COCOA (*THEOBROMA CACAO*) AS A NATURAL THERAPEUTIC AGENT FOR WOUND HEALING: A COMPREHENSIVE REVIEW

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ABSTRACT – *Wound healing is a complex biological process involving hemostasis, inflammation, proliferation, and tissue remodeling. Despite advances in wound management, chronic wounds remain a significant clinical challenge due to persistent inflammation, oxidative stress, microbial infection, and impaired tissue regeneration. Consequently, increasing interest has focused on plant-derived bioactive compounds as potential multifunctional therapeutic agents. Among these, Theobroma cacao L. has emerged as a promising natural resource because of its rich phytochemical composition, including flavanols, procyanidins, phenolic acids, methylxanthines, polysaccharides, fatty acids, vitamins, and minerals. These bioactive compounds exhibit antioxidant, anti-inflammatory, antimicrobial, angiogenic, and collagen-stimulating properties that collectively support tissue repair. This review summarizes the phytochemical composition of T. Cacao, its mechanisms of action, and current evidence supporting its wound-healing potential. In vitro, studies demonstrate that cocoa-derived compounds reduce oxidative stress, enhance fibroblast viability, stimulate collagen synthesis, and improve keratinocyte function. Animal studies further show accelerated wound closure, enhanced re-epithelialization, and improved tissue organization following topical application of cocoa extracts. Clinical studies, although limited, suggest beneficial effects on skin elasticity, hydration, and collagen metabolism. The review also highlights the emerging use of cocoa pod husks as sustainable sources of bioactive pectin for hydrogels, tissue engineering, and advanced wound dressings. Overall, current evidence supports T. cacao as a potential multifunctional natural therapeutic agent for wound healing, although standardized formulations and well-designed clinical trials are required before widespread clinical application*.

Keywords: Antioxidant, inflammation, polyphenols, skin regeneration, and wound healing

INTRODUCTION

As the body's primary protective barrier, the skin shields underlying tissues from physical injury, microbial invasion, and environmental stress while contributing to thermoregulation, immune defense, and fluid homeostasis (Fahimirad & Satei, 2025). Following tissue injury, repair proceeds through a coordinated sequence of overlapping events involving hemostasis, inflammation, proliferation, and remodeling (Y. Jiang *et al*., 2024). Under normal conditions, this response restores tissue integrity efficiently; however, diabetes, aging, infection, impaired circulation, oxidative stress, and persistent inflammation can interfere with one or more stages and lead to chronic wounds. Conditions such as diabetic foot ulcers, pressure ulcers, venous leg ulcers, and burns may consequently require prolonged care and can substantially affect quality of life and healthcare expenditure.

Contemporary wound care includes antibiotics, antiseptics, growth factors, and advanced wound dressings, which have contributed substantially to clinical management. Nevertheless, important limitations remain. Inappropriate or excessive antibiotic exposure contributes to antimicrobial resistance, while some synthetic interventions may cause adverse reactions or provide limited support for the biological processes required for tissue regeneration. These limitations have encouraged investigation of natural products, particularly medicinal plants, as potential complementary sources of multifunctional wound-healing agents (Yadav *et al*., 2020).

Wound dressing has improved patient care considerably. However, they are not without limitations. Excessive use of antibiotics has contributed to the growing problem of antimicrobial resistance, while some synthetic treatments may cause adverse reactions or fail to actively support tissue regeneration. As a result, researchers have increasingly turned their attention to natural products, particularly medicinal plants, which contain a wide range of bioactive compounds capable of acting on multiple biological pathways involved in wound repair (Yadav *et al*., 2020). Many plant-derived compounds possess antioxidant, anti-inflammatory, antimicrobial, and immunomodulatory properties, making them attractive alternatives or complementary therapies for chronic wound management.

Among these natural resources, *Theobroma cacao L*. has attracted attention beyond its established importance as a cocoa crop. Cocoa beans contain flavan-3-ols such as catechin and epicatechin, procyanidins, phenolic acids, methylxanthines, minerals, and fatty acids. Several of these constituents have been associated with antioxidant and anti-

inflammatory effects and with biological processes relevant to skin repair (Martina De Feo *et al*., 2020). Cocoa extracts have also demonstrated antimicrobial activity against wound-associated microorganisms, including *Staphylococcus aureus* and *Staphylococcus epidermidis*, together with improved wound contraction in experimental models (Budi Tunjung-Sari *et al*., 2016).

