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Serotonin-modulating therapies for the management of chronic wounds

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Introduction: Chronic wounds are a significant source of patient morbidity, and ineffective treatment can lead to complications that are difficult and costly to manage. Given the limitations of current therapies, repurposing medications with well-studied safety and accessibility profiles offers a promising strategy for advancing wound care.

Methods: A comprehensive review of the existing literature was conducted to evaluate the role of serotonin-modulating pharmacotherapy in wound healing.

Results: Serotonergic signaling plays a multifaceted role in wound healing and evidence increasingly supports serotonin-modulating pharmacotherapy as having favorable angio-regulatory, immunomodulatory, and antimicrobial wound healing effects. Preclinical and clinical studies have demonstrated that topical administration of serotonin-modulating pharmacotherapy may improve wound healing outcomes.

Discussion: findings of this study provide support for the use of serotonin-modulating pharmacotherapy, with a special focus on topical application, as an adjunctive treatment for chronic, non-healing wounds and highlight the need for further translational clinical investigation.

KEYWORDS

wound healing, chronic wounds, serotonin, selective-serotonin reuptake inhibitor, serotonin-modulating pharmacotherapy

1 Introduction

Chronic non-healing wounds, such as neuropathic and vascular ulcers, cause significant disability and increase the risk of pain, infection, sepsis, amputation, and other morbidities (Zhao et al., 2016). In the United States, chronic wounds affect nearly 2.5% of the population and contribute to an economic burden surpassing \$50 billion annually (Sen, 2019; Sen, 2021). Serotonin also known as 5-hydroxytryptamine (5-HT) is an extensively studied monoamine neurotransmitter that is also synthesized and used by peripheral cells (Malinin et al., 2004; Alstergren et al., 1999; Laberge et al., 1996; Nguyen et al., 2019). Tryptophan hydroxylase 1, a key peripheral serotonin-synthesizing enzyme, is expressed in lymphocytes, macrophages, mast cells, and T cells, while serotonin transporter (SERT) and 5-HT receptors are also present in macrophages, dendritic cells, and lymphocytes (Shah and Amini-Nik, 2017). In response to peripheral inflammation, both 5-HT and its receptors are upregulated, promoting key angiogenic and cellular wound healing pathways (Malinin et al., 2004; Alstergren et al., 1999; Laberge et al., 1996; Nguyen et al., 2019). At present, 5-HT is underappreciated in the

