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Harnessing Senolytic and Senomorphic Phytochemicals via Advanced Nanotechnology for Accelerated Tissue Regeneration and Chronic Wound Healing: A Comprehensive Review

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ABSTRACT:

Chronic wounds represent a major global healthcare challenge owing to their prolonged inflammatory state, impaired tissue regeneration, recurrent microbial colonization, and high risk of recurrence. Conventional wound management strategies, including debridement, antimicrobial therapy, advanced dressings, and growth factor-based interventions, primarily address the clinical manifestations of chronic wounds but often fail to correct the underlying molecular abnormalities responsible for delayed healing. Recent advances in ageing biology have identified cellular senescence as a critical driver of chronic wound pathology, where the persistent accumulation of senescent cells disrupts tissue homeostasis through excessive secretion of the senescence-associated secretory phenotype (SASP), leading to sustained inflammation, oxidative stress, extracellular matrix degradation, impaired angiogenesis, and defective tissue remodelling. These discoveries have shifted the therapeutic focus from symptomatic wound management towards targeted modulation of senescence-associated pathways. Among emerging therapeutic approaches, plant-derived senomorphic phytochemicals have gained considerable attention because of their ability to regulate multiple biological pathways simultaneously while maintaining favourable safety profiles. Unlike senolytic agents that eliminate senescent cells, senomorphic compounds suppress the detrimental secretory phenotype and restore cellular homeostasis without compromising the physiological functions of viable cells. Diverse classes of phytochemicals, including flavonoids, polyphenols, terpenoids,

alkaloids, lignans, saponins, and polysaccharides, have demonstrated antioxidant, anti-inflammatory, immunomodulatory, antimicrobial, pro-angiogenic, and extracellular matrix-regulating activities through modulation of key signalling pathways such as NF-κB, Nrf2, AMPK/SIRT1, PI3K/Akt, TGF-β, VEGF, and matrix metalloproteinases. Their multitarget pharmacological profile makes them promising candidates for addressing the complex pathophysiology of chronic wounds. This review critically examines current evidence on the role of senomorphic phytochemicals in chronic wound healing by integrating recent advances in cellular senescence biology, molecular pharmacology, phytochemistry, network pharmacology, molecular docking, multi-omics technologies, and nano-enabled drug delivery systems. Furthermore, the review discusses pharmaceutical formulation strategies based on Quality by Design (QbD) principles that enhance phytochemical stability, bioavailability, controlled release, and translational potential. Existing challenges related to phytochemical standardization, pharmacokinetic variability, regulatory approval, and clinical validation are also critically evaluated. By bridging traditional medicinal knowledge with modern pharmaceutical technologies, this review provides a comprehensive scientific framework for the development of next-generation senescence-targeted therapies aimed at improving chronic wound management and advancing precision regenerative medicine.

INTRODUCTION:

2. Literature Search Strategy and Methodology

This review was developed using a structured and transparent literature search strategy based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) framework to ensure comprehensive identification, selection, and critical appraisal of relevant scientific evidence. Although the present work is a comprehensive narrative review rather than a quantitative systematic review or meta-analysis, PRISMA principles were adopted to improve methodological rigor, minimize selection bias, and enhance reproducibility.

A systematic literature search was performed using internationally recognized electronic databases, including PubMed/MEDLINE, Scopus, Web of Science Core Collection, ScienceDirect, SpringerLink, Wiley Online Library, and Google Scholar. To strengthen the mechanistic and computational aspects of the review, specialized biomedical databases such as GeneCards, DrugBank, Therapeutic Target Database (TTD), STRING, UniProt, KEGG, Reactome, SwissTargetPrediction, and PubChem were additionally explored for target validation, protein interactions, biological pathways, and phytochemical information.

The search primarily included articles published between January 2010 and June 2026, with particular emphasis on literature published after 2020 to capture recent developments in cellular senescence, senotherapeutics, wound biology, phytochemistry, nanomedicine, and computational pharmacology. Earlier landmark publications were included only when they provided fundamental concepts essential for understanding cellular senescence and wound healing mechanisms.

Comprehensive Boolean search strategies combining Medical Subject Headings (MeSH) and free-text keywords were employed. The principal search terms included "cellular senescence," "senescence-associated secretory phenotype," "SASP," "senomorphic," "senolytic," "phytochemicals," "natural products," "chronic wound," "diabetic foot ulcer," "skin regeneration," "oxidative stress," "network pharmacology," "molecular docking," "multi-omics," "nanotechnology," "hydrogel," "drug delivery," and "Quality by Design." Search strategies were optimized for each database according to its indexing system to maximize both sensitivity and specificity.

Studies were considered eligible if they met predefined inclusion criteria. Original research articles, systematic reviews, meta-analyses, and high-quality review articles published in peer-reviewed English-language journals were included. Eligible studies investigated one or more of the following: cellular senescence and ageing biology, chronic wound pathophysiology, phytochemical-mediated modulation of molecular signalling pathways, senomorphic or senolytic interventions, nano-enabled wound therapeutics, computational drug discovery, molecular docking, network pharmacology, or translational regenerative medicine. Both experimental and clinical investigations, including in vitro, in vivo, ex vivo, and human studies, were considered where scientifically relevant.

Studies were excluded if they consisted solely of conference abstracts, editorials, commentaries, duplicate publications, non-peer-reviewed reports, or articles lacking mechanistic or pharmacological evidence. Publications unrelated to chronic wound healing or those describing traditional medicinal applications without scientific validation were also excluded to maintain the scientific quality and translational relevance of the review.

After retrieval, all references were imported into reference management software, where duplicate records were identified and removed before title and abstract screening. Full-text articles were subsequently evaluated according to predefined eligibility criteria. During data extraction, particular emphasis was placed on study design, methodological quality, molecular mechanisms, experimental models, phytochemical characteristics, formulation approaches, computational analyses, and translational significance.

The extracted evidence was organized into thematic categories, including cellular senescence biology, molecular signalling pathways, senomorphic phytochemicals, network pharmacology, molecular docking, multi-omics technologies, nano-enabled drug delivery systems, and clinical translation. This integrated approach enabled a critical evaluation of current evidence while identifying important knowledge gaps and future research priorities for senescence-targeted wound therapeutics.

Unlike conventional narrative reviews that primarily summarize published findings, the present review critically synthesizes multidisciplinary evidence by integrating molecular biology, pharmacognosy, pharmaceutical technology, computational biology, and regenerative medicine. This strategy provides a comprehensive scientific framework for understanding how senomorphic phytochemicals can be translated into next-generation therapeutic interventions for chronic wound management.

Table 1. Literature Search Strategy Adopted in the Present Review

Component	Description
Reporting guideline	PRISMA 2020
Databases searched	PubMed, Scopus, Web of Science, ScienceDirect, SpringerLink, Wiley Online Library, Google Scholar
Additional resources	GeneCards, DrugBank, STRING, UniProt, KEGG, Reactome, TTD, SwissTargetPrediction, PubChem
Publication period	January 2010 – June 2026
Study types	Original research, systematic reviews, meta-analyses, high-quality review articles
Language	English
Major themes	Cellular senescence, chronic wounds, phytochemicals, nanotechnology, network pharmacology, molecular docking, regenerative medicine
Exclusion criteria	Duplicates, conference abstracts, editorials, non-peer-reviewed articles, irrelevant studies

3. Global Epidemiology and Socioeconomic Burden of Chronic Wounds

Chronic wounds have emerged as a significant global healthcare challenge, affecting millions of individuals annually and imposing an escalating burden on healthcare systems. Unlike acute wounds that heal within a predictable timeframe, chronic wounds remain arrested in one or more phases of the healing cascade, resulting in prolonged inflammation, persistent tissue damage, recurrent infections, and delayed regeneration. Their increasing prevalence is largely attributed to population ageing, the rising incidence of diabetes mellitus, obesity, cardiovascular diseases, chronic venous insufficiency, peripheral arterial disease, and other lifestyle-related disorders. Collectively, these conditions have transformed chronic wound management into a major public health priority requiring multidisciplinary therapeutic approaches (4), (5), (28).

Among all chronic wound types, diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), pressure injuries (PIs), and arterial ulcers account for the majority of clinical cases. Diabetes mellitus remains the most important predisposing factor, with diabetic foot ulcers affecting approximately 19–34% of individuals with diabetes during their lifetime and representing one of the leading causes of non-traumatic lower-limb amputation worldwide. Peripheral neuropathy, vascular insufficiency, impaired immune responses, and chronic hyperglycaemia collectively contribute to defective tissue repair, making diabetic wounds particularly difficult to manage (5), (29).

Venous leg ulcers constitute the most common chronic wounds of the lower extremities, accounting for nearly 70% of chronic leg ulcer cases. Persistent venous hypertension, venous valve incompetence, microvascular dysfunction, and chronic inflammation impair oxygen and nutrient delivery, resulting in delayed epithelialization and frequent ulcer recurrence. Likewise, pressure injuries remain a major complication among hospitalized, critically ill, and immobilized patients. Sustained pressure over bony prominences compromises local blood flow, producing tissue ischemia, necrosis, secondary infection, and prolonged hospitalization. Arterial ulcers, although less common, are associated with severe peripheral arterial disease and often exhibit poor healing because of inadequate tissue perfusion and oxygenation (30), (31).

