapia skin peptide hydrogel dressings on burns.	Nano calcium hydroxyapatite powder (nHA) in two concentrations (0.5% and 1.0%) was synthesized according to the method described by Zhou et al. and subsequently characterized as a hydrogel	100 nm	Chitosan hydrogel (CS), tilapia peptides (TP), and burn cream (MEBO)	Sample: Rabbit Defect: Scalding Division: They were divided into four groups: control, group receiving burn cream, group receiving NHA/CS/TP-I hydrogel (0.5% nHA), and group receiving NHA/CS/TP-II hydrogel (1.0% nHA) Time of histopathologic examination: 3, 7, 14, and 21 days after surgery	The NHA/CS/TP(I) and NHA/CS/TP(II) hydrogels were similar in structure to the extracellular matrix (ECM). The NHA/CS/TP(II) hydrogel showed antibacterial efficacy and cytocompatibility, making it extremely beneficial for accelerating the healing process of burns.

Table 1. *Cont.*

Reference	Objectives	Form of Calcium Hydroxyapatite	Calcium Hydroxyapatite Particle Size	Associated Material	Intervention	Outcomes
Derakhshi et al., 2023 [19]	Modification of dressing synthesis with chitosan and Pluronic F-127, introducing hydrophobic components to adjust surface tension, reduce nanofiber size, and increase mechanical strength. Calcium hydroxyapatite (HAP) nanoparticles were added to accelerate tissue deposition in the repair process.	Powder	1–100 nm	Calcium chloride, sodium dihydrogen phosphate dihydrate, Pluronic P123, chitosan, and Pluronic F-127	Sample: Twenty-seven Wistar rats Defect: Dorsal Division: Three groups: one control group, one wound treatment group with calcium chloride, sodium dihydrogen phosphate dihydrate, and pluronic F-127 (CTS-PEO-F127) nanofibers, and one wound treatment group with nanofibers Time of histopathologic examination: 5, 10, and 15 days after injury	The nanofiber of the CTS-PEO-F127/HAP group stands out by improving the anti-inflammatory property, proliferation, and cell differentiation in wound healing. This non-toxic, nanotechnology-based dressing presents a significant advantage for effective clinical application in promoting wound healing.
Peifen et al., 2023 [12]	To develop a new dressing with sulfated silk fibroin (SSF), chitosan (CS), and hydroxyapatite (HAP), building a three-dimensional structure composed of SSF/CS/HAP, overcoming the limitations of a single material.	Modified powder	40 nm	Sulfated silk fibroin and chitosan	Sample: Eighteen female rats Defect: Neck skin of rats Division: They were divided into 3 groups (n = 6): a control group, a group that received the SSF/CS/HAP dressing, and a group that received the SF/CS/HAP dressing. Time for histopathological examination: 3, 7, and 14 days after surgery	The characterization tests, in vitro experiments, and rat wound healing experiments with a three-dimensional composite structure confirmed its high biocompatibility, promotion of cell adhesion and proliferation, and wound healing properties.

Table 1. *Cont.*

Reference	Objectives	Form of Calcium Hydroxyapatite	Calcium Hydroxyapatite Particle Size	Associated Material	Intervention	Outcomes
Lamkhao et al., 2023 [28]	The dressing, developed based on carboxymethylcellulose (CMC) hydrogel, was improved by the addition of shellac, without compromising the thermal and mechanical properties of CMC. Hydroxyapatite (HA) was incorporated into the dressing as a long-lasting antibacterial agent to promote tissue healing.	Modified powder	Not specified	Carboxymethylcellulose, Shellac	Sample: Fifteen domestic dogs Subject: Outpatients for field neutralization in a canine and feline population control project Area: Before and after hydrogel application Time to histopathologic examination: evaluated on days 3, 7, 10, and 14.	The properties of the dressing help to accelerate wound healing. Initial research suggests that these hydrogels have potential as effective components for surgical dressings that maintain moisture without causing irritation or allergy.
Fan et al., 2020 [29]	To prepare a nanofiber membrane composed of keratin and polyethylene oxide (PEO) reinforced with hydroxyapatite (HA) for the application of dressings, evaluating the biological, morphological, chemical, and mechanical properties of the nanofiber.	Modified powder	20 nm	Modified powder Keratin and polyethylene oxide (PEO)	Sample: 8 mice Defect: With burns in the dorsal region Division: Two groups (n = 4): a control group and a group receiving the keratin/PEO/HA dressing. Time of histopathologic examination: Histologic evaluation was performed on days 3, 7, 14, and 28.	The keratin/PEO/HA nanofiber membrane was effective in increasing the proliferation of L929 cells, showed advantages in reducing the inflammatory response in the infectious phase, and improved the skin repair process in the subsequent phases of tissue recovery.