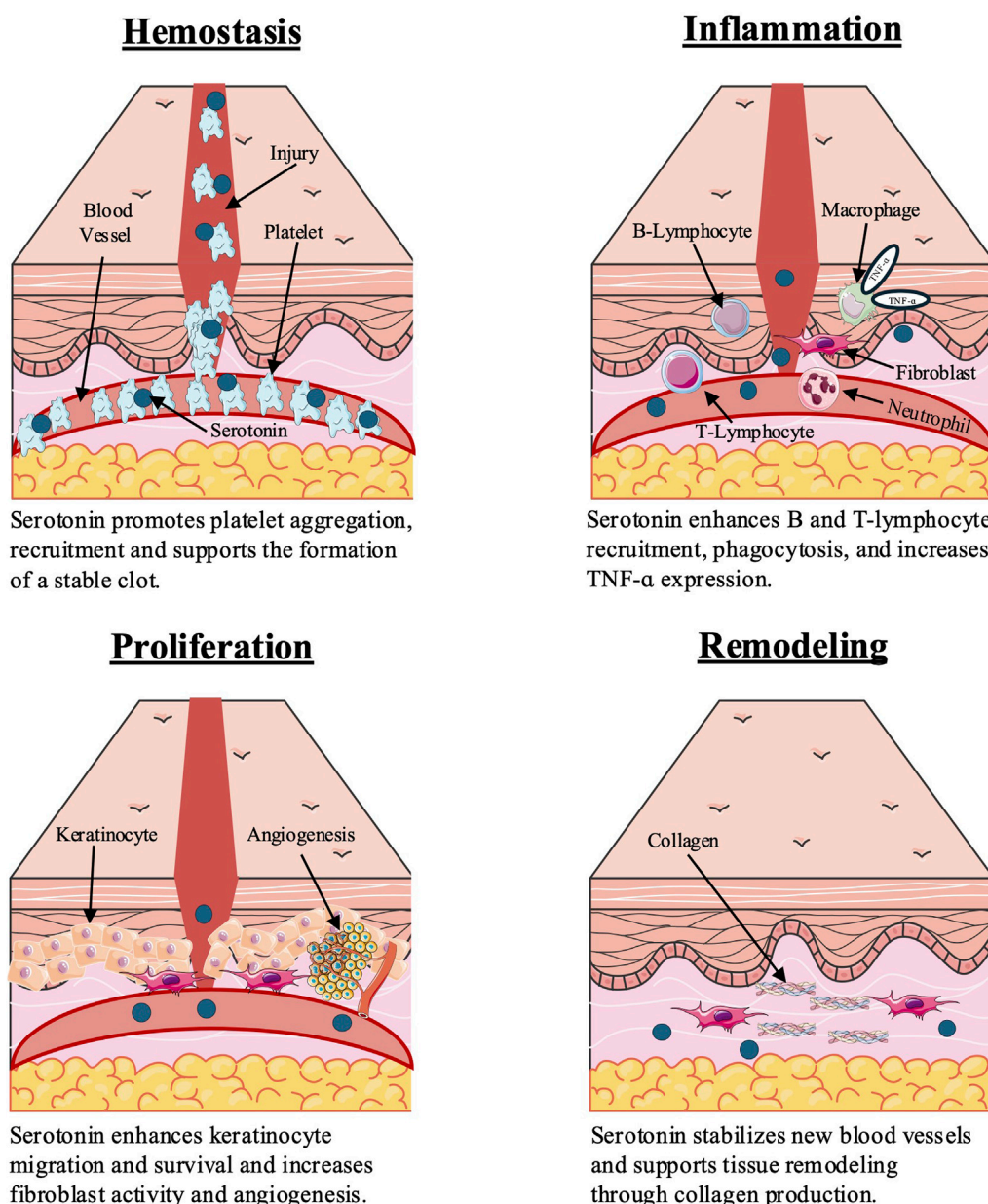


FIGURE 1
Serotonin influences wound healing stages through effects on platelets, immune cells, fibroblasts, and keratinocytes. Figure created by the authors based on findings from Enoch and Leaper (2008), Opneja et al. (2019), and Shah and Amini-Nik (2017).

wound healing literature, but its developing multifaceted involvement positions 5-HT signaling as a promising target for advanced wound care therapeutics.

2 Mechanistic basis and therapeutic rational for Serotonin/SSRIs in wound healing

2.1 Overview and clinical framing

5-HT plays regulatory roles in the four progressive, overlapping stages of wound healing: hemostasis, inflammation, proliferation,

and remodeling (Figure 1) (Enoch and Leaper, 2008; Eskeland et al., 2017). Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, citalopram, escitalopram, sertraline, and paroxetine, inhibit 5-HT reuptake at the synaptic cleft and are increasingly used across a broadening range of clinical applications including dermatologic diseases such as atopic dermatitis, contact dermatitis, and psoriasis, partially due to their well-documented downregulation of various proinflammatory cytokine signatures (Brody and Gu, 2020; Eskeland et al., 2017; Kiecka and Szczepanik, 2022; Shah and Amini-Nik, 2017). Emerging evidence supports the use of SSRIs to improve wound healing outcomes via angio-regulatory, immunomodulatory, and antimicrobial mechanisms, which remain under-characterized

and have not yet been comprehensively contextualized for cutaneous wound healing (Eskeland et al., 2017).

