

Advances in antioxidant therapies for epidermolysis bullosa management

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Abstract

Epidermolysis Bullosa (EB) is a rare genetic disorder characterized by skin and mucous membrane fragility. Oxidative stress is recognized as a major factor contributing to persistent and recurrent lesions. It can induce genomic damage, protein oxidation, lipid peroxidation, pathological angiogenesis and hypoxia.

Despite the severity of the condition, therapeutic options remain limited. Here we explore the potential role of antioxidant compounds in EB patients, incorporating these compounds as a novel cornerstone in EB management.

Key words: Epidermolysis bullosa, chronic wounds, antioxidants, oxidative stress, wound healing

Introduction

Epidermolysis Bullosa

The skin is characterized by remarkable resistance to mechanical stress and an ability to repair in response to injury. This resistance is primarily conferred by the intricate connection that exists between the epidermis and dermis, which are anchored to the basement membrane through the involvement of multiple structural proteins and extracellular matrix (ECM) components [1]. Therefore, when these proteins are absent or non-functional, the integrity of the skin gets compromised, leading to the formation of recurrent and chronic wounds, as observed in individuals with Epidermolysis Bullosa (EB).

EB is a complex and rare group of genetic skin fragility disorders, where the skin and mucous membranes are prone to damage from minor friction or mechanical trauma. Classification of EB is based on the specific location and depth of blister formation, inheritance patterns and genetic mutations involved. The two most severe forms are Recessive Dystrophic EB (RDEB) and Junctional EB (JEB). Nevertheless, all types of EB are characterized by fragile skin and various degrees of cutaneous manifestations from located blistering to



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more generalized wounding. The molecular defects can also lead to manifestations in other epithelialized tissues, such as the eyes, oral cavity, digestive tract, genitourinary and respiratory systems, leading to a predominant multi-organ impact. The potential widespread involvement, particularly in severe subtypes, can lead to substantial morbidity and mortality [2].

Currently, there is no cure for this disease, although novel therapies such as Vyjuvek (Krystal Biotech) and Filsuvez (Chiesi Farmaceutici) have been approved by the FDA [3–8]. Despite being promising, these therapies are limited to specific subtypes of EB and are associated with high costs, which restrict access to treatment for the EB population. Furthermore, according to Gorell ES et al., in the USA 26% of EB patients spent more than \$1000 per month on wound care supplies [9], while in the European Union the annual cost per patient is estimated at €53.000 overall [10,11].

Therefore, in most places, therapeutic approaches continue to primarily focus on pain and itch management, providing preventive and supportive care for complications such as anemia, malnutrition, and skin cancer [12]. Thus, the management of these patients is primarily supportive, focusing on relieving symptoms related to numerous non-healing wounds and their associated complications, which can be quite challenging [13].

Reactive oxygen species, free radicals and oxidative stress

Oxidative stress plays a pivotal role in the pathophysiology of many different diseases. It is defined as an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the body's ability to neutralize them with antioxidants or repair the resulting damages [14,15]. This imbalance leads to the oxidation of cellular components such as proteins, lipids and DNA, causing genomic damage, protein oxidation, lipid peroxidation, pathological angiogenesis and hypoxia, among others [16–20].

Free radicals are highly reactive molecules or atoms that contain one or more unpaired electrons. Due to their instability, they readily interact with cellular components, causing oxidative damage. These radicals are primarily generated as byproducts of normal cellular processes, such as mitochondrial respiration, and can also be produced through external factors like UV radiation, pollution and inflammation [21]. Once formed, free radicals interact with essential cellular structures, compromising cell function and viability if not promptly neutralized [22].

Among the different types of free radicals, ROS are particularly significant. These molecules are derived from oxygen metabolism and include superoxide anion (O_2^-), hydroxyl radical ($\cdot OH$), and hydrogen peroxide (H_2O_2), and are produced naturally during cellular metabolism [23,24]. While excessive ROS production results in oxidative stress and cellular damage, low levels of ROS play a crucial role in various cell signaling pathways. These pathways regulate processes such as cell proliferation, apoptosis, and immune responses. For instance, ROS modulate signaling cascades involving mitogen-activated protein kinases (MAPKs), nuclear factor kappa B (NF- κB), and hypoxia-inducible factor 1-alpha (HIF-1 α), which are essential for maintaining cellular homeostasis and responding to stress [25–27].

Given the role of oxidative stress in damaging cellular components, understanding how ROS influence wound healing in EB is crucial for developing effective antioxidant therapies.