Table 1. *Cont.*

Reference	Objectives	Form of Calcium Hydroxyapatite	Calcium Hydroxyapatite Particle Size	Associated Material	Intervention	Outcomes
Chen et al., 2021 [30]	To develop a simple and economical approach to produce nanometric borate active glass (BBG) coated with hydroxyapatite (nano-HCA@BG) through a dynamic flow treatment to reduce BBG degradation and maintain the concentration of bioactive ions sufficient for cell promotion and differentiation for efficacy in tissue repair.	Powder	Not specified	Nanometric active borate glass (BBG)	Sample: Fifteen mice Defect: Dorsal skin Division: Into 5 groups (n = 3): a control group, a group receiving only nano-hydroxyapatite, a group receiving only bioactive glass, a group receiving only BBG, and a group receiving nano-HCA@BG as treatment. Time of histopathologic examination: 0, 1, 3, 5, and 7 days.	The formation of nanoporous architecture coated with HCA significantly improves biocompatibility, promotes cell growth and proliferation, and is beneficial for wound healing in rodent skin defects.
Elsayed et al., 2020 [31]	To analyze the dressing composed of cellulose acetate (CA)-based electrospun nanofibrous structures encapsulated by modified hydroxyapatite (HAP) with different Cu ion contents in response to in vitro cell behavior in terms of its structure, surface morphology, and mechanical and antibacterial properties.	Modified powder	Not specified	Cellulose acetate (CA) and copper (Cu)	In vitro: Human fibroblast culture for 3 days, analyzed daily	The morphology affected the composition, with a slight variation in mechanical properties and a significant increase in antibacterial properties when more Cu was added. Cells not only adhered and proliferated on the surface but also preferred to grow deep into the fibers, highlighting the clinical potential of nanofibers as advanced dressings.

Table 1. *Cont.*

Reference	Objectives	Form of Calcium Hydroxyapatite	Calcium Hydroxyapatite Particle Size	Associated Material	Intervention	Outcomes
Wang et al., 2021 [32]	Development of a dressing based on nano-hydroxyapatite (n-HAP) and polymeric nanofibers (chitosan/gelatin polyelectrolyte complex (PEC)) with prolonged drug release using tetracycline hydrochloride (TCH) as a therapeutic model to evaluate appropriate mechanical properties.	Powder	Not specified	Gelatin/chitosan (CG), tetracycline hydrochloride	The nano-hydroxyapatite was loaded with a model antibiotic, tetracycline hydrochloride (TCH), and subsequently encapsulated in chitosan/gelatin polyelectrolyte complex (PEC) nanofibers with a typical core-shell geometry.	PEC nanofiber membranes reinforced with n-HAP will serve as a promising platform for the development of new antimicrobial dressings due to their good water retention, high stiffness, sustained long-term drug release, and antibacterial efficacy.
Zheng et al., 2022 [33]	To prepare an inorganic hemostatic aerogel, biocompatible nanowires of ultra-long hydroxyapatite (HAP) are used with polyvinyl alcohol (PVA) as an organic binder. The aerogel is prepared by lyophilization to form a porous three-dimensional structure with good plasticity and flexibility.	Ultra-long PAH nanowires	Not specified	Monosodium phosphate dihydrate (NaH2PO4·2H2O), sodium hydroxide (NaOH), and methanol	Sample: Twenty-four rats Defect: Dorsal skin Division: 4 groups: a control group, a group receiving gelatin only, a group receiving P-8HAP-2PVA aerogel, and a group receiving W-8HAP-2PVA aerogel. Time of histopathologic examination: days 0, 3, 6, 9, 12, and 15.	The aerogel named W-8HAP-2PVA can rapidly absorb water from blood to concentrate blood cells and platelets and accelerate hemostasis. It has good hemocompatibility and cytocompatibility and can promote the healing of skin wounds.