2.2 Hemostasis and angiogenesis

Within minutes of cutaneous injury in the hemostasis stage, thrombin triggers 5-HT release from platelets and endothelial cells, activating 5-HT receptors on the same cell types and initiating G-protein-mediated extracellular signal-regulated kinases 1 and 2 phosphorylation in the mitogen-activated protein kinase signaling pathway (Iwabayashi et al., 2012; Raote et al., 2007; Machida et al., 2013; Qin et al., 2013; Olszewska-Pazdrak and Carney, 2013; Gonzalez de Valdivia et al., 2017; Guo et al., 2022; Flaumenhaft and De Ceunynck, 2017; Huang et al., 2015; Tsopanoglou and Maragoudakis, 1999; Duerschmied et al., 2013). This early 5-HT autocrine signaling amplifies downstream pro-angiogenic cascades by upregulating vascular endothelial growth factor (VEGF) receptors and promoting release of VEGF, CXCL12, and matrix metalloproteinases, to sustain VEGF and nitric oxide-driven neovascularization (Almalki and Agrawal, 2017; Lin et al., 2023; Olszewska-Pazdrak and Carney, 2013; Guo et al., 2022; Flaumenhaft and De Ceunynck, 2017; Yang et al., 2005; Ceradini et al., 2004). SSRIs may be leveraged to attenuate dysregulated 5-HT signaling and to modulate the aberrant platelet and vascular responses in pathologic chronic wounds. For example, systemic SSRIs block SERT on platelets, preventing 5-HT uptake and causing a dose-dependent decrease, often exceeding 80%, in platelet 5-HT with greater effects seen after 6–12 weeks (Maguire et al., 1993; Kubera et al., 2001; Serebruany et al., 2001). Additionally, SSRIs lower plasma 5-HT, reduce key aggregation glycoproteins, and inhibit platelet signaling proteins involved in calcium mobilization release, which is a key step in platelet activation (Maguire et al., 1993; Kubera et al., 2001; Serebruany et al., 2001; Malinin et al., 2004). In contrast to CNS neurons which can synthesize 5-HT *de novo* via tryptophan hydroxylase, an enzyme which has enhanced expression in response to SSRIs, platelets cannot synthesize 5-HT and experience a depletion of intracellular stores to less than 2% of baseline after SSRI treatment (Shah and Amini-Nik, 2017). Relevant for poorly perfusing wounds, preliminary animal model studies have shown SSRIs may increase endothelial nitric oxide synthase activity and nitric oxide bioavailability (Pereira et al., 2015; Ofek et al., 2012). The platelet-inhibitory SSRI effects may also be particularly useful for targeting venous stasis ulcer disease processes as all classes of chronic venous insufficiency are linked to pathogenic platelet hyperactivity and increased platelet-monocyte and platelet-neutrophil aggregates, independent of whether a wound is present (Malinin et al., 2004).

2.3 Inflammation phase immunomodulation

The downregulatory effects of SSRIs on platelet 5-HT signaling may also modulate the inflammatory stage of wound healing where platelet-secreted 5-HT enhances recruitment and activation of neutrophils and macrophages, leading to unfavorable upregulation of key pro-inflammatory cytokines including tumor

necrosis factor alpha (TNF- α) and interleukin-12 (IL-12) in chronic wounds (Maguire et al., 1993; Kubera et al., 2001; Serebruany et al., 2001; Shah and Amini-Nik, 2017). Synergistically, *in vitro* SSRI exposure has been shown to increase natural killer cell, a negative regulator of wound-microenvironment pro-inflammatory signaling, activity thereby reducing inflammation via two converging, complementary mechanisms (Frank et al., 1999; Brubaker et al., 2011). Dendritic cells are also involved in the inflammatory stage and sequester 5-HT via SERT from activated T lymphocytes, subsequently presenting it to naïve T cells to promote their activation and adaptive immune response (Shah and Amini-Nik, 2017). In pathologic nonhealing wounds, T lymphocytes are elevated and exhibit dysfunctional signaling unresponsive to stimulation (Raziyeva et al., 2021; Havran and Jameson, 2010; Shah and Amini-Nik, 2017). SSRIs may reduce T lymphocyte proliferation, cytokine production, and induce apoptosis in unresponsive, constitutively activated T lymphocytes preferentially compared to mature naïve T lymphocytes (Shenoy et al., 2013; Di Rosso et al., 2016; Pállinger and Csaba, 2007; Gobin et al., 2013). A persistent inflammatory phase may be associated with dysregulated monopoiesis and sustained elevation of proinflammatory macrophages, a key cell-type for transition to the proliferative stage which has upregulated phagocytosis and TNF- α in response to 5-HT (Li et al., 2021; Malinin et al., 2004). In an *ex-vivo* study, SSRIs significantly reduced the expression of CXCR4, CD4, and CCR5 on both monocyte-derived macrophages (MDM) and peripheral blood mononuclear cells compared to control, suggesting an inhibitory role of SSRIs for macrophage proinflammatory signaling (Greeson et al., 2016). Other studies have demonstrated SSRI-associated reductions in MDM proinflammatory cytokines, reactive oxygen species, and antigen presentation to immune cells, which may be dysregulated in pathologic wound healing (Nazimek et al., 2017).