ROS in wound healing

Wound healing is a complex and dynamic process that aims to restore the integrity and function of skin injury following injury. This process consists of three highly integrated and overlapping phases: hemostasis and inflammation, proliferation and tissue remodeling/scar formation [28]. Each phase involves the coordinated action of various cell types and signaling molecules, with reactive species oxygen (ROS) playing a critical regulatory role throughout the process [29,30].

In the hemostasis and inflammation phase, injury triggers vasoconstriction and the formation of a clot composed of platelets, fibrin and extracellular matrix components, which serve as a scaffold for cells, such as neutrophils and monocytes [31]. Platelets release growth factors such as PDGF (platelet-derived growth factor) and TGF- β , which initiate tissue repair mechanisms [32,33]. At the same time, neutrophils are recruited in high numbers to the site of injury, where they generate ROS through an oxygen-consuming respiratory burst. These low levels of ROS are essential for eliminating pathogens and enhancing the production of chemotactic signals like CXCL8 (IL-8), which attract more immune cells to the site [34]. Neutrophils are cleared by macrophages soon after the injury, which engulf apoptotic neutrophils through a process called efferocytosis [35]. Macrophages also sustain their role in pathogen elimination by producing significant amounts of H₂O₂ as well as nitric oxide, which react to form peroxynitrite and hydroxyl radicals [36,37].

As inflammation progresses, ROS also act as signaling molecules to modulate macrophage polarization, promoting the transition from a pro-inflammatory (M1) phenotype to a reparative (M2) and anti-inflammatory phenotype, which is essential for resolving inflammation and initiating tissue repair [38].

During the proliferative phase, ROS plays a pivotal role in angiogenesis by upregulating vascular endothelial growth factor (VEGF) and activating endothelial cells [18]. This neovascularization ensures adequate oxygen and nutrient supply to regenerating tissue. Additionally, ROS influences the proliferation and migration of fibroblasts and keratinocytes, which are critical for the formation of granulation tissue and re-epithelization and mediates the tissue growth factor- α 1 (TGF- α 1) signaling pathway, improving the expression of fibroblasts growth factor (FGF) [39,40].

In the initial phase of tissue remodeling, ROS regulate the activity of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs), ensuring a balanced degradation and synthesis of ECM. This balance is necessary for proper scar formation and restoration of tissue strength and function [41].

While low levels of ROS are beneficial for these processes, it is crucial to maintain their concentration within a narrow range. Excessive or prolonged ROS production can lead to oxidative stress, causing tissue damage, chronic inflammation, and fibrosis, which are often observed in conditions such as EB [12].

Chronic wounds

According to Atkin et al., a wound is classified as chronic when it has not healed by 40–50% after four weeks despite receiving optimal standard care, which typically includes wound cleaning, debridement, infection control, and appropriate dressings [42]. These wounds often undergo a state of pathological inflammation because of a delayed, incomplete, or poorly coordinated healing process. Unlike normal inflammation, which is resolved after the initial injury,

pathological inflammation is characterized by persistent cytokine production, excessive immune cell infiltration, and impaired resolution mechanisms [43].

Chronic wounds in humans are known to contain elevated levels of oxidative stress, primarily due to persistent inflammation, impaired tissue repair mechanisms, and continuous exposure to ROS. These ROS can originate from neutrophil activity, mitochondrial dysfunction, and environmental factors [44]. These elevated ROS levels damage cellular components such as proteins, lipids, and DNA, further delaying wound healing. Moreover, the degree of chronicity of wounds appears to be influenced by the extended oxidative damage. This relationship was elegantly demonstrated by Kim JH, et al., who showed that in a diabetic mouse model wounds with higher oxidative stress levels exhibited delayed healing and increased inflammation [45]. This study underscores the importance of targeting oxidative stress as a therapeutic approach to improve wound healing outcomes, particularly in conditions like diabetes and EB, where chronic wounds are prevalent.

Chronic wounds are frequently associated with the presence of biofilms, which are structured communities of bacteria encased in a protective extracellular matrix [46]. These biofilms contribute to persistent inflammation and oxidative stress by creating a barrier that protects pathogens from the immune system and antimicrobial treatments [47]. The sustained presence of biofilms delays wound healing, exacerbates tissue damage and promotes wound chronicity. Therefore, managing oxidative stress in chronic wounds also require addressing biofilm formation and dysbiosis-hallmarks of chronic wounds that must be tackled simultaneously to achieve effecting healing [48].