Table 1. *Cont.*

Reference	Objectives	Form of Calcium Hydroxyapatite	Calcium Hydroxyapatite Particle Size	Associated Material	Intervention	Outcomes
Wang et al., 2022 [34]	To develop and study cobalt-doped hydroxyapatite (CoHap) particles with the structural properties of polycaprolactone (PCL) and carboxymethylcellulose (CMC) nanofibers for wound dressings for skin care applications.	Powder	Not specified	Cobalt, polycaprolactone (PCL) and carboxymethyl-cellulose (CMC)	Sample: Thirty Wistar rats Defect: Dorsal skin Division: 5 groups: a control group, a group that received PCL and CMC in the wound, a group that received PCL, CMC, and CoHA at 5%, a group that received PCL, CMC, and CoHA at 10%, and a group that received PCL, CMC, and CoHA at 15%. Time to histopathologic examination: days 0, 2, 4, 6, 8, 10, 12, and 14.	In vitro analysis showed satisfactory results and fully biocompatible structures. The 10% PCL/CMC/CoHA dressing showed the most satisfactory wound healing results based on the in vivo studies.
Han et al., 2020 [35]	To develop a dressing of titanium-doped hydroxyapatite (Ti-HAP) nanosticks synthesized and incorporated into a chitosan (CS) matrix for joint wound healing.	Powder	Not specified	Titanium, chitosan	In vitro: Ti-HAP nanosticks were synthesized by a hydrothermal method. In vivo: Rabbits with shoulder joint wounds were divided into three groups: a control group, a group receiving a CS/HAP dressing, and a group receiving a CS/Ti-HAP dressing.	The CS/Ti-HAP hydrogel dressing is highly antibacterial and cell compatible. It showed faster therapeutic efficacy than the chitosan and CS/HAP groups in the in vivo tests, indicating that it is a promising option for accelerating joint wound healing.
Cunha et al., 2020 [36]	To develop a chitosan-based material so that, using its excellent biomedical properties, it can be combined with the UV absorption properties of hydroxyapatite (HAp)-based powder.	Powder, natural form	Not specified	Chitosan (CS), iron (Fe)	The CS-FeHAP films were analyzed for morphology using scanning electron microscopy, while the composition and incorporation of the FeHAp powder into the CS matrix were determined using energy dispersive spectroscopy. Mechanical properties, film thickness, water uptake, corrosion, bioadhesive strength, color, porosity, antimicrobial activity, and cytotoxicity were also evaluated.	The combination of these characteristics formed an excellent film to be used in biomedical applications, such as dressings, as they can help reduce bacterial infections and, at the same time, protect wounds from exposure to UV light.

Table 1. *Cont.*

Reference	Objectives	Form of Calcium Hydroxyapatite	Calcium Hydroxyapatite Particle Size	Associated Material	Intervention	Outcomes
Grzeczkowicz et al., 2021 [37]	Developing multifunctional layers of polyelectrolytes reinforced by hydroxyapatite (HAP), gold nanoparticles (AuNPs), and/or fullerenol (FUOL) nanocomposites to obtain a dressing for bone and skin.	Aqueous paste	<50 nm	Gold nanoparticles (AuNPs), fullerenol (FUOL)	The wound crusts were examined using TEM, STEM, and EDX techniques. Human osteoblasts and fibroblasts were immobilized inside the scabs and the morphology of the systems was evaluated by SEM and their function was determined by flow cytometry. In addition, the internalization of the gold nanoparticles (AuNPs) was evaluated.	The membrane with fullerenol and bacteriostatic elements prevents the internalization of AuNPs by human fetal osteoblast cells, ensuring adequate cell counts and morphology. This material is effective for dressings at the bone–skin interface.
Li et al., 2023 [38]	To produce an injectable granular gel using tannic acid (TA), collagen microparticles (COL), and hydroxyapatite nanoparticles (nHA) for use in skin wounds, helping to reduce inflammation and improve the healing process.	Nano calcium hydroxyapatite	Not specified	Tannic acid together with collagen microbeads	Sample: Ten rats Defect: Back of the animal Division: Two lesions, one control and one experimental on the same animal Time for histopathological examination: at 7 and 14 days	Named COLmg@TA@nHA, the hydrogel has an optimized microstructure and macrostructure suitable for injectable application in skin lesions. In addition, it showed a reduction in the inflammatory response, an increase in α-SMA expression, and, consequently, promotion of the wound healing process.
Hutting et al., 2021 [39]	Assessing the viability of calcium hydroxyapatite with gentamicin in diabetic foot ulcers in patients diagnosed with osteomyelitis.	Hydroxyapatite biocomposite	Not specified	Gentamicin	Sample: 64 patients Defect: patients' extremities Division: 13 hospitals with diabetic patients with osteomyelitis and ulcers ideal for healing 3 groups: forefoot (n = 41), midfoot (n = 14), hindfoot (n = 9) Time to histopathologic examination: Not applicable	Gentamicin-loaded calcium sulfate biocomposite (CaS-HA) was viable in the majority (66%) of patients.