More recently, cocoa-processing by-products have attracted comparable interest. Cocoa pod husks, historically treated as agricultural waste, contain pectin, phenolic compounds, and other potentially useful constituents (Mares-Bou *et al*., 2025). These materials are increasingly being investigated for incorporation into wound dressings, drug-delivery platforms, and tissue-engineering systems (Fadda *et al*., 2025).

Despite these findings, evidence concerning cocoa and wound healing is distributed across studies of phytochemistry, cell biology, animal models, skin health, and biomaterials. The objective of this review is to synthesize the available evidence on the wound-healing potential of *T. cacao*, with emphasis on its phytochemical constituents, proposed biological mechanisms, preclinical and clinical findings, and emerging applications of cocoa pod husk-derived materials. The review also identifies important limitations and research gaps that should be addressed before cocoa-based interventions can be translated into routine wound care.

WOUND HEALING BIOLOGY

Wound healing is a coordinated biological response that restores tissue integrity after injury. The process does not occur as a series of strictly independent steps; instead, hemostasis, inflammation, proliferation, and remodeling overlap in time and are linked through interactions among platelets, immune cells, fibroblasts, keratinocytes, endothelial cells, extracellular matrix components, and signaling mediators. Disturbance of this coordination can prolong inflammation, impair tissue formation, and increase the likelihood of chronic wound development (Ozgok Kangal & Kopitnik, 2025).

Acute wounds generally progress toward closure within several weeks when local and systemic conditions are favorable. Chronic wounds, in contrast, may become trapped in a persistent inflammatory state associated with infection, oxidative imbalance, inadequate perfusion, or systemic disease such as diabetes. The resulting impairment of cell function and tissue regeneration delays closure and compromises tissue quality (Wilkinson & Hardman, 2023). A clear understanding of these biological events is therefore important when evaluating potential wound-healing agents.

Hemostasis Phase

Immediately after injury, disruption of blood vessels activates mechanisms that rapidly limit blood loss. Local vasoconstriction is followed by platelet adhesion and aggregation at exposed extracellular matrix surfaces, producing a temporary hemostatic plug. Activated platelets also release signaling molecules, including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF), thereby linking clot formation with subsequent inflammatory and regenerative responses (Opneja *et al*., 2019).

The fibrin-rich clot additionally forms a provisional extracellular matrix. Besides stabilizing the injured area, this matrix helps restrict microbial entry and provides a temporary substrate through which inflammatory cells and later fibroblasts can migrate (Nurden *et al*., 2008).

Inflammatory Phase

Inflammation follows hemostasis and is particularly active during the first several days after injury. Its principal functions are to remove microorganisms and damaged material and to create conditions that permit subsequent tissue formation (Y. Jiang *et al*., 2024). The response must remain appropriately controlled: inadequate inflammation can compromise host defense, whereas an excessive or prolonged response can prevent progression toward repair (Fahimirad & Satei, 2025).

Neutrophils are recruited early to the wound and contribute to microbial clearance through phagocytosis and the release of antimicrobial enzymes and reactive oxygen species (ROS). ROS participate in host defense, but excessive accumulation can damage cells and extracellular matrix components and can contribute to delayed healing, particularly in chronic and diabetic wounds (Hunt *et al*., 2024).

Within approximately 48–72 hours, macrophages become prominent within the wound environment (Krzyszczyk *et al*., 2018). Early pro-inflammatory macrophages produce mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), supporting pathogen clearance (Kuninaka *et al*., 2022). As repair progresses, macrophage activity shifts toward an anti-inflammatory, pro-reparative phenotype associated

with interleukin-10 (IL-10), TGF-β, fibroblast activity, angiogenesis, extracellular matrix formation, and remodeling. Failure to achieve this transition is characteristic of chronic wounds (Krzyszczyk *et al*., 2018).