In the context of EB, chronic wounds are particularly prone to dysbiosis and biofilm formation due to constant blistering and skin fragility characteristic of the disease. A longitudinal study from Fuentes I, et al. highlights that wounds in patients with RDEB are often colonized by bacterial species such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Corynebacterium diphtheriae* [49]. Moreover, increased bacterial colonization in RDEB wounds is not only a consequence of the compromised skin barrier but also results from an intrinsic defect in antibacterial immunity, which impairs macrophage and neutrophil activation, further exacerbating bacterial overgrowth [50]. These bacterial colonies form robust biofilms that hinder wound healing by promoting excessive inflammation, increasing oxidative stress, and reducing the efficacy of both topical and systemic treatments. Furthermore, the persistence of biofilms in EB wounds has been associated with a higher risk of infection and complications, including sepsis and systemic inflammation [49].

Excessive inflammation contributes to the development of chronic wounds and fibrosis, interfering with the normal phases of wound healing. In EB, high levels of inflammation have been linked to severe disease phenotypes [51–53] and to gene mutations associated to the metabolism of L-arginine, a substrate for nitric oxide synthesis [54]. The inflammatory response, while crucial for initiating tissue repair, can become dysregulated, leading to a persistent inflammation and fibrotic tissue remodeling. Inflammatory cells, such as macrophages and T-helper 2 (Th-2) cells, release cytokines like TGF- β , which activate dermal fibroblasts and promote ECM production [51]. Additionally, inflammation and oxidative stress creates positive feedback in EB, with TGF- β as intermediary [55,56]. This cytokine not only exacerbates oxidative damage but also stimulates myofibroblasts

differentiation and collagen synthesis, contributing to fibrosis [57]. Repeated cycles of mechanical injury and inflammation in EB lead to a failure to resolve inflammation properly, resulting in the pathological accumulation of ECM and tissue stiffening. Furthermore, the degradation of ECM proteins caused by persistent inflammation can release growth factors that destabilize tissue architecture, reinforcing the fibrotic cycle [51]. This continuous inflammatory state is closely associated with the severity of EB and the chronicity of wounds [58].

Targeting oxidative stress in chronic wounds may help mitigate the persistent inflammation and fibrosis that complicate healing in EB.

Potential therapies related to promoting the antioxidant status on EB

Antioxidants are chemical compounds that neutralize free radicals, preventing the oxidative damage to cellular components such as proteins, lipids, and DNA. Given the significant role of oxidative stress in cellular damage and disease progression, various antioxidant therapeutic strategies have been proposed. These strategies can broadly be categorized into enzymatic and non-enzymatic approaches, each targeting oxidative stress through different mechanisms.

Enzymatic strategies aim to enhance the activity of the body's natural antioxidant defenses, specifically enzymes that play a critical role in detoxifying ROS. Among these enzymes, superoxide dismutase is responsible for converting superoxide anion (O_2^-) into hydrogen peroxide (H_2O_2), a molecule that is less reactive and easier to neutralize [59]. To further detoxify hydrogen peroxide, catalase breaks it down into water and oxygen, thereby preventing the formation of the highly damaging hydroxyl radicals [60]. Another essential enzyme in this process is glutathione peroxidase, which reduces hydrogen peroxide and lipid peroxides by using glutathione (GSH) as a cofactor [61].

In contrast, non-enzymatic strategies involve small molecules and compounds that either directly neutralize free radicals or enhance the body's antioxidant defenses. One such approach is the direct removal of ROS using compounds like N-acetylcysteine (NAC), which not only scavenges ROS but also provides cysteine for GSH synthesis [62,63]. Alternatively, compounds such as α -lipoid acid can boost intracellular GSH levels by enhancing its synthesis or delivering it directly into cells [64]. Other molecules like curcumin and sulforaphane activate the nuclear factor erythroid-2 related factor 2 (Nrf2) pathway, leading to increased production of GSH and other antioxidant defenses [65–67]. Additionally, dietary antioxidants, including vitamin A, C, E, polyphenols and melatonin also play a crucial role in supporting these defenses [68–71].

Beyond enzymatic and non-enzymatic approaches, additional strategies such as inhibiting ROS/RNS production, using mitochondria-targeted antioxidants, and gene therapy approaches are also being explored [72,73]. These strategies aim to prevent oxidative damage at various stages of its progression.