The growing burden of chronic wounds extends far beyond clinical management. Patients frequently experience persistent pain, restricted mobility, reduced physical independence, sleep disturbances, psychological stress, anxiety, depression, social isolation, and diminished quality of life. These complications are further aggravated by repeated infections, unpleasant wound exudates, malodour, and the need for long-term dressing changes, collectively contributing to substantial emotional and psychosocial distress for both patients and caregivers (32).

The economic consequences are equally profound. Chronic wound care requires prolonged outpatient follow-up, repeated hospital admissions, surgical debridement, antimicrobial therapy, vascular interventions, rehabilitation, and long-term nursing support. Consequently, wound management consumes a considerable proportion of healthcare expenditure in both developed and developing countries. In addition to direct medical costs, indirect economic losses arising from work absenteeism, disability, premature retirement, and caregiver dependency substantially increase the overall societal burden. As healthcare systems continue to experience demographic transitions toward older populations, the financial impact of chronic wounds is expected to increase significantly over the coming decades (4), (33).

From a biological perspective, chronic wounds are now recognized as complex disorders involving dysregulation of multiple interconnected cellular and molecular processes rather than isolated defects in tissue repair. Persistent oxidative stress, excessive production of reactive oxygen species (ROS), microbial biofilm formation, extracellular matrix degradation, mitochondrial dysfunction, impaired angiogenesis, altered immune responses, and defective stem cell activity collectively create a hostile wound microenvironment that prevents normal healing progression. These pathological alterations interact continuously, amplifying inflammatory signalling and reducing the regenerative capacity of resident fibroblasts, keratinocytes, endothelial cells, and immune cells (7), (8), (34).

Among these interconnected mechanisms, cellular senescence has recently emerged as one of the principal biological drivers responsible for chronic wound persistence. Senescent cells accumulate progressively within the wound bed owing to repeated oxidative injury, DNA damage, metabolic stress, and chronic inflammation. The sustained secretion of pro-inflammatory mediators, proteolytic enzymes, and senescence-associated secretory phenotype (SASP) factors disrupts extracellular matrix homeostasis, inhibits angiogenesis, and promotes secondary senescence in neighbouring healthy cells, thereby establishing a self-perpetuating inflammatory microenvironment. These discoveries have fundamentally shifted wound-healing research from symptom-oriented management toward therapies that target the underlying mechanisms governing tissue ageing and regenerative failure (9), (11), (14).

This evolving understanding has stimulated considerable interest in regenerative strategies capable of modifying the chronic wound microenvironment at the molecular level. Among the most promising approaches are senomorphic phytochemicals, which possess the ability to simultaneously regulate oxidative stress, inflammation, mitochondrial dysfunction, angiogenesis, extracellular matrix remodelling, and cellular senescence through multiple signalling pathways. Their multitarget pharmacological profile offers a compelling therapeutic rationale for addressing the biological complexity of chronic wounds while complementing advances in nanotechnology, biomaterials, and precision drug delivery, topics discussed in the subsequent sections of this review.

Table 2. Global Characteristics of Major Chronic Wound Types

Wound type	Major risk factors	Principal pathological features	Major clinical consequences
Diabetic foot ulcer	Diabetes mellitus, peripheral neuropathy, ischemia	Chronic inflammation, infection, impaired angiogenesis	Amputation, osteomyelitis, disability
Venous leg ulcer	Chronic venous insufficiency, obesity, ageing	Venous hypertension, persistent inflammation	Recurrent ulceration, prolonged healing
Pressure injury	Immobility, spinal cord injury, malnutrition	Tissue ischemia and necrosis	Infection, prolonged hospitalization
Arterial ulcer	Peripheral arterial disease, smoking, atherosclerosis	Severe ischemia and hypoxia	Gangrene, limb loss

4. Cellular Senescence: A Central Driver of Chronic Wound Pathophysiology

Successful wound healing requires a finely regulated balance between inflammation, cellular proliferation, extracellular matrix (ECM) remodelling, and tissue regeneration. In chronic wounds, this balance is progressively disrupted by the accumulation of senescent cells, which profoundly alter the biological behaviour of the wound microenvironment. While transient cellular senescence is a physiological process that contributes to embryonic

development, tissue remodelling, and tumour suppression, persistent senescence becomes detrimental by promoting chronic inflammation and impairing regenerative capacity. Increasing evidence now identifies cellular senescence as one of the principal molecular mechanisms responsible for the transition from acute to chronic non-healing wounds (9), (10), (13).

Cellular senescence is initiated when cells experience persistent stress that exceeds their repair capacity. Multiple intrinsic and extrinsic stimuli—including oxidative stress, genomic instability, telomere shortening, mitochondrial dysfunction, chronic hyperglycaemia, ultraviolet radiation, inflammation, and microbial infection—activate the DNA damage response, ultimately leading to irreversible cell-cycle arrest. This process is primarily regulated through the p53/p21 and p16^{INK4a}/Rb signalling pathways, which prevent proliferation of damaged cells while maintaining their metabolic activity (12), (16), (35).

Unlike apoptotic cells, senescent cells remain viable and metabolically active. Their pathological significance arises from the development of the senescence-associated secretory phenotype (SASP), a complex secretome composed of pro-inflammatory cytokines, chemokines, growth factors, proteases, matrix metalloproteinases (MMPs), and extracellular vesicles. Continuous release of SASP mediators perpetuates inflammatory signalling, recruits immune cells, accelerates extracellular matrix degradation, suppresses angiogenesis, and induces secondary senescence in neighbouring healthy cells. Consequently, the wound microenvironment becomes trapped in a self-sustaining cycle of inflammation and tissue degeneration that prevents progression toward the proliferative and remodelling phases of healing (9), (15), (36).

Oxidative stress represents one of the strongest drivers of senescence in chronic wounds. Excessive production of reactive oxygen species (ROS) damages DNA, proteins, lipids, and mitochondria, thereby activating redox-sensitive signalling pathways such as NF-κB, MAPK, and mTOR. Simultaneously, impairment of endogenous antioxidant systems, particularly the Nrf2–Keap1 pathway, reduces cellular defence against oxidative injury. Persistent oxidative stress not only promotes senescence but also amplifies SASP production, creating a positive feedback loop that accelerates tissue damage and delays wound closure (37), (38).

Mitochondrial dysfunction further exacerbates chronic wound pathology by impairing cellular energy metabolism and increasing ROS generation. Senescent fibroblasts and keratinocytes exhibit defective mitochondrial biogenesis, reduced ATP production, altered mitochondrial dynamics, and diminished mitophagy. These abnormalities compromise collagen synthesis, cell migration, and proliferation, ultimately reducing the regenerative potential of the wound. Restoration of mitochondrial homeostasis through activation of AMPK/SIRT1 signalling has therefore emerged as an attractive therapeutic strategy for reversing senescence-associated dysfunction (39), (40).

Fibroblasts are among the earliest cells to undergo senescence within chronic wounds. Senescent fibroblasts demonstrate reduced proliferative capacity, impaired collagen synthesis, diminished responsiveness to growth factors, and excessive secretion of MMP-1, MMP-3, and MMP-9, resulting in accelerated degradation of extracellular matrix components. Similarly, senescent keratinocytes exhibit impaired migration and delayed re-epithelialization, whereas senescent endothelial cells display reduced angiogenic potential and diminished nitric oxide production. Collectively, these alterations compromise tissue regeneration and contribute directly to chronic wound persistence (41), (42).

Immune dysregulation further reinforces senescence-mediated tissue damage. Under physiological conditions, macrophages and natural killer cells recognize and eliminate senescent cells through immune surveillance. However, chronic wounds are characterized by defective clearance of senescent cells, allowing their progressive accumulation within the wound bed. Persistent activation of M1 macrophages and impaired transition toward the reparative M2 phenotype sustain inflammatory cytokine production, inhibit tissue regeneration, and promote chronicity. This failure of immune-mediated senescent cell clearance has become a key therapeutic target in regenerative medicine (43), (44).

Emerging evidence also demonstrates extensive crosstalk between senescence and extracellular matrix remodelling. Continuous secretion of MMPs, elastases, and cathepsins disrupts collagen architecture and degrades structural proteins essential for wound repair. Concurrently, dysregulation of transforming growth factor-β (TGF-β) signalling impairs fibroblast activation and collagen deposition, while suppression of vascular endothelial growth factor (VEGF) signalling limits neovascularization and oxygen delivery. These interconnected molecular

events create an unfavourable microenvironment incapable of supporting effective tissue regeneration (45), (46).

The recognition of cellular senescence as a dynamic and therapeutically modifiable process has transformed contemporary wound-healing research. Rather than focusing exclusively on infection control or wound closure, current strategies increasingly aim to restore tissue homeostasis by modulating senescence-associated pathways, reducing SASP production, improving mitochondrial function, and re-establishing regenerative signalling. Among these approaches, naturally occurring senomorphic phytochemicals have emerged as particularly promising candidates because of their ability to simultaneously regulate oxidative stress, inflammation, mitochondrial dysfunction, and extracellular matrix remodelling through multiple complementary molecular targets. This mechanistic foundation provides the basis for the subsequent discussion on phytochemical-mediated modulation of senescence pathways in chronic wound healing.