Table 1. *Cont.*

Reference	Objectives	Form of Calcium Hydroxyapatite	Calcium Hydroxyapatite Particle Size	Associated Material	Intervention	Outcomes
Ribeiro et al., 2021 [40]	To investigate the potential use of a composite matrix formed by electrospinning collagen and electrospraying nanofilled hydroxyapatite (nanoHA) to promote skin regeneration.	Nanofilled hydroxyapatite	Not specified	Type 1 collagen	Sample: 5 Wistar rats Defect: Dorsal skin Division: Two defects in the same animal, one control and one with implantation. Time for histopathologic examination: 7, 14, and 21 days	The collagen/nanoHA matrices promote cell adhesion and proliferation, while the nanoHA controllably releases calcium ions to enhance skin repair. The composite membranes with robust mechanical properties were well tolerated in in vivo studies, indicating their promising potential for skin regeneration applications.
Gao et al., 2022 [11]	Development of a biopaper composed of ultra-long hydroxyapatite (HAP) nanowires and carbon fibers (CF) with mechanical properties, flexibility, and biocompatibility to promote skin wound healing.	Previously prepared ultra-long calcium hydroxyapatite nanowires	10 nm	Carbon fibers	Human umbilical vein endothelial cells (HUVECs) were treated with hypoxia and plated in 96-well plates at a density of 2 × 105 cells. They were then exposed to HAPNW/CF biopaper at different doses (0, 62.5, 125, 250, 500, and 1000 μg-mL^{-1}) for 24 h. Cell viability was assessed using the CCK-8 kit according to the manufacturer's instructions.	The biopaper promoted skin healing by continuously releasing calcium ions and stimulating the expression of proteins related to angiogenesis, thereby accelerating healing in a skin trauma model. This study highlights the potential of HAPNW/CF biopaper for large-area skin wound dressings.
Mehedi Hasan et al., 2018 [41]	This study describes the preparation of a novel bioscaffold using alginate-di-aldehyde (ADA)-bonded gelatin (GEL) and nano-hydroxyapatite (nHAp) by lyophilization. The physicochemical properties of these scaffolds were evaluated to determine their suitability for tissue engineering.	Nano-hydroxyapatite derived from eggshells	45 nm	Gelatin (GEL) bound to alginate dialdehyde (ADA)	ADA was prepared by periodic oxidation of alginate. nHAp was prepared from eggshells by a wet-chemical method and showed crystalline properties and nanometric size (~45 nm) as confirmed by XRD and TEM analysis, respectively. The Ca/P ratio of nHAp was validated by EDX	The efficient synthesis of nano-hydroxyapatite (nHAp) and alginate-di-aldehyde (ADA) resulted in a lower molecular weight of ADA due to bond cleavage. The cross-linking, confirmed by ATR-IR analysis, improved the thermal stability. The addition of nHAp reduced porosity and degradation, increasing the biocompatibility of the scaffolds, indicating potential for biomedical applications.

Table 1. *Cont.*

Reference	Objectives	Form of Calcium Hydroxyapatite	Calcium Hydroxyapatite Particle Size	Associated Material	Intervention	Outcomes
Okabayashi et al., 2009 [42]	To create a new wound dressing that combines the biological properties of electrically polarized hydroxyapatite (pHA) and silk fibroin (SF) to help skin wounds heal in this way.	Polarized hydroxyapatite	Not specified	Silk fibroin (SF)	Sample: Porcine Defect: Dorsal skin Section: 3 defect sites in the same animal Time to histopathology: 11, 16, 18 days	The addition of pHA powder to liquid silk (SF) promotes the maturation of fibroblasts and collagen fibers. The pHA modifies the structure of the SF as a carrier, while the pHA powder particles induce fibroblast formation. These promising results highlight the potential of pHA/SF in healing and encourage future research on the polarization conditions of HA powder for fibroblast induction.

A total of 21 articles were presented in the results table. Of these, 90.5% of the authors used hydroxyapatite in combination with other materials, while only 9.5% used it in its pure form. This approach aims to provide greater clarity and understanding of the findings in the literature (Figure 2).

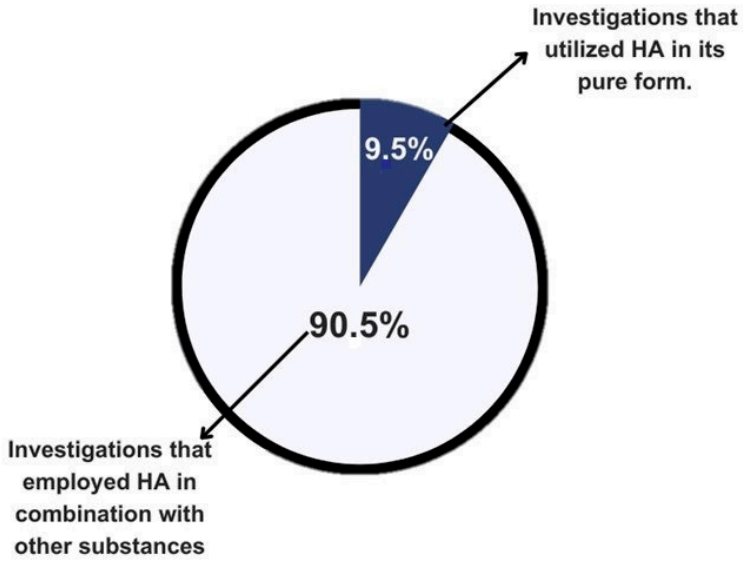

Figure 2. Graphical representation of the literature on the use of calcium hydroxyapatite by purity.