Preclinical and clinical studies have explored the efficacy of various antioxidants in modulating oxidative stress and improving wound healing outcomes. These studies have investigated different routes of administration, including topical, oral, and systemic delivery methods, highlighting the potential of antioxidant therapies to mitigate the damaging effects of oxidative stress in chronic wounds and other conditions characterized by excessive inflammation and fibrosis.

As previously mentioned, there is currently no cure for EB, but oxidative stress is known to play a crucial role in disease progression. Therefore, exploring novel antioxidants and their therapeutic applications remains highly relevant in this context (see Figure 1). In this review, we summarize the main preclinical and clinical studies to date, involving antioxidant compounds and their effects on EB patients, including different routes of administrations (see Figure 2).

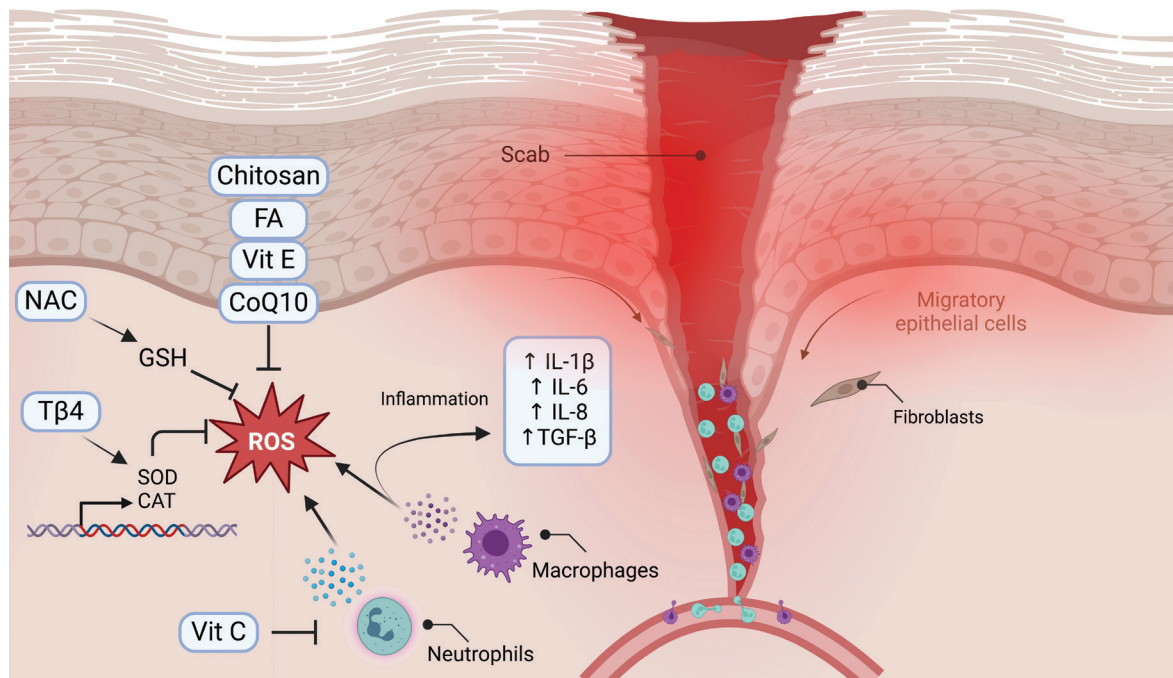


Figure 1. Wound healing and oxidative stress. Main sources of reactive oxygen species (ROS) along with antioxidant molecules described in this review. N-acetylcysteine (NAC), Ferulic acid (FA), Vitamin E (Vit E), Coenzyme Q10 (CoQ10), Vitamin C (Vit C), Thymosin beta-4 (Tβ4), Chitosan. Created with BioRender.com.