Several signaling networks help determine the balance between inflammation and tissue protection. Nuclear factor-kappa B (NF-κB) drives expression of numerous pro-inflammatory mediators, whereas nuclear factor erythroid 2-related factor 2 (Nrf2) promotes antioxidant defenses through induction of enzymes such as superoxide dismutase, catalase, and glutathione peroxidase (Martina De Feo *et al*., 2020). Appropriate regulation of these pathways is important for progression through wound healing (Cai *et al*., 2023). Plant polyphenols are of particular interest because some can influence inflammatory signaling and cellular antioxidant responses simultaneously (Singh *et al*., 2020).

Proliferative Phase

The proliferative phase marks the period in which provisional repair is converted into newly formed tissue. It commonly becomes prominent several days after injury and involves fibroblast expansion, extracellular matrix deposition, angiogenesis, re-epithelialization, and wound contraction (Ozgok Kangal & Kopitnik, 2025; D. Jiang *et al*., 2023).

Fibroblasts generate major extracellular matrix constituents, including collagen, fibronectin, elastin, hyaluronic acid, and proteoglycans (Talbott *et al*., 2022). Type III collagen is particularly important in early granulation tissue formation (Cialdai *et al*., 2022). Fibroblast activity is influenced by growth factors such as PDGF, fibroblast growth factor (FGF), TGF-β, and VEGF, while endothelial cells form new vessels to improve oxygen and nutrient delivery to the regenerating tissue.

At the same time, keratinocytes migrate and proliferate across the wound to restore epidermal continuity (Wilkinson & Hardman, 2023). Myofibroblasts contribute to contraction of the wound margins and maturation of the newly deposited matrix (Sue Porter, 2007). These processes collectively rebuild tissue architecture and establish the conditions required for remodeling. Accordingly, interventions that support fibroblast activity, collagen formation, angiogenesis, and keratinocyte migration while limiting excessive oxidative stress may improve repair (Yahfoufi *et al*., 2018).

Remodeling Phase

The remodeling phase represents the longer-term maturation of repaired tissue and may continue for months or years. During this period, the extracellular matrix is reorganized and the mechanical properties of the scar progressively improve (Sangha *et al*., 2024).

Collagen deposited during proliferation is reorganized as type III collagen is progressively replaced by the stronger type I form. Fiber alignment also changes in response to mechanical forces, with matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) regulating turnover (Mathew-Steiner *et al*., 2021). Excessive MMP activity can weaken the repair by accelerating matrix degradation, whereas inadequate turnover can favor excessive fibrosis and scar formation (Bourboulia & Stetler-Stevenson, 2010).

Fibroblast numbers gradually decline through apoptosis as extracellular matrix synthesis decreases. Similarly, newly formed blood vessels regress once metabolic demands diminish (Puhaindran, 2008), leaving behind a mature vascular network capable of maintaining tissue viability. Healed skin generally does not recover the full mechanical strength of uninjured tissue, although tensile strength increases progressively during maturation and may reach approximately 70–80% of normal skin. Scar characteristics depend on collagen organization, vascular changes, resolution of inflammation, and mechanical loading. Abnormal remodeling can contribute to hypertrophic scars, keloids, and other forms of impaired repair (Sangha *et al*., 2024).

WOUND HEALING CHALLENGES AND PLANT THERAPEUTICS

Successful healing depends on interacting with local and systemic conditions. Local determinants include wound dimensions and depth, microbial burden, tissue perfusion, oxygen availability, moisture, and repeated mechanical stress (Guo & DiPietro, 2010). Inadequate oxygenation can compromise ATP generation and collagen synthesis, whereas infection can prolong inflammation and increase extracellular matrix degradation.

Systemic influences are equally important. Aging can reduce fibroblast proliferation and collagen production, while diabetes can disrupt immune responses, angiogenesis, and growth-factor signaling (Wallace & Zito, 2019). Hyperglycemia is also associated with increased ROS generation and advanced glycation end-product formation, both of which favor persistent inflammation and delayed repair. Nutritional deficiencies, obesity, smoking, alcohol exposure, corticosteroid therapy, chemotherapy, and vascular disease may further

interfere with normal healing (Anderson & Hamm, 2012).