2.4 Proliferation: keratinocyte and fibroblast responses

In regard to proliferative phase keratinocytes, topical 5-HT has been shown to enhance survival, migration, and wound area reduction in a dose-dependent manner, accelerating closure in both *in vitro* and *in vivo* models (Polanski et al., 1995; Sternberg et al., 1987; Nguyen et al., 2019; Sadiq et al., 2018; Lenz et al., 2001; Malinin et al., 2004; Seuwen et al., 1988; Rodriguez-Barucg et al., 2024). Improved keratinocyte scratch closure rates due to increased proliferation were reversed following treatment with ketanserin, a 5-HT receptor antagonist, supporting SSRI dependence on 5-HT keratinocyte signaling (Rodriguez-Barucg et al., 2024). This study also identified improved phosphorylation profiles and 350 differentially expressed genes in SSRI-treated keratinocytes with reactome analysis suggesting altered mitochondrial and ribonucleotide metabolism and thermogenesis (Rodriguez-Barucg et al., 2024). In fibroblasts, 5-HT promotes survival, activity, proliferation, and collagen production, while also synergizing with FGF-2 to enhance tissue proliferation (Polanski et al., 1995; Sternberg et al., 1987; Nguyen et al., 2019; Sadiq et al., 2018; Lenz et al., 2001; Malinin et al., 2004; Seuwen et al., 1988). These effects involve active transport, increased oxygen formation, protein

phosphorylation, and 5-HT receptor-mediated mitogenesis, adhesion, and multiplication in culture (Polanski et al., 1995; Sternberg et al., 1987; Nguyen et al., 2019; Sadiq et al., 2018; Lenz et al., 2001; Malinin et al., 2004; Seuwen et al., 1988). The effects of SSRIs on certain chronic wound mechanism which have implicated 5-HT signaling remain unassessed; these include 5-HT-induced B-lymphocyte proliferation, afferent nerve ending stimulation and pain response and the potential of SSRIs to alter β -receptor function in wound cells, similar to SSRI-induced postsynaptic β -receptor downregulation in the brain (Malinin et al., 2004).

2.5 Selective serotonin reuptake inhibitors and wound microbiome

Recurrent or chronic infection is a known contributor to impaired wound healing and, in a retrospective analysis of 2963 patients, it was found that the predominant bacterial species in chronic wounds were *S. epidermidis*, *S. aureus*, *Corynebacterium*, and *Pseudomonadaceae* (Kiecka and Szczepanik, 2022). Biofilms, which hinder antibiotic treatment by using extracellular polymeric substance barriers and efflux pumps, are associated with delayed healing and increased infection risk in chronic wounds (Gompelman et al., 2016; Wall et al., 2019; Pereira et al., 2021). Polymicrobial interactions, involving species like *Staphylococcus aureus* and *Pseudomonas aeruginosa* may enhance biofilm pathogenicity via exchange of antibiotic resistance genes, like those producing antibiotic-degrading enzymes (Ponde et al., 2021; Cheong et al., 2021; Orazi and O'Toole, 2019).

Among SSRIs, fluoxetine and sertraline have the strongest antimicrobial effects; these SSRIs are more hydrophobic than others and may diffuse more easily across the phospholipid membrane to interact with cellular machinery (Kiecka and Szczepanik, 2022). These SSRIs, at sub-minimum inhibitory concentrations, have been shown to prevent biofilm production via ALS3 protein-binding and reduce mature biofilm metabolism (Oliveira et al., 2018; Costa Silva et al., 2017; Rodrigues et al., 2023). Fluoxetine has been shown to have *in vitro* effect against multi-resistant *S. aureus*, *E. faecalis*, *S. epidermidis*, *E. coli* and *P. aeruginosa* and decreases biofilm formation of *S. aureus* clinical isolate UAMS-1 (Dafinone et al., 2025). There is also evidence suggesting fluoxetine synergizes polymyxin B bactericidal effects in 80% of gram-negative isolates, outperforming fosfomycin and meropenem combinations (Ahmed et al., 2024). Fluoxetine topical application to infected wounds may also decrease purulence and hinder hematogenous bacterial invasion (Dafinone et al., 2025). Fluoxetine has also shown effectiveness against fluconazole-resistant *Candida* strains, and its administration leads to significant dose-dependent reductions in biofilm metabolism, 96% for *C. krusei*, and biomass, 82% for *C. glabrata* (Costa Silva et al., 2017). Sertraline inhibits the growth of *S. aureus*, *E. coli*, *P. aeruginosa*, and other Gram-positive bacteria such as *S. epidermidis* and *E. faecalis*, and shows synergy with antibiotics, including reductions in minimum inhibitory concentration of tetracycline and ciprofloxacin against *C. urealyticum* and quinolone-resistant strains