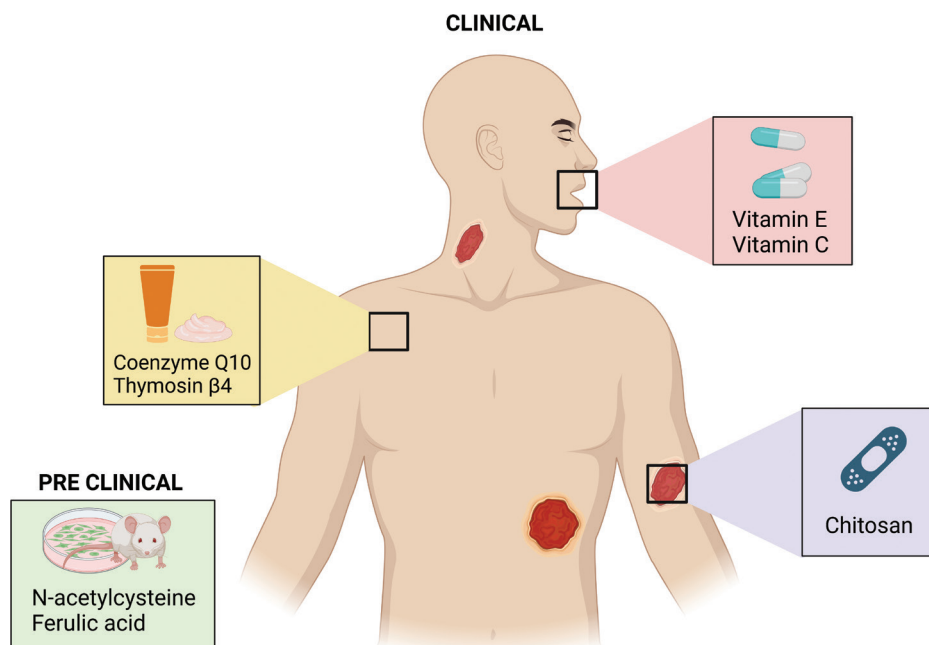


Figure 2. Antioxidant species used in pre-clinical and clinical studies for the treatment of Epidermolysis bullosa. Antioxidant compounds described in this review and its reported administration routes. Created with BioRender.com.

N-acetylcysteine

N-acetylcysteine (NAC), an amino acid derivative, has anti-inflammatory and potent antioxidant properties, acting as a precursor for the synthesis of GSH, a crucial endogenous antioxidant in the human body. GSH plays a vital role in neutralizing harmful ROS and free radicals, which are responsible for oxidative stress and cellular damage. NAC has shown promise in protecting cells from oxidative injury, promoting tissue repair, wound healing and enhancing cellular resilience [74].

Additionally, NAC possesses the ability to disrupt biofilms by breaking down the extracellular polymeric substances (EPS) that protect bacterial colonies, thereby facilitating wound healing and improving the efficacy of antimicrobial treatments [75,76]. This property of NAC is particularly relevant for managing chronic wounds in EB patients, as NAC has been shown to disrupt biofilms formed by *Pseudomonas aeruginosa* and *Staphylococcus aureus* – two bacteria frequently identified in EB wounds [49].

This ability has led to its research and applications in a wide range of dermatological conditions, such as ichthyosis, atopic dermatitis, acne, xeroderma pigmentosum, among others [77].

The topical form of this compound exhibits a bioavailability of less than 3%. It has demonstrated excellent tolerability and a lack of toxic effects through transcutaneous absorption. Due to the intensity of its scent, it is recommended to use preparations containing fragrance to enhance patient adherence to the treatment.

NAC has been evaluated in a pre-clinical study, showing promising results in decreasing inflammation and fibrosis in fibroblasts derived from patients with RDEB [78]. However, the study was conducted on isolated cells from only three patients, highlighting the need for further research to move towards a clinical study.

Ferulic acid

Ferulic acid (FA), a hydroxycinnamic acid widely distributed in plant cells, has emerged as a compelling antioxidant with diverse therapeutic implications. Renowned for its robust free radical scavenging abilities and anti-inflammatory properties, FA has been extensively investigated for its potential benefits in some dermatological conditions such as atopic dermatitis and addressing photoaging [79,80].

Its anti-inflammatory effects are mediated by the activation of Nrf2 at the wound edge, emphasize its potential in addressing oxidative stress and inflammation in wounds. This mechanism suggests a potential therapeutic relevance for managing the cutaneous manifestations of EB. Furthermore, a study revealed that FA can induce migration in primary keratinocytes and facilitate rapid wound closure via modulation of keratin 6a and inhibition of nuclear β -catenin.

As with NAC, FA and derivatives also exhibit antimicrobial properties, inhibiting the growth of bacteria such as *E. coli*, *P. aeruginosa* and *S. aureus*, interfering with biofilm formation [81,82]. This dual action on keratinocyte function and inflammatory regulation positions FA as a promising therapeutic agent for wound healing in EB patients, offering insights into innovative strategies for managing this challenging condition [83].