Oxidative stress is particularly relevant because excessive ROS can damage cellular components, inhibit fibroblast proliferation, impair angiogenesis, interfere with collagen deposition, and activate inflammatory signaling (Singh *et al*., 2020). This makes agents that can simultaneously influence redox balance, inflammation, and tissue regeneration attractive candidates for further investigation.

Plant-derived therapeutics have therefore been investigated as potential adjuncts for wound management because many contain groups of compounds with complementary biological activities (Sun *et al*., 2024). Polyphenols, flavonoids, phenolic acids, terpenoids, polysaccharides, and alkaloids have been associated with antioxidant, anti-inflammatory, antimicrobial, angiogenic, collagen-related, and immunomodulatory effects (Rudrapal *et al*., 2022). Selected examples are presented in Table 1. Their ability to affect several processes involved in repair is particularly relevant to chronic wounds, where multiple pathological mechanisms may coexist.

Theobroma cacao is of particular interest within this broader group because it contains flavan-3-ols, including catechin, epicatechin, and procyanidins, as well as phenolic acids, methylxanthines, polysaccharides, minerals, and unsaturated fatty acids. The principal cocoa phytochemical groups and their potential relevance to wound healing are summarized in Table 2.

These constituents may influence several processes associated with tissue repair, including oxidative stress, inflammatory signaling, extracellular matrix turnover, and cellular responses. Together, the reported activities provide a rationale for examining cocoa as a multifunctional candidate for wound-healing applications (Sitarek *et al*., 2024).

PRECLINICAL AND CLINICAL STUDIES SUPPORTING THE WOUND-HEALING POTENTIAL OF THEOBROMA CACAO

Research on Theobroma cacao has expanded from its established nutritional and cardiovascular applications toward possible roles in skin and tissue biology (Sitarek *et al*., 2024). Earlier work emphasized antioxidant and cardiometabolic effects (Scapagnini *et al*., 2014), whereas more recent studies have examined mechanisms relevant to tissue repair, including redox regulation, inflammation, angiogenesis, collagen deposition, extracellular matrix remodeling, and re-epithelialization (Maliha Shahbaz *et al*., 2018).

The evidence base nevertheless remains uneven. Direct wound-healing studies are concentrated in cell and animal experiments, while the available human studies have mainly assessed skin condition rather than treatment of established wounds. The findings are therefore useful for identifying plausible mechanisms and therapeutic directions, but they should not be interpreted as definitive evidence of clinical wound-healing efficacy.

In Vitro Studies

Antioxidant Protection Against Oxidative Stress

Oxidative stress is one of the biological factors that can delay repair. Excessive ROS can interfere with fibroblast proliferation and keratinocyte migration, damage extracellular matrix proteins, and sustain inflammatory signaling (Xu *et al*., 2024). Consequently, restoration of an appropriate cellular redox environment is an important consideration in the development of wound-healing interventions (Nabavi *et al*., 2015).

Experimental studies indicate that cocoa polyphenols can reduce intracellular ROS and support endogenous antioxidant defenses (Rimbach *et al*., 2009). In human dermal fibroblasts, cocoa-derived constituents have been associated with improved viability under oxidative stress and lower production of inflammatory mediators (Mello *et al*., 2022; Mares-Bou *et al*., 2025). These effects have been linked particularly to flavanols and phenolic acids, which can scavenge reactive species and influence antioxidant signaling (Magrone *et al*., 2017).

Recent work on pectin obtained from cocoa pod husks has also reported good cytocompatibility with human dermal fibroblasts. At appropriate concentrations, cocoa-derived pectin reduced oxidative stress and modulated inflammatory mediators, indicating that cocoa-processing residues may retain constituents relevant to tissue repair (Bevilaqua *et al*., 2026).

Fibroblast Proliferation and Collagen Production

Fibroblasts are central to tissue formation because they synthesize collagen and other extracellular matrix components that provide structural support during regeneration (Bainbridge, 2013). Experimental evidence indicates that cocoa polyphenols can support fibroblast survival and preserve collagen-related activity under oxidative stress (Abdul Karim *et al*., 2014).