4. Discussion

Considering the growing demand in recent decades for the integration of advanced technologies with the manufacturing of biomaterials and cell culture systems, we have observed a remarkable increase in the development of biomimetic tissues [17]. However, some authors point out that despite scientific advancements, the complexity of manufacturing processes and the costs involved in developing these technologies still represent significant challenges, resulting in a considerable gap in the implementation of these technologies in clinical practice [27,31,42]. The new advancements aim to create immunomodulatory biomaterials, with evaluations that encompass in vivo models and prioritize in vitro models whenever possible [16].

One of the greatest challenges of this new technological era has been the skin, the body's main barrier, which is frequently exposed to various potential hazards. Its recovery is essential to perform its protective functions, both extrinsic and intrinsic, including vitamin D synthesis, immune defense, and excretion, among others [23,43,44]. According to Dam et al., 2023 [45], effective skin regeneration remains one of the biggest challenges due to its complex structure and the need to replicate its diverse functions. Several sectors have directed considerable resources towards the modulation of synthetic skin (in vitro) to mitigate the ongoing legal and ethical issues associated with product testing on skin and the use of animals, achieving gradual results but not highly utilized [16].

Current research on the application of calcium hydroxyapatite (HAp) in skin wound healing reveals a series of benefits, such as increased cell proliferation and promotion of neovascularization. Systematic studies indicate that HAp can stimulate collagen production, cell proliferation, and angiogenesis, which are crucial for skin regeneration [46]. However, there is still a significant lack of long-term studies evaluating the efficacy and safety of these materials in large-scale clinical trials that address existing methodological limitations and expand the understanding of long-term effects, thus ensuring a safe and effective transition to clinical practice [46,47].

This investigation consisted of conducting a comprehensive review of scientific articles indexed in databases, according to established descriptors and criteria for inclusion and exclusion of articles. The main objective was to explore the existing literature on the use of calcium hydroxyapatite and its contribution to the tissue repair process in the skin,

presenting evidence, practical considerations, and possible applications of this substance. Among the various benefits of HAp highlighted in this study, its effectiveness in stimulating wound healing through mechanical, antibacterial, and regenerative properties via induced neovascularization stands out [48].

There is a preference for calcium hydroxyapatite (HAp) nanoparticles due to their high surface-to-volume ratio, which theoretically improves the interaction of this material with cells and tissues, promoting more efficient regeneration [45]. However, this type of ratio can also increase the chemical reactivity of the nanoparticles, potentially causing undesirable cytotoxic effects at certain concentrations [47]. Kawai et al., 2011 [27], report that the nanoparticles have the potential to release calcium ions in the acidic environments found in wounds in a controlled manner. Furthermore, it is important to note that the size of HAp nanoparticles can reach up to 100 nm, facilitating rapid and deep penetration into tissues, ensuring uniform and sustained distribution of therapeutic agents throughout the wound [49]. Despite the potential for controlled release, there are still significant technical challenges related to the safe amount of release, especially in smaller nanoparticles (<50 nm), and it is necessary to ensure that it supports the healing tissue for the required time without causing adverse inflammatory responses [47]. It is found that research addressing the inflammatory response, biocompatibility, and controlled distribution of calcium hydroxyapatite nanoparticles is necessary to ensure complete safety in their clinical application.

The origin of HAp can be natural, found mainly in bones, representing a significant percentage of their composition, or synthetic, a compound of calcium phosphate ($Ca_{10}(PO_4)_6(OH)_2$) similar to an important component present in bone tissue and commonly used as artificial bone [28], which induces osseointegration due to its biocompatibility properties [50]. However, there are two factors that need to be investigated in depth: the origin and the synthesis method, as these could significantly influence the performance of the material [51,52].

According to the findings of this review, the most commonly used form of HA in the presented literature was powder, without prior preparation, with 61.9% of the authors preferring its use in this format [2,19,26,30,32,34–36]. Meanwhile, 19% of the authors considered it important to modify the powder or prepare it before the experiment to facilitate handling of the material according to the application of each study [12,28,29] (Figure 3). This divergence in preparation leads to a lack of standardization in study methods, which could hinder future studies when making direct comparisons of the results [53].