The evaluation of FA and RRR- α -tocopherol (α T), either administered independently or in association, in RDEB fibroblasts (RDEBF) demonstrated a

consistent reduction in ROS levels. Under basal conditions, 80 μM αT exhibited the highest efficacy, whereas the combination of 40 μM FA and 80 μM αT proved most effective under pro-oxidant stimuli. Notably, in RDEBFs derived from a patient with a severe form of the disorder, treatment with FA+ αT resulted in decreased levels of pSmad2/3 levels and reduced expression of specific pro-fibrotic genes such as collagen I and periostin, which are hallmarks of this disease [78]. However, the expression of other genes encoding pro-fibrotic markers, including tenascin-C and TGF β -induced protein, remained unaltered. These proteins are typically upregulated in EB, play key roles in ECM remodeling and tissue stiffening, and are associated with fibrotic features such as pseudosyndactyly [84,85].

Functional assays revealed that antioxidant treatment, particularly with FA+ αT , diminished the contractile capacity of these fibroblasts. These findings suggest a potential beneficial effect of the antioxidant combination on the fibrotic phenotype in RDEBFs, emphasizing its relevance as a therapeutic strategy for managing oxidative stress in the context of EB.

Vitamin E

Vitamin E (Vit E), is a lipophilic antioxidant known for its ability to neutralize free-radical and protect intracellular organelles from lipid peroxidation. There are eight types of Vit E derivatives; γ -tocopherol is the most abundant tocopherol in diet, whereas RRR- α -tocopherol is the predominant in human tissues and serum [86]. Topical application of vitamin E has been shown to ameliorate photoaging, decreases lipid peroxidation and photocarcinogenesis, reduce MMP-1 transcription levels, and limit thymine dimer formation [87].

In the context of EB, it is hypothesized that a genetic defect may impair the storage or utilization of vitamin E in tissues, potentially requiring additional supplementation [87,88]. Several studies have suggested that RRR- α -tocopherol and its derivatives is the most potent form for therapeutic use [89].

In a study performed in 1974, three patients with (DEB) responded positively to treatment with an initial dose of 600 IU per day, followed by a maintenance dose of 300 IU. This positive response was reflected in a notable reduction in blister formation compared to when they were not receiving vitamin E supplementation. Collagenase levels were also analyzed in two patients, showing increased activity in blister areas compared to unaffected skin.

After 30 days of vitamin E therapy, collagenase levels in the affected areas returned to normal [90].

In a study performed in 1973, two sisters with DEB were treated with 1600 IU of vitamin E per day, divided into four doses of 400 UI each. The treatment lasted for 8 weeks, followed by an 8-week placebo period. Both showed marked reduction in blister formation while taking the vitamin E compared to placebo. Neither noticed any other effects, adverse or beneficial, while on either medication [91].

More recently, the efficiency of vitamin E was studied on Kindler EB (KEB)-derived cells. KEB keratinocytes exhibited increased UV-B sensitivity, characterized by upregulation of pro-inflammatory cytokines (IL-1 β , IL-6, and TNF- α), p38 hyperactivation, and elevated levels of ROS. Treatment with Trolox, a vitamin E analog, significantly reduced intracellular ROS levels and p38 activation in KEB patient's keratinocytes, suggesting that UV-B induced apoptosis can be mitigated by Trolox as a topical antioxidant treatment [92].

While some case reports support the efficacy of vitamin E as a treatment for EB, others have shown no effects [93]. It is important to note that the existing literature predominantly comprises older case reports and recent comprehensive studies are lacking. A double-blind study with a larger cohort of patients is needed to conclusively determinate the therapeutic potential of vitamin E in EB management.

Coenzyme Q10

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a liposoluble antioxidant that plays a pivotal role in mitochondrial electron transport chain function. Beyond the well-established role in cellular energy production, CoQ10 has gained significant attention for its antioxidant capacity, as their redox forms within the mitochondrial membrane enhance the efficiency of the electron transport, which facilitates the recycling of other antioxidants, such as vitamin C and vitamin E, and directly combats free radicals or oxidants, by reducing and neutralizing the harmful compounds [94].

The antioxidant potential of this coenzyme has prompted research into its potential use as a treatment for chronic diseases in which oxidative stress and inflammation are hallmarks, such as cardiovascular, renal, chronic pulmonary and neurodegenerative diseases [95]. Some skin conditions like psoriasis and dermatitis have also been studied with promising results [96–98].

Studies suggest that CoQ10 may have a cutaneous healing effect *in vivo* and *in vitro* [98,99]. Currently, vehicles are being tested to enhance the solubility and penetration of coenzyme CoQ10 for improved wound healing, since CoQ10 has a high molecular weight, high lipophilicity and poor solubility [100].