Table 3. Major Biological Consequences of Cellular Senescence in Chronic Wounds

Biological alteration	Mechanism	Impact on wound healing
Persistent SASP secretion	Release of IL-6, IL-1β, TNF-α, MMPs	Sustained inflammation and tissue damage
Oxidative stress	Excess ROS generation and impaired Nrf2 signalling	DNA damage and delayed tissue repair
Mitochondrial dysfunction	Reduced ATP production and impaired mitophagy	Decreased cell proliferation and migration
Fibroblast senescence	Reduced collagen synthesis and ECM remodelling	Delayed granulation tissue formation
Endothelial cell senescence	Reduced VEGF signalling and angiogenesis	Poor vascularization
Immune dysfunction	Impaired clearance of senescent cells	Persistence of chronic inflammation

5. Molecular Signalling Pathways Governing Senescence and Wound Repair

The development of chronic wounds is driven by a complex network of interconnected signalling pathways that regulate inflammation, oxidative stress, cellular metabolism, angiogenesis, extracellular matrix remodelling, and tissue regeneration. Under physiological conditions, these pathways function in a coordinated manner to ensure timely wound closure and restoration of tissue homeostasis. However, persistent cellular stress, ageing, metabolic disorders, and chronic inflammation disrupt this regulatory balance, leading to activation of senescence-associated signalling networks that impair healing. Understanding these molecular pathways is essential for identifying therapeutic targets and explaining how senomorphic phytochemicals exert their beneficial effects.

Among the most extensively studied pathways, NF-κB serves as a master regulator of inflammation and senescence. Chronic activation of NF-κB stimulates the transcription of numerous pro-inflammatory mediators, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), cyclooxygenase-2 (COX-2), and multiple matrix metalloproteinases. Sustained NF-κB activation promotes development of the senescence-associated secretory phenotype (SASP), amplifying inflammatory signalling and accelerating extracellular matrix degradation within chronic wounds. Excessive NF-κB activity has been consistently associated with delayed wound healing, increased oxidative stress, and impaired tissue regeneration, making it a primary target for senescence-modulating therapies (47), (48).

Counterbalancing inflammatory signalling, the Nrf2–Keap1 pathway functions as the principal cellular defence mechanism against oxidative stress. Upon activation, Nrf2 translocates to the nucleus and stimulates transcription of antioxidant enzymes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), catalase, glutathione peroxidase, and NAD(P)H quinone oxidoreductase-1 (NQO1). In chronic wounds, impaired Nrf2 activity reduces antioxidant protection, leading to excessive accumulation of reactive oxygen species and progressive cellular damage. Restoration of Nrf2 signalling has therefore emerged as a promising strategy for reducing oxidative stress-induced senescence and promoting tissue repair (49), (50).

Cellular energy homeostasis is largely regulated through the AMPK/SIRT1 signalling axis, which plays a central role in mitochondrial function, autophagy, metabolism, and longevity. Activation of AMP-activated protein kinase (AMPK) enhances mitochondrial biogenesis, stimulates autophagic clearance of damaged organelles, and improves cellular resistance to oxidative stress. Sirtuin-1 (SIRT1), a NAD+-dependent deacetylase, further contributes to cellular survival by modulating FOXO transcription factors, p53 activity, and mitochondrial metabolism. Reduced AMPK/SIRT1 signalling is frequently observed in chronic wounds and aged tissues, contributing to impaired regeneration and accumulation of senescent cells. Therapeutic activation of this pathway

has demonstrated beneficial effects on wound healing through restoration of mitochondrial homeostasis and suppression of inflammatory responses (51), (52).

The PI3K/Akt pathway represents another critical regulator of cell survival, proliferation, migration, and angiogenesis. Physiological activation of PI3K/Akt signalling promotes keratinocyte migration, fibroblast proliferation, endothelial cell survival, and vascular formation, all of which are essential for effective wound repair. However, chronic metabolic stress and prolonged inflammation can dysregulate PI3K/Akt signalling, contributing to impaired regenerative responses. Emerging evidence suggests that controlled activation of PI3K/Akt may counteract senescence-associated dysfunction while enhancing tissue regeneration (53).

Angiogenesis is predominantly regulated through vascular endothelial growth factor (VEGF) signalling, which controls endothelial cell proliferation, migration, and new blood vessel formation. Adequate vascularization is essential for supplying oxygen, nutrients, immune cells, and growth factors to the healing wound. Chronic wounds often exhibit reduced VEGF expression and impaired angiogenic responses, resulting in persistent hypoxia and delayed tissue repair. Restoration of VEGF-mediated angiogenesis has therefore become a major objective in regenerative wound therapies (54).

Extracellular matrix deposition and tissue remodelling are strongly influenced by transforming growth factor-β (TGF-β) signalling. TGF-β regulates fibroblast activation, collagen synthesis, myofibroblast differentiation, and granulation tissue formation. Controlled TGF-β activity is essential for normal wound healing; however, excessive or dysregulated signalling may contribute to fibrosis, whereas insufficient activity impairs matrix deposition and tissue regeneration. The dual role of TGF-β highlights the importance of maintaining precise signalling balance during wound repair (55).

The mTOR pathway serves as a nutrient-sensing regulator of cellular growth, metabolism, and protein synthesis. Although transient mTOR activation supports tissue regeneration, chronic mTOR hyperactivation has been linked to accelerated ageing, cellular senescence, impaired autophagy, and persistent inflammation. Inhibition of excessive mTOR signalling has shown potential to reduce senescence-associated pathology and improve regenerative outcomes, particularly in ageing-related disorders (56).

Recent studies have also identified important roles for Wnt/β-catenin signalling in skin regeneration and stem cell maintenance. Proper Wnt signalling promotes keratinocyte proliferation, hair follicle regeneration, and tissue remodelling. However, aberrant Wnt activity can contribute to pathological fibrosis and impaired tissue architecture. Interactions between Wnt, TGF-β, PI3K/Akt, and NF-κB pathways further demonstrate the highly integrated nature of wound-healing signalling networks (57).

Importantly, these pathways do not function independently. Instead, they form an interconnected molecular network in which oxidative stress, inflammation, mitochondrial dysfunction, and senescence reinforce one another through continuous signalling crosstalk. Persistent activation of NF-κB and mTOR stimulates SASP production, while impaired Nrf2 and AMPK/SIRT1 signalling reduces cellular resilience against stress. Simultaneously, altered VEGF and TGF-β activity compromises angiogenesis and extracellular matrix remodelling. This interconnected network ultimately determines whether tissue repair progresses successfully or transitions into chronic non-healing pathology (58).

The therapeutic significance of these pathways lies in their ability to serve as common molecular targets for numerous naturally occurring phytochemicals. Unlike single-target synthetic drugs, many phytochemicals simultaneously modulate multiple signalling cascades, enabling coordinated regulation of inflammation, oxidative stress, angiogenesis, and cellular senescence. This multitarget pharmacological profile provides the mechanistic basis for the emerging concept of senomorphic phytochemicals, which will be discussed in the subsequent section.

Table 4. Major Signalling Pathways Involved in Senescence-Mediated Wound Healing

Pathway	Major Functions	Dysregulation in Chronic Wounds
NF-κB	Inflammation, SASP regulation	Persistent inflammation and ECM degradation
Nrf2–Keap1	Antioxidant defence	Excessive oxidative stress
AMPK/SIRT1	Mitochondrial homeostasis, autophagy	Cellular ageing and metabolic dysfunction
PI3K/Akt	Cell survival and proliferation	Impaired regeneration
VEGF	Angiogenesis and vascular repair	Reduced blood vessel formation
TGF-β	ECM synthesis and remodelling	Defective tissue repair or fibrosis

mTOR	Growth and metabolism	Accelerated senescence and impaired autophagy
Wnt/β-catenin	Stem cell regulation and regeneration	Abnormal tissue remodelling

6. Senomorphic Phytochemicals: Classification, Sources, and Mechanistic Basis

Natural products have served as an invaluable source of therapeutic agents for centuries, and nearly half of the currently approved drugs are either directly derived from natural compounds or inspired by their chemical scaffolds. In recent years, plant-derived phytochemicals have attracted renewed interest in regenerative medicine because of their ability to simultaneously regulate multiple signalling pathways involved in inflammation, oxidative stress, mitochondrial dysfunction, angiogenesis, extracellular matrix remodelling, and cellular senescence. This multitarget pharmacological profile distinguishes phytochemicals from conventional synthetic drugs and makes them particularly attractive for managing complex disorders such as chronic wounds, where numerous pathological mechanisms operate simultaneously (20), (59).

Unlike senolytic agents, which selectively eliminate senescent cells through apoptosis, senomorphic phytochemicals suppress the detrimental biological activities of senescent cells without inducing cell death. Their principal therapeutic action involves modulation of the senescence-associated secretory phenotype (SASP), thereby reducing chronic inflammation while preserving the beneficial physiological roles of transient senescence in tissue repair. This approach is increasingly considered safer for long-term clinical application because it minimizes the risk of disrupting normal tissue homeostasis and regenerative processes (14), (17).

Phytochemicals comprise a chemically diverse group of secondary plant metabolites that can be broadly classified into polyphenols, flavonoids, phenolic acids, terpenoids, alkaloids, lignans, coumarins, saponins, tannins, quinones, and polysaccharides. Although structurally distinct, many of these compounds share common biological activities, including antioxidant, anti-inflammatory, antimicrobial, immunomodulatory, anti-fibrotic, and pro-angiogenic effects. Importantly, their pharmacological actions arise from coordinated modulation of multiple molecular targets rather than inhibition of a single signalling pathway, enabling a more comprehensive therapeutic response within the chronic wound microenvironment (60).