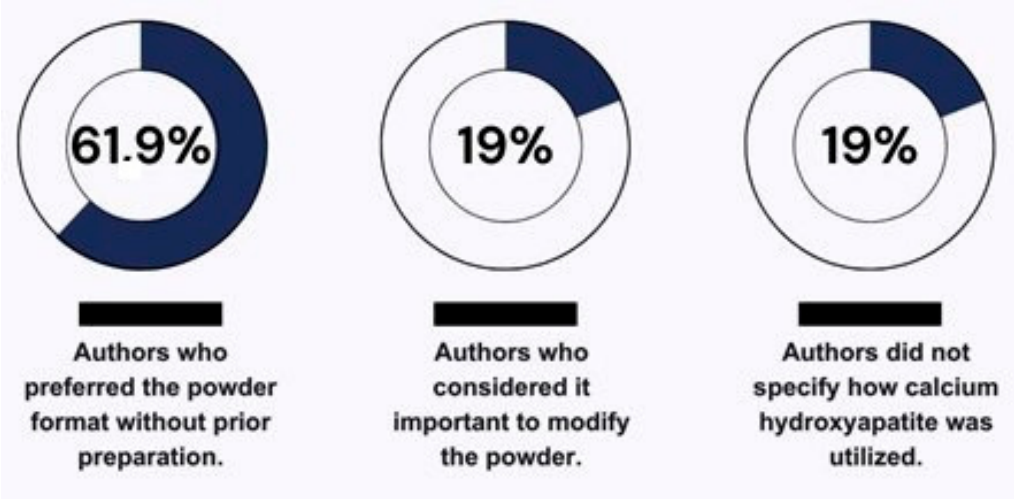

Figure 3. Illustration of the varied utilization of calcium hydroxyapatite by the authors.

During the thorough analysis of the articles presented in Table 1, it was observed that out of the 21 articles, 20 utilized the nanoparticle form of calcium hydroxyapatite. Of these, only five articles described the exact dimensions [2,12,29,40,41]. It is important to emphasize, as mentioned in the previous paragraphs, that knowing the exact size of the HAp nanoparticles is crucial to enable other researchers to optimize their properties for specific applications. Addressing these challenges is essential for effective implementation in clinical practice, ensuring maximum therapeutic efficacy in future studies.

Regarding the associated material, most of the articles used calcium hydroxyapatite in conjunction with other materials. Only two articles [26,27] used it in its pure form. The most employed compound with calcium hydroxyapatite was chitosan [2,12,19,32,35,36], a polymer that stimulates wound healing and improves hemostasis by promoting collagen synthesis by fibroblasts (Figure 4). This substance, with anti-hemorrhagic and antimicrobial properties [54–56], increases the stability of the growth factor in grafts. The combination of chitosan and hydroxyapatite appears promising but requires more long-term clinical studies to validate its efficacy and safety [57] (Figure 4).