(Dafinone et al., 2025). While generally less effective against Gram-negative species, it demonstrates activity against *H. influenzae*, *M. catarrhalis*, *C. jejuni*, *Acinetobacter* spp., and can inhibit biofilm production in coagulase-negative staphylococci (Dafinone et al., 2025). In addition to the immunomodulatory properties of SSRIs, the antimicrobial properties of SSRIs make them promising adjuncts for difficult-to-treat wound bacterial and fungal infection.

3 Topical selective serotonin reuptake inhibitors and wound healing studies

3.1 Pre-clinical studies

Evidence from preclinical studies suggest topical SSRI application may improve wound healing. An *in vivo* study of diabetic mouse wound models revealed topical fluoxetine treatment promoted re-epithelialization, with significant decreases in wound area and exudate. Topical fluoxetine treatment also increased angiogenesis, suggested by higher CD31⁺ endothelial cell counts and visible small vessels, while reducing inflammatory macrophages and shifting their phenotype towards a pro-reparative state (Nguyen et al., 2019). In another study where wounds were created in rats, chronic topical fluoxetine administration improved mean wound lengths compared to acute administration in the initial 4 days; wounds in both chronic and acute fluoxetine treatment groups healed completely by day 10, while the placebo group did not fully heal by the study's conclusion (Farahani et al., 2007). In rats subjected to stress which decreased wound healing rate, topical fluoxetine treatment increased healing rate, leukocyte healing response, and normalized epithelialization and epithelial cell structure (Farahani et al., 2007). Bioelectronic delivery of topical fluoxetine in a murine punch wound model increased re-epithelialization by nearly 40% compared to control; this was accompanied by anti-inflammatory M2 macrophage infiltration without pro-inflammatory M1 presence, leading to a reduced M1/M2 ratio over time, indicative of accelerated transition to the reparative phase of wound healing (Li et al., 2024; Asefifeyzabadi et al., 2024). In a porcine model also using bioelectronic delivery, topical fluoxetine produced similar re-epithelialization improvements, also with corresponding improvements in the wound macrophage and cytokine profile (Li et al., 2025). There is an advantage to topical, as opposed to systemic, administration: preclinical data indicate that topical fluoxetine application leads to plasma fluoxetine concentrations that are twofold lower than those achieved with oral fluoxetine at therapeutic neurological doses. Importantly, topical fluoxetine treatment does not affect plasma levels of 5-HT, highlighting its potential for localized therapy with minimal systemic impact (Nguyen et al., 2019).

3.2 Clinical studies

In view of the pro-reparative outcomes noted with agonists of the 5-HT receptors, it may be counterintuitive to propose that

TABLE 1 Clinical studies investigating topical serotonin-modulating medications and chronic wound healing.

Treatment	Participants (n)	Ulcer etiology	Findings	Reference
2% Ketanserin BID	72	VLU, Decubitus, or Ischemic	Ketanserin significantly improved granulation ($p < 0.05$), epithelialization, and reduced wound area faster than placebo, with 36% complete healing by week 8	Janssen et al. (1989)
2% Ketanserin BID	23	VLU	Ketanserin significantly improved granulation tissue formation compared to placebo ($p < 0.05$) and showed better epithelialization and healing ($p < 0.01$)	Roelens (1989)
2% Ketanserin BID	12	DFU	Ketanserin significantly reduced ulcer area by 94% ($p < 0.001$) and improved relative wound area and healing index values from week 4 onward ($p < 0.05$)	Quatresooz et al. (2006)
2% Ketanserin BID	140	DFU	At 12 weeks, ketanserin reduced ulcer area by 87% vs. 63% for placebo, significantly accelerating wound healing	Martínez-de Jesús et al. (1997)
10% Iproniazid BID	28	Decubitus or Traumatic	After 1 week, iproniazid-treated lesions healed 52% vs. 27% for saline ($p < 0.05$), and differences remained significant after 2 weeks	Goldstein et al. (1962)

antagonists may have a similar result. However, existing clinical studies have investigated ketanserin. Although ketanserin does not increase serotonin levels, its wound healing effects are thought to result from its antiplatelet properties and ability to improve microvascular perfusion, rather than through direct serotonergic signaling (Malinin et al., 2004; Hedner and Persson, 1988). Separately, iproniazid (an irreversible monoamine oxidase inhibitor that limits the breakdown of serotonin) may promote reparative effects by increasing extracellular 5-HT and enhancing downstream receptor activation (Gillman, 2005). There are no ongoing or previous clinical trials investigating topical SSRIs for the treatment of chronic wounds (ClinicalTrials.gov).