Among these phytochemical classes, polyphenols represent one of the most extensively investigated groups. Compounds such as resveratrol, curcumin, epigallocatechin-3-gallate (EGCG), and ellagic acid have demonstrated potent senomorphic activity through suppression of NF-κB signalling, activation of Nrf2-mediated antioxidant defence, enhancement of AMPK/SIRT1 signalling, and attenuation of oxidative stress-induced DNA damage. These compounds also improve mitochondrial function, reduce SASP production, and promote collagen synthesis, thereby facilitating tissue regeneration (61), (62).

Flavonoids, including quercetin, luteolin, apigenin, kaempferol, baicalein, and naringenin, constitute another important class of senescence-modulating compounds. Their therapeutic effects extend beyond free radical scavenging and include regulation of inflammatory cytokines, inhibition of matrix metalloproteinases, promotion of endothelial cell function, and enhancement of fibroblast migration. Several flavonoids have additionally been reported to modulate macrophage polarization, favouring transition from the pro-inflammatory M1 phenotype toward the tissue-repairing M2 phenotype, thereby improving the regenerative microenvironment (63), (64).

Terpenoids have similarly demonstrated broad pharmacological activities relevant to chronic wound management. Bioactive molecules such as asiaticoside, madecassoside, glycyrrhizin, and ginsenosides promote fibroblast proliferation, collagen deposition, angiogenesis, and extracellular matrix remodelling while simultaneously reducing inflammatory mediator production. Their ability to regulate TGF-β and VEGF signalling further supports their application in tissue regeneration and wound repair (65).

Other phytochemical groups, including alkaloids, lignans, coumarins, saponins, and plant polysaccharides, also contribute significantly to senomorphic activity through complementary mechanisms. These compounds have been shown to regulate immune cell activation, suppress oxidative stress, improve mitochondrial bioenergetics, stimulate growth factor production, and enhance keratinocyte and fibroblast proliferation. Although many remain less extensively investigated than flavonoids or polyphenols, accumulating experimental evidence suggests that they may provide valuable therapeutic opportunities, particularly when used in combination with other phytochemicals (66).

One of the defining characteristics of senomorphic phytochemicals is their network pharmacology. Unlike conventional pharmaceuticals designed to target a single receptor or enzyme, phytochemicals interact with

multiple proteins and signalling cascades simultaneously. This systems-level pharmacology enables coordinated regulation of inflammation, oxidative stress, angiogenesis, extracellular matrix remodelling, immune responses, and cellular metabolism. Such multitarget activity is particularly advantageous in chronic wounds because the disease process involves extensive crosstalk among numerous molecular pathways rather than dysfunction of a single biological target (67).

Despite these promising biological activities, translation of phytochemicals into clinical practice remains limited by several pharmaceutical challenges. Many bioactive compounds exhibit poor aqueous solubility, limited oral bioavailability, rapid metabolism, low chemical stability, and inadequate penetration into damaged tissues. Consequently, their therapeutic efficacy often differs substantially between experimental models and clinical settings. These limitations have accelerated the development of advanced formulation strategies, including nanoencapsulation, lipid-based carriers, hydrogels, polymeric nanoparticles, electrospun nanofibres, and stimuli-responsive wound dressings, which will be discussed in later sections of this review (22).

Collectively, current evidence suggests that senomorphic phytochemicals represent a promising class of multifunctional therapeutic agents capable of targeting the molecular complexity of chronic wounds. Rather than acting as simple antioxidants or anti-inflammatory agents, these compounds restore tissue homeostasis through coordinated regulation of interconnected signalling pathways governing senescence, oxidative stress, mitochondrial function, immune responses, angiogenesis, and extracellular matrix remodelling. Their mechanistic diversity provides a strong scientific foundation for the subsequent discussion of individual phytochemicals and their molecular targets in chronic wound healing.

Table 5. Major Classes of Senomorphic Phytochemicals and Their Biological Activities

Phytochemical class	Representative compounds	Principal molecular targets	Major pharmacological effects
Polyphenols	Resveratrol, Curcumin, EGCG, Ellagic acid	NF-κB, Nrf2, AMPK/SIRT1	Antioxidant, anti-inflammatory, mitochondrial protection
Flavonoids	Quercetin, Kaempferol, Apigenin, Luteolin	PI3K/Akt, NF-κB, Nrf2	SASP suppression, angiogenesis, ECM regulation
Terpenoids	Asiaticoside, Madecassoside, Ginsenosides	TGF-β, VEGF, MAPK	Collagen synthesis, fibroblast proliferation
Alkaloids	Berberine, Matrine	AMPK, mTOR	Metabolic regulation, anti-inflammatory activity
Saponins	Ginsenosides, Glycyrrhizin	VEGF, TGF-β	Angiogenesis, wound contraction
Polysaccharides	Aloe polysaccharides, β-glucans	Immune signalling	Immunomodulation and tissue regeneration

7. Senomorphic Phytochemicals Targeting Cellular Senescence in Chronic Wound Healing

The therapeutic potential of senomorphic phytochemicals arises from their ability to simultaneously regulate multiple biological processes that collectively determine wound repair. Unlike conventional pharmacological agents designed to inhibit a single molecular target, phytochemicals exert pleiotropic effects by modulating interconnected signalling pathways involved in oxidative stress, inflammation, mitochondrial homeostasis, extracellular matrix (ECM) remodelling, angiogenesis, and immune regulation. This systems-level pharmacology is particularly advantageous in chronic wounds, where persistent senescence results from dysregulation of several overlapping molecular mechanisms rather than a single pathogenic pathway (20), (67).

Current evidence indicates that senomorphic phytochemicals primarily function by suppressing the senescence-associated secretory phenotype (SASP), thereby interrupting the vicious cycle of chronic inflammation and tissue degeneration. Downregulation of pro-inflammatory mediators, including IL-1β, IL-6, TNF-α, cyclooxygenase-2 (COX-2), and matrix metalloproteinases, reduces inflammatory amplification within the wound microenvironment while preserving the physiological functions of viable cells. Simultaneously, activation of endogenous antioxidant systems limits oxidative damage, protects mitochondrial integrity, and improves cellular resilience against environmental stressors. These coordinated actions restore the biological conditions required for progression from the inflammatory phase toward tissue regeneration (61), (68).

Among naturally occurring senomorphic compounds, quercetin remains one of the most extensively investigated flavonoids. Experimental studies have demonstrated that quercetin suppresses NF-κB activation, reduces ROS accumulation, inhibits SASP-associated cytokine production, and enhances Nrf2-dependent antioxidant responses. In wound-healing models, these effects translate into accelerated fibroblast proliferation, improved

keratinocyte migration, enhanced collagen deposition, and reduced inflammatory infiltration. Quercetin has also been reported to improve endothelial function, thereby supporting angiogenesis and tissue oxygenation within chronic wounds (64), (69).

Resveratrol, a stilbene polyphenol predominantly found in grapes and berries, exhibits broad senomorphic activity through activation of the AMPK/SIRT1 signalling pathway. SIRT1 activation enhances mitochondrial biogenesis, promotes autophagic clearance of damaged organelles, suppresses oxidative stress, and modulates p53-mediated cellular senescence. In addition, resveratrol attenuates inflammatory signalling by inhibiting NF-κB activation while simultaneously promoting angiogenesis through improved endothelial nitric oxide bioavailability. These combined actions contribute to enhanced tissue regeneration and reduced senescence-associated dysfunction (61), (70).

Another extensively studied phytochemical is curcumin, the principal polyphenolic constituent of *Curcuma longa*. Curcumin exhibits potent antioxidant and anti-inflammatory properties through simultaneous modulation of NF-κB, Nrf2, PI3K/Akt, MAPK, and TGF-β signalling pathways. Numerous experimental studies have demonstrated that curcumin reduces oxidative DNA damage, suppresses inflammatory cytokine production, inhibits matrix metalloproteinase activity, and stimulates fibroblast proliferation and collagen synthesis. Furthermore, curcumin-loaded nanoformulations have demonstrated substantially improved bioavailability and wound-healing efficacy compared with free curcumin, highlighting the importance of advanced pharmaceutical delivery systems (62), (71).

Epigallocatechin-3-gallate (EGCG), the major catechin present in green tea, represents another promising senomorphic phytochemical. EGCG effectively scavenges reactive oxygen species, inhibits activation of NF-κB and MAPK pathways, suppresses inflammatory cytokine production, and protects mitochondrial function. Additionally, EGCG promotes keratinocyte proliferation and endothelial cell survival while reducing excessive extracellular matrix degradation through inhibition of matrix metalloproteinases. These activities collectively support tissue regeneration while limiting chronic inflammatory damage (72).

Besides these extensively investigated compounds, increasing attention has been directed toward phytochemicals such as luteolin, apigenin, kaempferol, baicalein, berberine, asiaticoside, madecassoside, glycyrrhizin, ginsenosides, ellagic acid, and aloe-derived polysaccharides. Although their precise molecular mechanisms vary, most exhibit overlapping pharmacological actions involving suppression of inflammatory signalling, activation of antioxidant pathways, enhancement of angiogenesis, regulation of fibroblast function, and attenuation of senescence-associated cellular dysfunction. These observations suggest that senomorphic activity is not restricted to individual phytochemicals but rather represents a shared pharmacological characteristic among numerous structurally diverse natural products (65), (66), (73).