A phase 1 clinical trial ([NCT02793960](https://clinicaltrials.gov/ct2/show/study/NCT02793960)) sponsored by Shasa Hu was performed in 2016 to evaluate the safety and tolerability of a topical 3% q10 cream (BPM31510) in EB patients aged 12 years and older. The trial's secondary objectives included evaluating pharmacokinetics and assessing factors such as quality of life, healing time, resistance to trauma and decrease in pain and blister formation. Although the study results for the phase 1 clinical trial have not been posted, preliminary evidence suggests that BPM31510 demonstrated efficacy and was well tolerated in patients with EB. These encouraging results have led to FDA Orphan-Drug Designation and the planning of a phase II/III trial in collaboration with Debra of America [101].

Vitamin C

Vitamin C, also known as ascorbic acid (AA) is a water-soluble molecule with potent antioxidant effects, widely recognized for its role in neutralizing free radicals and protecting cells from oxidative damage. This essential vitamin is a key cofactor in the biosynthesis of collagen, a critical component of the ECM that provides structural integrity to the skin and facilitates wound healing [102,103]. Moreover, during the inflammatory phase of wound healing, AA is required for neutrophil apoptosis and clearance by macrophages [104,105]. Since this step is often dysregulated in chronic wounds, adequate levels of AA may help resolve inflammation and facilitate the transition to the proliferative phase of healing. Given these properties, AA has been used to enhance wound healing

in a randomized, double-blind, placebo-controlled trial involving patients with chronic foot ulcers. Supplementation with 500 mg of slow-release AA daily significantly improved healing outcomes such as ulcer size reduction and healing time. After eight weeks of treatment, patients receiving AA showed a median healing of 100%, compared to a 14% increase in ulcer size in the placebo group. Notably, all patients in the AA group achieved healing without amputation, while 44% of the control group did not heal their ulcers [106].

In patients with EB, studies have identified low plasma AA levels in a significant proportion of individuals, particularly those within severe RDEB subtype [107]. This deficiency is often attributable to dysphagia, oral and esophageal blisters and dietary limitations associated with the disease.

Considering these challenges, the development of topical delivery systems, such as AA-infused dressings or scaffolds, may offer an effective alternative. These systems can provide controlled and sustained release of AA directly to the wound site, maximizing its therapeutic benefits [108]. This method of delivery bypasses gastrointestinal absorption issues and leverages AA's ability to neutralize ROS and reduce inflammation, which are all critical for wound healing in EB patients.

Thymosin Beta-4

Thymosin beta-4 (T β 4) is a highly conserved peptide found in several tissues in the human body including brain, liver, kidney, testis and cell lines like macrophages, platelets and lymphocytes [109]. This peptide exhibits diverse biological functions which include anti-inflammatory [110], antiapoptotic, pro-angiogenic and re-epithelialization properties, promoting regeneration and wound repair [111]. T β 4 has previously demonstrated effectiveness in dermal wounds, corneal wound healing [112], heart disease [113], kidney disease [114], among others [115].

Its efficacy in dermal healing has been probed in various animal models, including rats and mice as well as in 3S human studies [116] by accelerating cellular migration and tissue remodeling [117]. T β 4 also prevents damage from elevated levels of ROS by stimulating the expression of antioxidant enzymes such as superoxide dismutase and catalase at transcriptional and translational levels [113].

A phase 2 randomized, placebo-controlled clinical trial ([NCT00311766](#)) conducted by RegeneRx Biopharmaceuticals, Inc. assessed the safety and efficacy of T β 4 in patients with EB. T β 4 was administered using a topical hydrogel formulation containing placebo, 0.01%, 0.03% and 0.1% of T β 4 (w/w). No statistical differences were seen in healing at any of the doses over the placebo and the trial was completed with fewer patients than expected. Despite this, a tendency toward accelerated healing was noted in the group treated with 0.03% of T β 4 [116].

In 2017, RegeneRx and Lenus Therapeutics, LLC (Lenus), received permission from the FDA to sponsor a phase 3 clinical trial using a topical gel formulation of 0.03% T β 4 (RGN-137) to treat patients with EB. In 2018 started a small phase 2 open trial ([NCT03578029](#)) and they reported that 3 patients have been enrolled and 1 of them positively responded to this formulation. Nevertheless, no further clinical activity has been reported to date and the study ended by business decision [118].

Chitosan

Chitosan is a natural polymer derived from chitin (a component of exoskeletons of crustacean shells and insects). It is a complex carbohydrate, composed of long chains of polysaccharides made up of units of D-glucosamine and N-acetyl-glucosamine [119].