In a double-blind placebo-controlled clinical trial of various chronic wounds, topical ketanserin 2% BID application was associated with greater re-epithelialization, granulation tissue formation, and wound area reduction rate (Janssen et al., 1989). Other studies of topical ketanserin 2% BID for VLUs and DFUs showed similar improvements in wound healing measures in addition to reductions in transudate and erythema (Roelens, 1989). In a double-blind intra-individual comparative study, diabetic participants with ≥ 2 chronic leg ulcers were randomized to receive topical 2% ketanserin BID on one ulcer and placebo on another ulcer for 8 weeks, in adjunct to SOC. The mean weekly reduction in wound area was significantly greater for ketanserin-treated ulcers (10.25%) compared to placebo-treated ulcers (2.5%) (Quatresooz et al., 2006). One trial investigating topical 10% iproniazid BID for 2 weeks for the treatment of chronic ulcers showed significantly increased rates of healing throughout the trial compared to placebo control (Goldstein et al., 1962). These studies are summarized in Table 1.

4 Selective serotonin reuptake inhibitor-associated cutaneous adverse drug reactions

Oral SSRI-associated cutaneous adverse drug reactions (CADRs) have been reported in the literature. One systematic

review of 173 cases found fluoxetine is the most commonly reported SSRI with CADRs, followed by sertraline and paroxetine. CADRs were frequently petechiae, ecchymoses, alopecia, and photo-dermatoses (Masuka et al., 2022). SSRI-related petechiae and ecchymoses may be attributed to SSRI-induced platelet inhibition; however, a study of oral fluoxetine found no significant difference in cutaneous microcirculation compared to control (Andrade et al., 2010; Edinoff et al., 2022; Mück-Weymann and Rechlin, 1996). Notably, there are no reports of adverse drug reactions for topical SSRI administration. Therefore, topical delivery of SSRIs for the treatment of chronic wounds or wound infections is preferred, to maximize concentrations of the drug at the wound while minimizing systemic absorption. Indeed, these approaches are under investigation, including delivery via hydrogels, microparticles, nano capsules, or bioelectronic delivery devices (Josino et al., 2021; Dos Santos et al., 2020). Topical use would be expected to minimize serotonergic effects; although, patients on dual antiplatelet therapy or anticoagulation should still be monitored clinically.

5 Conclusion

With their immunomodulatory and antimicrobial properties, repurposing 5-HT modulating pharmacotherapy, including SSRIs, for topical administration may offer significant benefits in treating chronic wounds, as supported by both preclinical and clinical evidence. Further clinical research and pharmacokinetic studies are essential to fully evaluate the potential of SSRIs in improving wound healing outcomes and to establish their role as a viable adjunctive therapeutic option in chronic wound care.

Author contributions

AB: Conceptualization, Writing – review and editing, Project administration, Writing – original draft, Methodology. AM: Project administration, Writing – original draft, Methodology,

Writing – review and editing, Conceptualization. JG-K: Writing – review and editing, Writing – original draft. JDP: Writing – review and editing. CH-V: Writing – review and editing, Writing – original draft. LA: Writing – review and editing, Writing – original draft. SD: Supervision, Conceptualization, Writing – review and editing. RRI: Writing – review and editing, Supervision, Conceptualization.

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This manuscript includes adapted and modified versions of the following icons by Servier Medical Art: “skin-normal,” “platelet-2,” “b-lymphocyte,” “macrophage,” “neutrophil-granulocyte-1,” “lymphoid-stem-cell,” “fibroblast-1,” “keratinocyte-1,” “angiogenesis,” and “collagen-3d.” All original images are available at <https://smart.servier.com> and are licensed under the [Creative Commons Attribution 3.0 Unported License \(CC BY 3.0\)](#). The modified versions are published under the same license, with appropriate attribution.

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