An important characteristic of phytochemical therapy is the presence of synergistic pharmacological interactions. Unlike monotherapy directed toward a single molecular target, combinations of phytochemicals frequently produce additive or synergistic modulation of multiple signalling pathways. For example, simultaneous regulation of NF-κB and Nrf2 pathways may suppress inflammation while enhancing antioxidant defence, whereas concurrent activation of AMPK/SIRT1 and VEGF signalling may improve mitochondrial homeostasis together with angiogenesis. Such synergistic interactions are particularly valuable in chronic wound management because they more closely resemble the complex biological requirements of tissue regeneration (74).

Despite encouraging preclinical evidence, several challenges continue to limit clinical translation of senomorphic phytochemicals. Variability in phytochemical composition, inadequate standardization of botanical extracts, poor pharmacokinetic characteristics, limited tissue penetration, rapid metabolic degradation, and inconsistent formulation quality contribute to differences in therapeutic outcomes among experimental studies. Addressing these limitations requires integration of phytochemical standardization, advanced analytical characterization, Quality by Design (QbD)-based formulation development, and nano-enabled drug delivery systems capable of improving local bioavailability and sustained therapeutic release (22), (75).

Overall, accumulating experimental evidence strongly supports senomorphic phytochemicals as promising multitarget therapeutic agents capable of modulating the molecular mechanisms responsible for chronic wound persistence. Their ability to simultaneously regulate oxidative stress, inflammation, mitochondrial dysfunction,

extracellular matrix remodelling, angiogenesis, and immune responses provides a strong mechanistic foundation for their incorporation into next-generation regenerative therapies. Nevertheless, successful clinical translation will depend on rigorous pharmaceutical development, standardized manufacturing, and well-designed clinical trials that establish their long-term efficacy and safety.

Table 6. Representative Senomorphic Phytochemicals and Their Molecular Actions in Chronic Wound Healing

Phytochemical	Major molecular targets	Principal biological effects	Wound-healing outcome
Quercetin	NF-κB, Nrf2	SASP inhibition, antioxidant activity	Enhanced fibroblast migration and collagen synthesis
Resveratrol	AMPK, SIRT1, NF-κB	Mitochondrial protection, anti-inflammatory activity	Improved angiogenesis and tissue regeneration
Curcumin	NF-κB, PI3K/Akt, TGF-β	Anti-inflammatory, antioxidant, ECM modulation	Accelerated wound closure
EGCG	NF-κB, MAPK, Nrf2	ROS scavenging, MMP inhibition	Reduced inflammation and enhanced epithelialization
Asiaticoside	TGF-β, VEGF	Collagen synthesis and angiogenesis	Improved granulation tissue formation
Berberine	AMPK, mTOR	Metabolic regulation and anti-inflammatory activity	Reduced oxidative stress and improved healing

8. Network Pharmacology, Molecular Docking, and Multi-Omics Approaches in the Discovery of Senomorphic Phytochemicals

The discovery of bioactive phytochemicals has traditionally relied on empirical screening and experimental validation, approaches that are often laborious, time-consuming, and unable to fully capture the complex pharmacology of natural products. Recent advances in computational biology have transformed this paradigm by enabling systematic identification of molecular targets, signalling networks, and biological pathways associated with disease progression. Among these technologies, network pharmacology, molecular docking, molecular dynamics simulations, and multi-omics analyses have become indispensable tools for understanding how senomorphic phytochemicals regulate chronic wound healing at the systems level. These approaches are particularly valuable because phytochemicals generally exert therapeutic effects through simultaneous modulation of multiple molecular targets rather than single receptor interactions, thereby aligning closely with the multifactorial pathogenesis of chronic wounds (67), (76).

Network pharmacology integrates pharmacology, systems biology, bioinformatics, and computational science to construct interaction networks linking phytochemicals, molecular targets, signalling pathways, and disease phenotypes. Instead of following the traditional "one drug–one target" concept, network pharmacology embraces a "multi-component–multi-target–multi-pathway" strategy that better reflects the biological complexity of herbal medicines. In chronic wound research, this methodology enables identification of critical molecular hubs involved in senescence, oxidative stress, inflammation, extracellular matrix remodelling, and angiogenesis, thereby facilitating rational selection of candidate phytochemicals for further investigation (77).

A typical network pharmacology workflow begins with identification of phytochemical constituents from databases such as TCMSP, PubChem, ChEMBL, IMPPAT, and ETCM, followed by prediction of potential protein targets using resources including SwissTargetPrediction, DrugBank, GeneCards, and the Therapeutic Target Database (TTD). Disease-associated genes are subsequently integrated with protein–protein interaction (PPI) networks generated through the STRING database. Functional enrichment analyses using Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Reactome identify biological pathways that are significantly associated with chronic wound pathology. Hub genes are finally prioritized through topological analysis, providing mechanistic insight into phytochemical-mediated therapeutic actions (78), (79).
Studies applying network pharmacology to wound healing consistently identify TNF, IL6, AKT1, TP53, VEGFA, EGFR, MAPK1, MMP9, HIF1A, CXCL8, STAT3, NFKB1, SIRT1, TGFB1, and NFE2L2 (Nrf2) as major regulatory nodes. These proteins govern inflammatory responses, oxidative stress, angiogenesis, collagen synthesis, immune regulation, mitochondrial function, and extracellular matrix remodelling. Their repeated identification across independent studies highlights their importance as potential therapeutic targets for senomorphic phytochemicals and reinforces the concept that successful wound repair requires simultaneous modulation of multiple signalling pathways rather than isolated molecular interventions (80).

Following target identification, molecular docking is routinely employed to evaluate the binding affinity between phytochemicals and disease-associated proteins. Molecular docking predicts the orientation, stability, hydrogen bonding, hydrophobic interactions, and binding energies of ligand–protein complexes, thereby providing valuable

mechanistic evidence supporting phytochemical activity. Compounds exhibiting favourable docking scores against proteins such as NF-κB, MMP-9, VEGFR2, TGF-β receptor, SIRT1, PI3K, AKT1, and Nrf2 are considered promising candidates for subsequent experimental validation. Although docking cannot substitute for biological experiments, it substantially improves efficiency by prioritizing compounds with the highest therapeutic potential (81).

Increasingly, docking studies are complemented by molecular dynamics (MD) simulations, which evaluate the stability of ligand–protein complexes under dynamic physiological conditions. Parameters such as root mean square deviation (RMSD), root mean square fluctuation (RMSF), hydrogen bond occupancy, radius of gyration, solvent-accessible surface area (SASA), and binding free energy calculations provide insight into conformational stability and interaction persistence. Integration of docking with molecular dynamics therefore enhances confidence in computational predictions before experimental investigation (82).

The emergence of multi-omics technologies has further expanded understanding of chronic wound biology by enabling comprehensive characterization of molecular alterations across different biological levels. Transcriptomics identifies changes in gene expression associated with inflammation, senescence, and tissue regeneration; proteomics characterizes alterations in cytokines, growth factors, extracellular matrix proteins, and signalling molecules; metabolomics reveals metabolic disturbances linked to oxidative stress and mitochondrial dysfunction; while epigenomics provides insight into DNA methylation, histone modifications, and non-coding RNA regulation of wound healing. Integration of these datasets allows construction of highly detailed molecular maps describing the progression from normal tissue repair to chronic wound pathology (83), (84).

Recent advances in artificial intelligence (AI) and machine learning have further strengthened computational drug discovery by facilitating prediction of phytochemical targets, biological activity, toxicity, pharmacokinetic behaviour, and molecular interactions using large-scale biomedical datasets. Machine learning algorithms can rapidly analyse complex biological networks that would be difficult to interpret manually, thereby accelerating identification of promising senomorphic compounds. Although these technologies remain largely investigational in wound therapeutics, they are expected to play an increasingly important role in precision phytopharmaceutical development over the coming decade (85).

Despite remarkable progress, computational approaches possess inherent limitations. Most predictions remain dependent upon database completeness, algorithm accuracy, and availability of high-quality experimental datasets. Molecular docking generally evaluates static protein structures, whereas biological systems are highly dynamic and influenced by numerous physiological variables. Similarly, network pharmacology identifies associations rather than definitive causal relationships. Consequently, computational findings must always be interpreted alongside rigorous in vitro, in vivo, and clinical validation before therapeutic conclusions can be drawn (76).

Nevertheless, integration of network pharmacology, molecular docking, multi-omics technologies, and artificial intelligence provides an unprecedented opportunity to accelerate the discovery of senomorphic phytochemicals for chronic wound management. These complementary methodologies facilitate systematic identification of therapeutic targets, elucidation of molecular mechanisms, and rational optimization of phytochemical formulations. Their continued integration with pharmaceutical sciences is expected to substantially improve the translation of natural products into evidence-based regenerative therapeutics.