Chitosan has several interesting properties. It exhibits immune-boosting, anti-inflammatory, antitumoral, and antioxidant properties [120,121]. In addition, chitosan inhibits the growth of a wide variety of fungi, yeasts, and bacteria [119].

Regarding the latter, many *in vitro* and *in vivo* studies have demonstrated chitosan's redox-regulatory activity. It effectively inhibits the production of ROS and prevents lipid oxidation, resulting in a notable decrease in serum free fatty acids and malondialdehyde concentrations. Furthermore, chitosan demonstrates the capacity to boost intracellular antioxidant enzymes within biological systems [122].

Besides its antibacterial and antioxidant properties, it has hemostatic properties and acts as a bioadhesive material, which is a very promising alternative for wound dressings [123]. A clinical trial is currently recruiting to evaluate the efficacy and safety of wound dressings formulated with chitosan in chronic wounds ([NCT05312762](#)).

On the other hand, a small pilot study in 2014 investigated the efficacy of a natural fiber dressing, made from natural acylated chitosan (KytoCel®), in children with EB. Early results showed that wound healing improved significantly in nine out of ten children, even in those with the most severe form of EB (recessive dystrophic), indicating that this dressing can be helpful in treating recalcitrant wounds in infant EB patients [124].

Conclusion

In summary, this exploration of antioxidants in the context of EB sheds light on promising avenues for enhancing wound healing and mitigating inflammation on individuals with this rare and hard to treat genetic disorder. The diverse range of antioxidants discussed-whether a single compound or in synergistic combinations- offers potential interventions that could significantly improve clinical outcomes and quality of life in EB patients.

Despite this, it is important to exercise caution, as excessive antioxidant use has been associated with potential adverse effects, including an increased risk of certain types of cancer. Some studies suggest that high doses of antioxidants, such as vitamin C and vitamin E, may interfere with the body's natural oxidative balance, potentially promoting the survival of damaged cells and contributing to tumor progression [125,126]. Beyond this increased risk of cancer, excessive antioxidant supplementation can interfere with essential oxidative processes, increase the risk of hemorrhage, cause nutrient imbalances, and weaken the immune response [127,128]. Therefore, it is crucial to carefully consider the dosage, duration, and patient-specific factors when using antioxidants to manage wound healing. Moreover, in RDEB patients, who are at increased risk of developing squamous cell carcinoma (sCC) [129,130], excessive antioxidant use may inadvertently promote the survival of damaged cells, potentially contributing to tumor progression [130].

Additionally, it is important to recognize that oxidative stress is often a secondary contributor to disease pathology in EB. Consequently, while antioxidant therapies may enhance antioxidant defense mechanisms, they might not significantly impact the overall progression of the disease if the primary drivers of pathology remain undressed. This highlights the importance of a multifaceted therapeutic approach that targets both oxidative stress and the underlying genetic and inflammatory components of EB.

As summarized in Table 1, clinical trials for EB-specific interventions remain limited, with ongoing studies investigating agents like thymosin beta-4 (T β 4), N-acetylcysteine (NAC), and coenzyme Q10 (CoQ10). These efforts underscore the need for further rigorous clinical research to validate the efficacy and safety of antioxidant therapies and to translate these findings into effective, patient-centered treatments.

Table 1. Summary of clinical trials and studies utilizing antioxidant compounds for the treatment of Epidermolysis bullosa.

Type of study	Status	Investigation drug	Formulation	EB Type
Case report [90]	Completed	Vitamin E (RRR- α -tocopherol)	Orally administered	DEB
Case report [91]	Completed	Vitamin E (RRR- α -tocopherol)	Orally administered	DEB
Phase 1 clinical trial [101] (NCT02793960)	Completed	BPM31510 (Coenzyme Q10)	Topical cream	All EB types
Phase 2 clinical trial [116] (NCT00311766)	Terminated (lack of patient's availability and expiration of the study drug)	Thymosin beta 4	Topical cream	All EB types
Phase 2 clinical trial [118] (NCT03578029)	Terminated (business decision)	RGN-137 (Thymosin beta 4)	Topical gel	JEB, RDEB
Case report [124]	Completed	Chitosan	Wound dressings (topical)	All EB types

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

Conceptualization: EC, IF, AM. Data curation: IF. Funding acquisition: IF. Writing – original draft: EC, IF, AM. Writing – review and editing: IF, FP, AM, MLC, EC.

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Data availability

All of the data that support the findings of this study are available in the main text.

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