Cacao powder has also been associated with increased collagen synthesis and lower expression of

matrix metalloproteinase-1 (MMP-1), an enzyme involved in collagen degradation (Kim *et al*., 2016). Limiting excessive MMP activity can help preserve extracellular matrix integrity during remodeling (Mukherjee *et al*., 2013). In parallel, enhanced antioxidant enzyme activity may protect fibroblasts from oxidative injury. The combined effects suggest that cocoa-derived flavanols could influence both

Table 1: Selected medicinal plants and their principal wound-healing functions

Plant	Aurthors	Study type	Main wound-healing findings
Aloe vera	Hekmatpou *et al*., 2019	Systematic review of human clinical trials	Accelerated wound healing and reduced inflammation.
Curcuma longa	Pitic *et al*., 2026	In vitro study	Enhanced epithelial migration and antimicrobial activity.
Punica granatum	Halicioglu *et al*., 2025	Animal study (rat)	Improved granulation tissue formation and reduced inflammation.
Calendula officinalis	Giana Silveira Giostri *et al*., 2022	Randomized clinical trial (human)	Accelerated re-epithelialization and increased healing speed in acute hand and finger wounds
Plantago major	Kartini *et al*., 2021	Animal study (hyperglycemic rats)	Accelerated wound closure and stimulated fibroblast activity.
Achillea millefolium	Ghasemi *et al*., 2023	Animal study (rats)	Increased collagen deposition and accelerated wound closure.
Eucalyptus globulus	Indrawati *et al*., 2021	Animal study (Wistar rats)	Enhanced angiogenesis through increased VEGF expression.
Panax ginseng	Namgoong *et al*., 2019	In vitro (human diabetic fibroblasts)	Enhanced fibroblast proliferation, collagen synthesis, and VEGF/TGF-β1 production.
Calotropis procera	Nunes *et al*., 2024	Clinical study (leprosy patients)	Promoted faster healing of chronic plantar ulcers
Musa sapientum	Cheng *et al*., 2024	Animal study (diabetic rats)	Accelerated wound closure and collagen deposition

Table 2: Major phytochemical groups present in Theobroma cacao and their potential roles in wound healing

Compound Group	Major Components	Biological Functions Relevant to Wound Healing	Reference
Flavanols	Catechin, Epicatechin	Antioxidants, anti-inflammatory, collagen synthesis, angiogenesis	Sitarek *et al*., 2024
Procyanidins	Dimers to decamers	ROS scavenging, antimicrobial activity, extracellular matrix protection	Martina De Feo *et al*., 2020
Phenolic acids	Gallic acid, Protocatechuic acid, Ferulic acid	Antioxidant, anti-inflammatory	Belwal *et al*., 2022
Methylxanthines	Theobromine, Caffeine	Vasodilatory and microcirculatory effects, possible anti-inflammatory and analgesic activity	Gu & Lambert, 2013
Polysaccharides	Pectin, cellulose, hemicellulose	Hydrogel formation, wound dressing matrices	Vriesmann & de Oliveira Petkowicz, 2017

collagen formation and its degradation, although direct wound-healing confirmation remains necessary (Lee *et al*., 2024).

Keratinocyte Function and Re-Epithelialization

Effective wound closure requires keratinocytes to migrate and proliferate across the injured surface so that epidermal continuity can be restored (Mao *et al*., 2025). Experimental work with human keratinocytes indicates that cocoa-derived constituents can increase hyaluronic acid production, support cellular hydration, and strengthen antioxidant defenses.

Cacao powder has additionally been reported to alter expression of genes associated with skin-barrier maintenance (Lee *et al*., 2024) and to protect keratinocytes from UV-associated oxidative injury (Kim *et al*., 2016). Because these studies were primarily designed to examine skin aging rather than wound repair, their findings should be regarded as mechanistic support rather than direct evidence of therapeutic wound closure.

In Vivo Studies

Rabbit Skin Infection Model

Direct wound-healing evidence includes a rabbit skin model in which researchers evaluated ethanolic cocoa extract against wounds infected with Staphylococcus aureus and Staphylococcus epidermidis. Extracts prepared from unfermented cocoa beans showed concentration-dependent antibacterial activity, with reported minimum inhibitory concentrations of approximately 342 mg/mL for S. aureus and 360 mg/mL for S. epidermidis (Budi Tunjung-Sari *et al*., 2016).