Table 7. Computational Approaches Used for Discovery of Senomorphic Phytochemicals

Computational approach	Primary objective	Major databases/software	Application in chronic wound research
Network pharmacology	Identify multitarget interactions	TCMSP, GeneCards, STRING, DrugBank	Target identification and pathway analysis
Molecular docking	Predict ligand–protein binding	AutoDock Vina, Schrödinger, MOE	Binding affinity evaluation
Molecular dynamics simulation	Assess stability of complexes	GROMACS, AMBER, Desmond	Dynamic interaction analysis
Transcriptomics	Gene expression profiling	GEO, ArrayExpress	Identification of senescence-related genes
Proteomics	Protein expression analysis	UniProt, PRIDE	Biomarker discovery
Metabolomics	Metabolic pathway analysis	HMDB, MetaboAnalyst	Cellular metabolism in wound healing
Artificial intelligence	Drug prediction and	Machine learning algorithms	Candidate prioritization

	optimization		

9. Nano-Enabled Delivery Systems for Senomorphic Phytochemicals in Chronic Wound Healing

Despite the remarkable pharmacological potential of senomorphic phytochemicals, their successful clinical translation remains limited by several pharmaceutical challenges, including poor aqueous solubility, low chemical stability, rapid metabolism, limited skin permeability, and inadequate retention at the wound site. These limitations frequently result in suboptimal therapeutic concentrations within damaged tissues and reduced clinical efficacy. Consequently, considerable research has focused on the development of advanced nano-enabled delivery systems capable of improving phytochemical bioavailability, protecting labile compounds from degradation, and enabling controlled, localized drug release. Such technologies have emerged as a promising strategy for enhancing the therapeutic performance of phytochemicals while simultaneously creating a favourable microenvironment for tissue regeneration (22), (75).

Among the available delivery platforms, polymeric nanoparticles have attracted significant attention owing to their excellent biocompatibility, biodegradability, and ability to encapsulate both hydrophilic and hydrophobic phytochemicals. Natural polymers such as chitosan, alginate, gelatin, hyaluronic acid, and cellulose derivatives, together with synthetic polymers including poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL), have been widely investigated as carrier materials. Encapsulation within polymeric nanoparticles improves drug stability, prolongs local retention, enables sustained release, and enhances penetration into damaged tissues. Moreover, these carriers can be engineered to respond to changes in pH, enzyme activity, or oxidative stress, allowing controlled release within the pathological wound environment (21), (86).

Lipid-based nanocarriers, including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, and liposomes, represent another effective approach for improving phytochemical delivery. Their lipid composition closely resembles biological membranes, facilitating enhanced dermal penetration and cellular uptake. These systems are particularly advantageous for lipophilic compounds such as curcumin, resveratrol, and quercetin, whose poor aqueous solubility has historically limited therapeutic application. Controlled encapsulation within lipid nanocarriers not only improves chemical stability but also prolongs drug residence time and reduces dosing frequency, thereby enhancing patient compliance (87).

Hydrogels have emerged as one of the most promising platforms for chronic wound management because they combine efficient drug delivery with maintenance of a moist wound environment. Modern hydrogel systems provide mechanical protection, absorb excessive wound exudates, facilitate oxygen diffusion, and support cellular migration while serving as reservoirs for sustained phytochemical release. Incorporation of nanoparticles within hydrogel matrices has further improved mechanical strength, release kinetics, antimicrobial activity, and tissue compatibility. Injectable and stimuli-responsive hydrogels capable of releasing therapeutic agents in response to pH, temperature, reactive oxygen species, or enzymatic activity have shown particular promise for personalized wound treatment (88), (89).

Recent advances have also led to the development of electrospun nanofibrous scaffolds, which closely mimic the architecture of the native extracellular matrix. Their high surface-area-to-volume ratio, interconnected porosity, and excellent oxygen permeability create an ideal environment for fibroblast attachment, keratinocyte migration, and neovascularization. Phytochemical-loaded nanofibres enable prolonged local drug delivery while simultaneously functioning as bioactive wound dressings that support tissue regeneration. Incorporation of natural polymers, growth factors, antimicrobial agents, or metallic nanoparticles further expands their regenerative potential (90).

Among inorganic nanomaterials, zinc oxide nanoparticles (ZnO NPs) have gained considerable interest because of their intrinsic antimicrobial, antioxidant, and wound-healing properties. Zinc plays a critical physiological role in collagen synthesis, DNA replication, enzyme activation, and immune regulation, all of which are essential for normal tissue repair. Green synthesis of ZnO nanoparticles using medicinal plant extracts has emerged as an environmentally sustainable approach that combines the biological activities of phytochemicals with the physicochemical advantages of nanomaterials. Such hybrid systems often demonstrate synergistic antimicrobial activity, improved antioxidant capacity, enhanced angiogenesis, and accelerated wound closure compared with either phytochemicals or nanoparticles alone (91), (92).

Another rapidly evolving strategy involves stimuli-responsive and smart wound dressings capable of adapting to

changes within the wound microenvironment. These intelligent systems respond to pH alterations, oxidative stress, bacterial enzymes, glucose concentrations, or temperature changes by releasing therapeutic agents only when required. Integration of biosensors with responsive biomaterials has further enabled real-time monitoring of wound status, including infection, inflammation, oxygenation, and exudate composition. Such technologies represent an important step toward precision wound management by allowing simultaneous diagnosis and therapy through a single multifunctional platform (93).

While nano-enabled formulations substantially improve phytochemical delivery, their successful clinical translation requires careful consideration of safety, reproducibility, and regulatory compliance. Parameters such as particle size, surface charge, encapsulation efficiency, release kinetics, sterilization methods, biodegradability, and long-term toxicity must be thoroughly characterized during formulation development. Adoption of Quality by Design (QbD) principles, standardized manufacturing protocols, and comprehensive physicochemical characterization is therefore essential to ensure batch-to-batch consistency and facilitate regulatory approval for clinical application (94).

Collectively, nano-enabled delivery systems provide an effective strategy for overcoming the pharmaceutical limitations of senomorphic phytochemicals while maximizing their therapeutic efficacy. By improving local bioavailability, protecting bioactive molecules from degradation, enabling controlled release, and enhancing tissue penetration, these advanced formulations substantially strengthen the translational potential of phytochemical-based wound therapeutics. Continued integration of nanotechnology with regenerative medicine, biomaterials science, and computational formulation design is expected to accelerate the development of next-generation therapies for chronic wound management.

Table 8. Nano-Enabled Delivery Platforms for Senomorphic Phytochemicals

Delivery system	Major advantages	Representative phytochemicals	Therapeutic benefits
Polymeric nanoparticles	Sustained release, biodegradability	Quercetin, Curcumin, Resveratrol	Improved stability and local retention
Liposomes & lipid nanoparticles	Enhanced skin penetration	Curcumin, EGCG, Resveratrol	Increased bioavailability
Hydrogels	Moist environment, controlled release	Polyphenols, flavonoids	Accelerated tissue regeneration
Electrospun nanofibres	ECM mimicry, high porosity	Curcumin, Asiaticoside	Enhanced cell adhesion and angiogenesis
ZnO nanoparticle composites	Antimicrobial and antioxidant activity	Herbal extracts + ZnO NPs	Improved wound closure and infection control
Smart/stimuli-responsive dressings	On-demand drug release	Multiple phytochemicals	Precision wound therapy

10. Preclinical and Clinical Evidence Supporting Senomorphic Phytochemicals in Chronic Wound Healing

The growing understanding of cellular senescence has stimulated extensive investigation into phytochemical-based interventions capable of restoring tissue homeostasis in chronic wounds. Over the past decade, numerous in vitro, in vivo, and clinical studies have demonstrated that senomorphic phytochemicals not only suppress inflammation and oxidative stress but also enhance angiogenesis, extracellular matrix remodelling, epithelial regeneration, and immune regulation. Collectively, these findings provide strong biological support for incorporating natural products into advanced wound management strategies. However, despite encouraging experimental evidence, translation into routine clinical practice remains limited by insufficient high-quality clinical trials and variability in phytochemical formulations (95).

Preclinical Evidence

Experimental cell culture studies have consistently demonstrated that senomorphic phytochemicals improve the biological functions of cells directly involved in wound repair. In fibroblasts, compounds such as quercetin, curcumin, resveratrol, and epigallocatechin-3-gallate (EGCG) enhance proliferation, migration, collagen synthesis, and extracellular matrix organization while simultaneously reducing oxidative stress and inflammatory cytokine production. Similar protective effects have been observed in keratinocytes, where phytochemicals accelerate re-epithelialization by improving cell migration and maintaining mitochondrial integrity. Endothelial cell studies further indicate enhanced angiogenesis through increased VEGF expression and improved nitric oxide signalling, supporting restoration of vascular function within damaged tissues (61), (70), (96).

Animal models have provided further mechanistic evidence for the therapeutic efficacy of senomorphic

phytochemicals. Studies using diabetic mice, streptozotocin-induced diabetic rats, pressure ulcer models, and excisional wound models consistently demonstrate accelerated wound closure following treatment with phytochemical-based formulations. Histological analyses reveal increased collagen deposition, enhanced granulation tissue formation, improved neovascularization, reduced inflammatory cell infiltration, and faster re-epithelialization compared with untreated controls. Molecular analyses additionally confirm suppression of NF-κB signalling, activation of Nrf2-mediated antioxidant responses, increased SIRT1 expression, and decreased production of senescence-associated inflammatory mediators, indicating that phytochemicals directly influence the molecular pathways governing wound repair (71), (97).