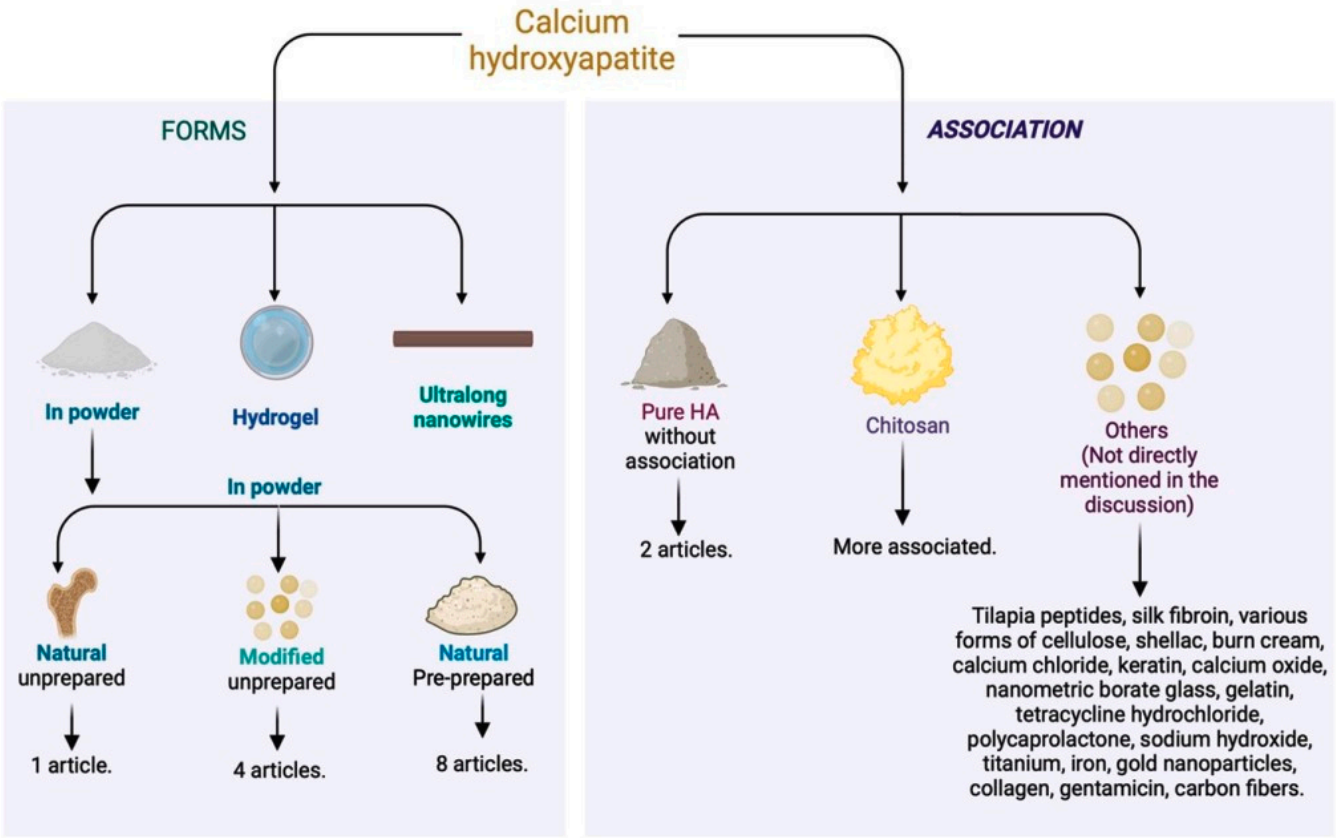

Figure 4. Different forms of calcium hydroxyapatite used in the literature and associated materials for skin tissue regeneration.

The combination of these materials results in antibacterial efficacy and cytocompatibility, accelerating the healing of burns and other skin wounds. In addition to the use of hydroxyapatite, combinations were explored to enhance the action of chitosan. In one study, more promising results were obtained by combining chitosan, hydroxyapatite nanorods, and titanium (Ti) [35]. Another approach involved the incorporation of nano-hydroxyapatite and tetracycline hydrochloride into the polyelectrolyte complex nanofibers of chitosan [34], providing prolonged drug release effects.

Two experimental studies highlighted the promising potential of calcium hydroxyapatite in different wound healing approaches. In the first study, conducted on rabbits, the combination of calcium hydroxyapatite in two concentrations (0.5% and 1.0%) with chitosan, tilapia peptide, and burn ointment (MEBO) demonstrated ideal antibacterial efficacy and cytocompatibility to accelerate the healing process in burns [2]. However, it is crucial to evaluate the applicability of these results in humans through rigorous clinical trials [39]. In the second study, the research focused on the use of pure calcium hydroxyapatite combined with gentamicin to evaluate the feasibility of combining the two materials in diabetic foot ulcers. This study was conducted on rats, and it was observed that collagen matrices containing hydroxyapatite successfully demonstrated cell adhesion and proliferation, allowing a remarkable improvement in skin repair [39]. These results suggest significant potential for the treatment of chronic conditions, but translation to clinical practice requires further validation [58].

The creation of a flexible biopaper, by combining ultralong calcium hydroxyapatite nanowires with carbon fibers, enabled wound healing with mechanical properties through the continuous release of calcium ions and promotion of angiogenesis [11].

Other authors decided to investigate the inorganic hemostatic efficacy of ultralong calcium hydroxyapatite (HA) nanowires through an aerogel. The experiment was conducted on the skin of rats, and the results confirmed the promotion of wound healing, attributed to the water absorption capacity present in the blood, thus concentrating blood platelets [34]. Of the 21 articles listed in the table, calcium hydroxyapatite was used in 76.19% of them in various forms and combinations for the preparation of dressings. The remaining 23.81% of the studies adopted this substance in different approaches, including skin regeneration through intraincisional application [19] and injectable hydrogel [39].

The literature review opened a window of possibilities regarding the application sites and the preference for specific animal models, leading to a study of the various contexts in which these animals were chosen and used. The studies predominantly used rats as experimental models [19,33,34,38,40] and mice [27,29,30]. These rodent species are preferred due to their genetic similarity to humans, availability, and cost-effectiveness [58]. However, extrapolating the results from animal models to humans should be performed with caution, considering the significant physiological differences [59].

Most authors standardized their histopathological analysis periods, with evaluations commonly conducted at 2 days [30,34], 3 days [3], 5 days [19], and 7 days [38,40], highlighting a uniformity in approaches. Another study chose a different schedule, combining hours and days [25], facilitating a deeper understanding of the results. Some researchers selected the histopathological analysis periods based on the specific objectives of their studies [2,12,28,29,42]. Despite the different methodologies for histopathological evaluations, the results were similar among the studies (Figure 5).

The use of calcium hydroxyapatite is not limited to tissue repair in healthy skin. One study addresses the use of hydroxyapatite (HA) as a therapeutic agent for skin repair in diabetic patients with chronic ulcers [39]. Considering this work as part of our investigation highlights its importance as a promising perspective for future research focused on the specific evaluation of lesions associated with or exacerbated by diabetes, resulting in chronic ulcers. Subsequent research is recommended to explore the therapeutic potential of calcium hydroxyapatite in the treatment of these lesions resulting from the diabetic condition.