Topical cocoa-extract cream accelerated wound contraction relative to the untreated groups, with the 8% formulation producing the strongest response among the tested cocoa preparations. The extract did not exceed the antibiotic control but performed better than the cream base alone. These effects may reflect the combined antimicrobial and tissue-supportive activities of cocoa constituents, including catechins and procyanidins (Sitarek *et al*., 2024; Fideles *et al*., 2023).

Gingival Incision Wound Model

An oral wound model provides additional evidence. Cocoa bean extract gels containing 8% or 16% cocoa extract were applied to gingival incision wounds in Wistar rats. The 16% formulation accelerated wound closure relative to the untreated and positive-control groups, while histology showed more complete re-epithelialization and improved tissue organization after ten days. The 8% gel produced smaller and less consistent differences. These results indicate that formulation concentration may influence efficacy and that cocoa constituents can remain active in a topical gel applied to oral soft tissue (Chairunas & Abdat, 2022).

Anti-Inflammatory Animal Studies

Although not all animal studies of cocoa were designed as wound-healing experiments, investigations of its anti-inflammatory effects provide supporting mechanistic evidence. In an acute pain model, cocoa administration reduced TNF-α concentrations and behavioral measures of pain (Ramos-Romero *et al*., 2008). Since excessive TNF-α signaling can contribute to persistent inflammation during wound repair, this observation is biologically relevant, although it does not by itself demonstrate improved wound healing (Ramiro *et al*., 2005).

Reviews of experimental evidence also report that cocoa flavanols can influence NF-κB activation, inflammatory cytokine production, and oxidative stress in animal models (Rodríguez-Ramiro *et al*., 2013). These observations support the plausibility of an anti-inflammatory contribution to cocoa-associated wound repair, but direct wound-healing studies remain more informative for therapeutic claims.

Clinical Studies

Cocoa Flavanols and Skin Photoaging

A randomized, double-blind, placebo-controlled trial examined daily supplementation with 320 mg cocoa flavanols for 24 weeks in women with moderate photoaging. Cocoa-flavanol intake improved facial wrinkle severity and skin elasticity relative to placebo, whereas the change in skin hydration was not statistically significant (Yoon *et al*., 2016). These outcomes suggest effects on dermal structure and extracellular matrix biology, but because the participants were not being treated for wounds, the findings should be considered indirect evidence relevant to tissue regeneration (Heinrich *et al*., 2006).

Cacao Powder Supplementation

A separate 12-week clinical study evaluated daily cacao powder consumption and reported improvements in skin hydration, wrinkle depth, and overall skin condition (Lee *et al*., 2024). Corresponding in vitro experiments showed increased collagen synthesis, greater antioxidant enzyme activity, lower MMP-1 expression, and increased hyaluronic acid production. These observations strengthen the mechanistic rationale for cocoa-related skin benefits, but they do not establish efficacy for clinical wound treatment.

EMERGING BIOMATERIAL APPLICATIONS

Recent regenerative-medicine research has increasingly explored plant-derived bioactive compounds as components of advanced wound dressings (Javed *et al*., 2026). Biomaterials containing antioxidant polyphenols may provide local biological activity while maintaining conditions favorable to repair (Fadda *et al*., 2025). Although the cited plant-based hydrogel studies were not specifically formulated with cocoa, they demonstrate how polyphenol-containing systems can influence angiogenesis, inflammation, mitochondrial function, and diabetic wound healing (Kaparekar & Anandasadagopan, 2022). These studies illustrate the broader therapeutic framework within which cocoa polyphenols may be incorporated into future multifunctional wound dressings (Antonio *et al*., 2011).

Plant-derived antioxidant dressings have also shown biocompatibility, reduced oxidative stress, and improved skin regeneration in experimental settings (Anjum *et al*., 2025). These findings provide a broader materials-science context for future incorporation of cocoa polyphenols or cocoa pod husk pectin into multifunctional wound-care systems.