Recent studies employing nanoparticle-mediated phytochemical delivery have demonstrated even greater therapeutic benefits. Nanoencapsulation significantly enhances local drug retention, improves penetration through damaged skin, protects unstable phytochemicals from degradation, and enables sustained release at the wound site. Experimental comparisons frequently report superior wound contraction, enhanced collagen maturation, reduced bacterial colonization, and improved angiogenesis with nanoformulated phytochemicals compared with conventional preparations. These findings highlight the importance of advanced pharmaceutical technologies in maximizing therapeutic outcomes (75), (87).

Clinical Evidence

Clinical evidence supporting senomorphic phytochemicals is steadily increasing, although it remains less extensive than preclinical research. Randomized clinical trials evaluating topical preparations containing curcumin, Centella asiatica extracts, Aloe vera, honey-derived phytoconstituents, Calendula officinalis, and green tea polyphenols have reported improvements in wound closure rates, pain reduction, infection control, granulation tissue formation, and epithelial regeneration across various wound types, including diabetic foot ulcers, venous leg ulcers, burns, and postoperative wounds. Most studies also report favourable safety profiles with minimal local irritation or systemic toxicity, supporting the suitability of phytochemical-based therapies for prolonged application (98), (99).

Among these natural products, Centella asiatica has demonstrated particularly consistent clinical efficacy. Triterpenoids such as asiaticoside and madecassoside stimulate fibroblast proliferation, collagen synthesis, angiogenesis, and extracellular matrix remodelling, resulting in improved tissue repair and reduced scar formation. Similarly, topical curcumin formulations have shown significant anti-inflammatory and antioxidant effects that contribute to accelerated healing of chronic wounds, although formulation-dependent variability continues to influence clinical outcomes (65), (71).

Several systematic reviews have concluded that phytochemical-containing dressings and topical formulations generally improve wound healing compared with conventional treatment alone. Nevertheless, considerable heterogeneity exists among published studies regarding phytochemical source, extraction methods, formulation characteristics, dosage, treatment duration, patient selection, and clinical outcome measures. This variability complicates direct comparison between studies and limits the ability to establish standardized therapeutic recommendations (100).

Current Evidence Gaps

Despite encouraging findings, important limitations continue to restrict widespread clinical implementation of senomorphic phytochemicals. Most published clinical trials involve relatively small patient populations, short follow-up periods, and single-centre study designs. Furthermore, few investigations specifically evaluate biomarkers of cellular senescence, making it difficult to determine whether observed clinical improvements result directly from modulation of senescence-associated pathways or from general anti-inflammatory and antioxidant effects. Standardized assessment of biomarkers such as p16^INK4a, p21, SA-β-gal, SASP cytokines, and mitochondrial function would substantially strengthen future translational research (43), (68).

Another major challenge involves the lack of pharmaceutical standardization. Differences in botanical origin, cultivation conditions, extraction procedures, phytochemical composition, and formulation technologies contribute to substantial variability in therapeutic efficacy. Adoption of Good Agricultural and Collection Practices (GACP), standardized phytochemical characterization, validated analytical methods, and Quality by Design (QbD)-based manufacturing protocols will be essential for ensuring reproducibility and regulatory acceptance of phytochemical therapeutics (94).

Overall, current evidence strongly supports the therapeutic potential of senomorphic phytochemicals in chronic wound management. Experimental studies consistently demonstrate favourable molecular and cellular effects, while emerging clinical data indicate encouraging improvements in healing outcomes and patient safety. However, definitive clinical translation will require well-designed multicentre randomized controlled trials, standardized formulations, biomarker-guided therapeutic evaluation, and long-term safety assessment before these therapies can be fully integrated into evidence-based wound care.

Table 9. Summary of Current Evidence for Senomorphic Phytochemicals in Chronic Wound Healing

Evidence level	Major findings	Current limitations
In vitro studies	Improved fibroblast proliferation, keratinocyte migration, reduced oxidative stress and SASP	Simplified biological models
Animal studies	Accelerated wound closure, angiogenesis, collagen deposition, reduced inflammation	Limited translation to human physiology
Clinical studies	Improved healing rates, reduced pain and infection, good safety profile	Small sample size, formulation variability
Systematic reviews	Overall positive therapeutic trends	Heterogeneous methodologies and insufficient biomarker evaluation

11. Current Challenges, Future Perspectives, and Emerging Directions

The therapeutic application of senomorphic phytochemicals represents one of the most promising advances in regenerative medicine for chronic wound management. Their ability to simultaneously regulate inflammation, oxidative stress, mitochondrial dysfunction, angiogenesis, extracellular matrix (ECM) remodelling, and cellular senescence offers a distinct advantage over conventional therapies that generally target individual pathological mechanisms. Nevertheless, despite substantial progress in experimental research, several scientific, pharmaceutical, clinical, and regulatory challenges continue to impede successful translation into routine clinical practice. Addressing these limitations will be essential for realizing the full therapeutic potential of phytochemical-based senomorphic interventions.

One of the most significant challenges is the complex chemical composition and inherent variability of medicinal plants. The phytochemical profile of herbal materials is influenced by numerous factors, including geographical origin, climatic conditions, cultivation practices, harvesting time, post-harvest processing, extraction methods, and storage conditions. Consequently, different batches of the same botanical species may contain markedly different concentrations of bioactive constituents, leading to inconsistent pharmacological activity and variable therapeutic outcomes. Standardization of botanical raw materials through Good Agricultural and Collection Practices (GACP), validated extraction protocols, chromatographic fingerprinting, and quantitative phytochemical profiling is therefore indispensable for ensuring reproducibility and product quality (101).

Another major limitation involves the poor pharmacokinetic properties of many phytochemicals. Numerous senomorphic compounds exhibit low aqueous solubility, limited membrane permeability, rapid metabolism, poor systemic bioavailability, and insufficient tissue retention. Although nano-enabled drug delivery systems have substantially improved these characteristics, formulation optimization remains necessary to achieve controlled release, targeted delivery, enhanced stability, and long-term therapeutic efficacy. Future pharmaceutical research should prioritize scalable manufacturing processes that combine advanced biomaterials with reproducible quality control while maintaining cost-effectiveness suitable for widespread clinical implementation (75), (87).

The lack of standardized preclinical models further complicates interpretation of existing evidence. Current experimental studies employ diverse animal species, wound models, treatment regimens, outcome measures, and analytical techniques, making direct comparison between studies difficult. Moreover, commonly used rodent models often fail to fully reproduce the pathophysiological complexity of human chronic wounds, particularly those associated with diabetes, ageing, vascular insufficiency, and polymicrobial infection. Development of more clinically relevant experimental models, including human skin equivalents, three-dimensional organoid cultures, organ-on-chip platforms, and advanced bioengineered tissues, may substantially improve translational accuracy (96).

Clinical translation is additionally hindered by the limited availability of robust randomized controlled trials. Although numerous pilot studies report encouraging outcomes, most involve relatively small patient cohorts, short treatment durations, and heterogeneous methodologies. Differences in wound type, phytochemical formulation,

dosing strategies, treatment protocols, and outcome assessment further reduce comparability across studies. Large multicentre clinical trials employing standardized formulations, harmonized reporting criteria, and objective molecular biomarkers will therefore be necessary to establish definitive evidence for clinical efficacy and long-term safety (100).

An important future direction involves the incorporation of biomarker-guided precision medicine into chronic wound management. Rather than applying identical treatments to all patients, individualized therapeutic strategies based on molecular profiling may improve treatment outcomes. Biomarkers including p16^INK4a, p21, SA-β-gal, inflammatory cytokines, oxidative stress markers, mitochondrial function indicators, and transcriptomic signatures may enable early identification of senescence-dominant wounds and facilitate personalized therapeutic selection. Such biomarker-driven approaches could improve patient stratification, optimize treatment timing, and enhance clinical response while minimizing unnecessary interventions (43), (83).

The rapid evolution of multi-omics technologies is expected to further transform phytochemical research. Integration of genomics, transcriptomics, proteomics, metabolomics, epigenomics, and single-cell sequencing now enables comprehensive characterization of the molecular networks underlying chronic wound progression. These technologies facilitate identification of novel therapeutic targets, biomarker discovery, and mechanistic understanding of phytochemical activity at unprecedented resolution. Future integration of multi-omics datasets with systems biology approaches will likely accelerate discovery of next-generation senomorphic compounds and combination therapies (84).

Artificial intelligence (AI) and machine learning are also emerging as powerful tools for phytopharmaceutical development. AI-driven algorithms can analyse extensive biological datasets to predict phytochemical–target interactions, optimize molecular structures, identify synergistic phytochemical combinations, and forecast pharmacokinetic or toxicological behaviour. Machine learning models further support formulation optimization, image-based wound assessment, and prediction of therapeutic outcomes, thereby contributing to more efficient and personalized wound care. As biomedical datasets continue to expand, AI-assisted drug discovery is expected to become an integral component of regenerative medicine research (85).

Another promising direction involves the development of smart multifunctional wound dressings that combine phytochemicals with nanotechnology, biosensors, and responsive biomaterials. Future wound dressings may continuously monitor pH, temperature, oxygen tension, glucose concentration, bacterial burden, and inflammatory biomarkers while simultaneously delivering phytochemicals in response to real-time physiological changes. Such integrated theranostic systems have the potential to transform chronic wound management from passive wound coverage to active, adaptive, and personalized therapy (93).