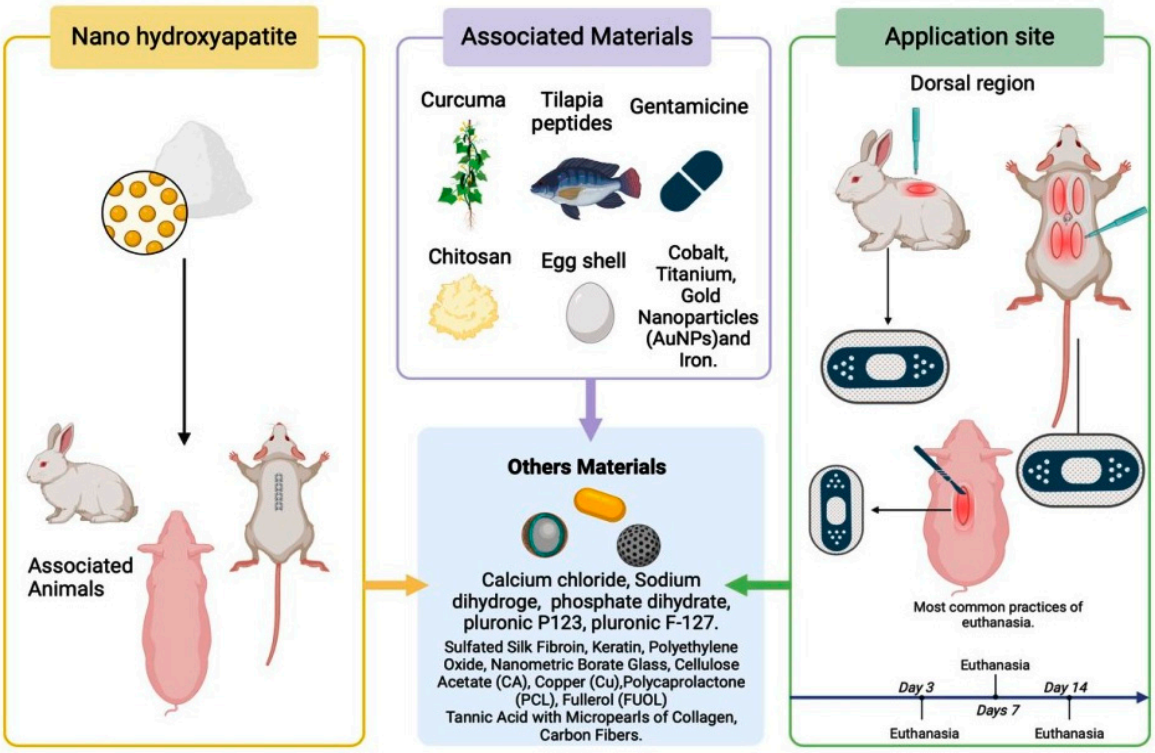

Figure 5. Representation of the components associated with hydroxyapatite, highlighting its use in animals in their respective locations.

5. Conclusions

In conclusion, the findings of this review emphasize the crucial role of calcium hydroxyapatite in skin regeneration and wound healing. While its benefits are well documented in bone regeneration and as a filling material, there is a clear need to explore its effectiveness in skin regeneration further. This is particularly important in medical fields like dermatology and surgery, where treating skin wounds is a top priority. Moreover, the urgency to speed up healing processes, especially in patients with conditions like diabetes, underscores the importance of more research and practical use of calcium hydroxyapatite. Future studies should focus on understanding its potential in its pure form, without other materials, to firmly establish its benefits in skin repair.

The promising results outlined here set the stage for integrating nano-composite biomaterials based on calcium hydroxyapatite into regenerative medicine, offering new possibilities for tissue engineering and wound management. Ultimately, nano hydroxyapatite emerges as a versatile and effective option, poised to transform the field of wound healing and regenerative medicine.

Author Contributions: Conceptualization, P.T.E.C., C.P.C.d.S., D.V.B. and R.L.B.; Methodology, P.T.E.C., C.P.C.d.S., T.M.C., L.P.V.A. and R.L.B.; Formal Analysis, P.T.E.C., C.P.C.d.S., T.M.C. and L.P.V.A.; Investigation, P.T.E.C., C.P.C.d.S., D.V.B. and R.L.B.; Data Curation, P.T.E.C., C.P.C.d.S., T.M.C. and L.P.V.A.; Writing—Original Draft Preparation, P.T.E.C. and C.P.C.d.S.; Writing—Review and Editing, D.V.B. and R.L.B.; Visualization, P.T.E.C., C.P.C.d.S., T.M.C., L.P.V.A. and D.V.B.; Supervision, R.L.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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