Cocoa Pod Husk: From Agricultural Waste to Biomedical Resource

The cocoa industry generates substantial quantities of pod-husk biomass. Cocoa pod husks have been reported to represent approximately 70–75% of fruit weight and have traditionally been discarded or directed to relatively low-value uses such as composting and animal feed (Lu *et al*., 2018). Current circular-bioeconomy approaches instead seek to recover higher-value materials from this biomass.

Chemical analyses indicate that cocoa pod husks contain pectin, cellulose, hemicellulose, lignin, phenolic acids, flavonoids, minerals, and dietary fiber (Anoraga *et al*., 2024). This composition makes the husk a potential renewable feedstock for both polymeric materials and bioactive compounds. Ascorbic-acid-assisted extraction has been used to obtain cocoa pectin with a reported galacturonic-acid content above 74% while retaining antioxidant metabolites such as protocatechuic acid and catechol.

The resulting pectin has shown cytocompatibility with human dermal fibroblasts (Mares-Bou *et al*., 2025), together with reductions in intracellular ROS (Hennessey-Ramos *et al*., 2021) and modulation of inflammatory cytokines including interleukin-6 (Yahya *et al*., 2021). These observations suggest that cocoa pod husk-derived pectin may contribute biological activity in addition to its structural role. Valorization of the husk could therefore simultaneously address agricultural waste and provide a renewable material platform for regenerative applications.

Cocoa-Derived Polysaccharides for Hydrogel Applications

Hydrogels are widely studied for wound care because their hydrated networks can help maintain a moist wound environment, support cell migration, permit gas exchange, absorb exudate, and serve as carriers for controlled release (Said *et al*., 2023).

Cocoa pod husk pectin has characteristics relevant to hydrogel formation. Its galacturonic-acid-rich structure can participate in ionic cross-linking, while associated phenolic constituents may contribute antioxidant and anti-inflammatory activity (Vriesmann & de Oliveira Petkowicz, 2017). These properties create the possibility of combining the physical function of a hydrogel with biological activity derived from cocoa-processing residues.

Relative to some conventional synthetic materials, cocoa-derived polysaccharides may offer biodegradability, renewable sourcing, cytocompatibility, and compatibility with other biodegradable polymers, alongside potential antioxidant and anti-inflammatory properties (Chandel *et al*., 2022). Further formulation and safety studies are nevertheless required before these potential advantages can be translated into clinically suitable wound dressings.

Cocoa Polyphenols in Advanced Drug Delivery Systems

A practical limitation of many plant-derived polyphenols is their sensitivity to environmental and physiological conditions. Exposure to oxygen, light, moisture, or enzymatic processes can reduce stability and biological availability. Encapsulation within biodegradable delivery systems is one strategy for improving protection and localized release (Gaspar *et al*., 2012).

Potential delivery platforms include hydrogels, nanofibers, electrospun membranes, liposomes, polymeric nanoparticles, and biodegradable films. Such systems may protect flavanols from degradation and provide sustained release at the wound site (Kaparekar & Anandasadagopan, 2022).

Localized delivery may therefore offer advantages over conventional topical formulations,

including prolonged local activity, improved retention at the wound surface, reduced dosing frequency, and potentially lower systemic exposure. These benefits remain prospective for cocoa-derived formulations and require validation in formulation, safety, and clinical studies.

CONCLUSIONS

The available evidence indicates that *Theobroma cacao* is a promising multifunctional natural resource for wound-healing research. Its flavanols, procyanidins, phenolic acids, polysaccharides, and other constituents have been associated with antioxidant, anti-inflammatory, antimicrobial, collagen-related, and tissue-regenerative activities. In vitro and animal studies provide the strongest direct support, including evidence for reduced oxidative stress, improved fibroblast responses, enhanced re-epithelialization, antimicrobial effects, and faster wound closure. Human studies are currently indirect and have mainly examined skin structure, hydration, elasticity, or photoaging rather than established wounds. Cocoa pod husk also represents a potentially valuable source of pectin and other compounds for hydrogels and advanced wound-care materials. However, translation into clinical practice is constrained by variation in phytochemical composition, differences among extracts and formulations, limited standardization, and the small number of well-controlled human studies. Future research should prioritize standardized cocoa preparations, mechanistic and formulation studies, appropriate safety assessment, and adequately powered clinical trials specifically designed to evaluate wound-healing outcomes.

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