Regulatory harmonization remains another important consideration. Despite increasing commercial interest in phytopharmaceutical products, regulatory requirements differ considerably among countries regarding botanical standardization, manufacturing quality, efficacy evaluation, and clinical evidence. Establishment of internationally harmonized regulatory frameworks, together with adoption of Quality by Design (QbD) principles, Good Manufacturing Practices (GMP), and standardized analytical methodologies, will be essential for facilitating global commercialization and clinical acceptance of phytochemical-based therapeutics (94).
Overall, the future of senomorphic phytochemicals extends beyond the development of individual natural compounds. The field is evolving toward precision phytopharmaceuticals, where standardized botanical products, advanced nanotechnology, computational drug discovery, artificial intelligence, biomarker-guided therapy, and smart biomaterials converge to create personalized regenerative treatments. Achieving this vision will require close collaboration among pharmacologists, pharmaceutical scientists, molecular biologists, biomaterials engineers, clinicians, computational scientists, and regulatory agencies. Such multidisciplinary integration has the potential to establish senomorphic phytochemicals as a new generation of evidence-based therapeutics for chronic wound management.

Table 10. Major Challenges and Future Opportunities in Senomorphic Phytochemical Research

Current challenge	Clinical impact	Future opportunity
Variability of phytochemical composition	Inconsistent therapeutic efficacy	Standardized botanical sourcing and phytochemical fingerprinting
Poor bioavailability	Reduced tissue exposure	Nano-enabled and targeted delivery systems
Limited clinical trials	Weak clinical evidence	Large multicentre randomized controlled studies

Lack of senescence biomarkers	Difficult patient stratification	Biomarker-guided precision medicine
Inadequate disease models	Poor translational relevance	Human organoids, skin-on-chip, and bioengineered wound models
Regulatory heterogeneity	Delayed clinical translation	Harmonized international regulatory frameworks
Fragmented biological datasets	Limited mechanistic understanding	Multi-omics integration and systems pharmacology
Conventional wound dressings	Passive wound management	Smart theranostic wound dressings with AI integration

12. CONCLUSION:

Cellular senescence has emerged as a fundamental biological process that shapes both physiological tissue repair and pathological wound chronicity. While transient senescence plays an essential role in coordinating inflammation, tissue remodelling, and regeneration during normal wound healing, persistent accumulation of senescent cells disrupts tissue homeostasis through sustained production of the senescence-associated secretory phenotype (SASP), excessive oxidative stress, mitochondrial dysfunction, impaired angiogenesis, extracellular matrix degradation, and chronic inflammation. These interconnected pathological events contribute significantly to the development of non-healing wounds, particularly in ageing individuals and patients with diabetes mellitus, vascular disorders, pressure injuries, and other chronic inflammatory conditions. Consequently, modulation of cellular senescence has become an increasingly attractive therapeutic strategy for promoting regenerative wound repair.

This review comprehensively highlights the growing evidence supporting senomorphic phytochemicals as promising multifunctional therapeutic agents capable of restoring the molecular balance of the chronic wound microenvironment. Unlike senolytic therapies, which selectively eliminate senescent cells, senomorphic phytochemicals preserve the beneficial physiological functions of transient senescence while suppressing detrimental SASP-mediated signalling. Through coordinated regulation of multiple molecular pathways—including NF-κB, Nrf2, AMPK/SIRT1, PI3K/Akt, TGF-β, VEGF, mTOR, and Wnt/β-catenin—these natural compounds simultaneously attenuate oxidative stress, reduce chronic inflammation, improve mitochondrial function, stimulate angiogenesis, enhance extracellular matrix remodelling, and support tissue regeneration. Such multitarget pharmacological activity represents a major therapeutic advantage over conventional single-target interventions for complex disorders such as chronic wounds.

Among the diverse classes of phytochemicals, polyphenols, flavonoids, terpenoids, alkaloids, saponins, and polysaccharides have demonstrated significant senomorphic potential in experimental wound models. Bioactive molecules including quercetin, resveratrol, curcumin, epigallocatechin-3-gallate, asiaticoside, berberine, and related phytoconstituents consistently improve fibroblast proliferation, keratinocyte migration, collagen synthesis, vascular regeneration, and immune modulation while suppressing inflammatory mediators and oxidative damage. Importantly, their therapeutic effects arise through coordinated modulation of interconnected signalling networks rather than isolated molecular targets, reflecting the systems-level complexity of wound repair. This characteristic makes phytochemicals particularly suitable for managing chronic wounds, where multiple pathological pathways remain simultaneously dysregulated.

The review further demonstrates how modern computational technologies have transformed phytochemical research. Network pharmacology, molecular docking, molecular dynamics simulations, and multi-omics approaches have substantially improved understanding of the molecular mechanisms underlying phytochemical activity by identifying critical therapeutic targets and signalling networks associated with chronic wound healing. These computational methodologies not only accelerate discovery of novel senomorphic compounds but also provide mechanistic evidence that complements traditional experimental studies. Integration of artificial intelligence and machine learning with systems pharmacology is expected to further enhance target prediction, compound prioritization, formulation optimization, and personalized therapeutic development in the coming years.

Another major advancement discussed in this review is the application of nano-enabled drug delivery systems to overcome the pharmaceutical limitations of phytochemicals. Poor aqueous solubility, limited bioavailability, rapid metabolism, and inadequate tissue penetration have historically restricted the clinical translation of many natural products. Polymeric nanoparticles, lipid-based nanocarriers, hydrogels, electrospun nanofibres, zinc oxide nanoparticle composites, and stimuli-responsive wound dressings now provide effective strategies for improving

local drug retention, controlled release, and therapeutic efficacy. The convergence of nanotechnology with phytopharmaceutical sciences represents an important milestone in the development of advanced regenerative therapies for chronic wound management.

Although current preclinical evidence strongly supports the biological efficacy of senomorphic phytochemicals, clinical translation remains at an early stage. Most available human studies demonstrate encouraging improvements in wound closure, granulation tissue formation, angiogenesis, and patient safety; however, substantial heterogeneity exists regarding botanical standardization, extraction methods, formulation design, dosage regimens, clinical endpoints, and study quality. Consequently, there remains an urgent need for well-designed multicentre randomized controlled trials employing standardized phytochemical preparations, validated senescence biomarkers, harmonized reporting standards, and long-term follow-up to establish definitive clinical efficacy and safety.

Future progress in this field will depend upon a multidisciplinary integration of pharmaceutical sciences, molecular biology, biomaterials engineering, computational biology, regenerative medicine, and clinical research. Development of standardized phytopharmaceutical products, biomarker-guided precision medicine, smart theranostic wound dressings, advanced organoid and skin-on-chip models, and artificial intelligence-assisted drug discovery will collectively accelerate translation from laboratory research to clinical practice. Furthermore, implementation of Quality by Design (QbD), Good Manufacturing Practices (GMP), and internationally harmonized regulatory frameworks will be essential to ensure reproducibility, product quality, and global regulatory acceptance.

In conclusion, senomorphic phytochemicals represent a rapidly evolving therapeutic paradigm that bridges traditional medicinal knowledge with contemporary molecular medicine, pharmaceutical technology, and computational drug discovery. Their unique ability to modulate multiple interconnected signalling pathways responsible for chronic wound pathology positions them as promising candidates for next-generation regenerative therapeutics. Continued interdisciplinary research, supported by rigorous mechanistic investigations, standardized pharmaceutical development, and high-quality clinical validation, is expected to facilitate the successful translation of these natural compounds into evidence-based therapies capable of improving outcomes for millions of patients suffering from chronic wounds worldwide.

ABBREVIATIONS:

Abbreviation	Full Form
AI	Artificial Intelligence
Akt	Protein Kinase B
AMPK	AMP-Activated Protein Kinase
ATP	Adenosine Triphosphate
CAT	Catalase
CQA	Critical Quality Attribute
CPP	Critical Process Parameter
DoE	Design of Experiments
ECM	Extracellular Matrix
EGCG	Epigallocatechin-3-gallate
EMT	Epithelial–Mesenchymal Transition
GO	Gene Ontology
GMP	Good Manufacturing Practice
GACP	Good Agricultural and Collection Practice
HIF-1α	Hypoxia-Inducible Factor-1 Alpha
IL	Interleukin
KEGG	Kyoto Encyclopedia of Genes and Genomes
MAPK	Mitogen-Activated Protein Kinase
MD	Molecular Dynamics
MMP	Matrix Metalloproteinase
mTOR	Mammalian Target of Rapamycin
NF-κB	Nuclear Factor-kappa B
Nrf2	Nuclear Factor Erythroid 2-Related Factor 2

PI3K	Phosphoinositide 3-Kinase
PPI	Protein–Protein Interaction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QbD	Quality by Design
ROS	Reactive Oxygen Species
SA-β-gal	Senescence-Associated β-Galactosidase
SASP	Senescence-Associated Secretory Phenotype
SIRT1	Sirtuin-1
SLN	Solid Lipid Nanoparticle
STRING	Search Tool for the Retrieval of Interacting Genes/Proteins
TGF-β	Transforming Growth Factor-Beta
TNF-α	Tumor Necrosis Factor-Alpha
VEGF	Vascular Endothelial Growth Factor
ZnO NP	Zinc Oxide Nanoparticle

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angiogenesis, extracellular matrix remodelling, and tissue regeneration.
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