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Canna Indica L. Harnessing leaf extract for targeted fibroblast proliferation.

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ABSTRACT

Cutaneous wounds that fail to close in an orderly and timely manner continue to burden patients and health systems, and the dermal fibroblast is central to their repair because it builds the new connective tissue that fills and strengthens the injured site. Plant-derived preparations have long been applied to wounds in traditional medicine, and modern research increasingly links their benefit to secondary metabolites that influence inflammation, oxidative stress, cell proliferation and matrix deposition. Canna indica L. (Cannaceae), known as Indian shot, is a widely distributed ornamental and medicinal herb whose crushed plant material is traditionally applied to cuts and bruises and which is reported to contain phenolics, flavonoids, tannins, alkaloids and terpenoid-type compounds. This review brings together current knowledge on the botany, ethnomedicinal background, phytochemistry and reported pharmacology of C. indica and sets it against present understanding of fibroblast biology in wound repair. The molecular regulators of fibroblast proliferation, including growth factor, transforming growth factor-β, PI3K/Akt, MAPK/ERK, Wnt, NF-κB and Nrf2 signalling, are discussed, followed by an analysis of how the phytochemical classes found in the leaf could plausibly act on these routes. Extraction and standardisation strategies, preclinical models, formulation approaches, safety aspects and the need to avoid uncontrolled proliferation leading to hypertrophic scarring are also considered. Although the phytochemical and antioxidant profile of the leaf supports a rational case for its use in tissue repair, direct experimental proof that C. indica leaf extract promotes fibroblast proliferation is, to the best of our knowledge, still limited. The article is intended as a hypothesis-building review that identifies research gaps rather than as a summary of proven efficacy. Standardised extracts, well-designed cell-based assays, mechanistic studies and controlled in vivo work are therefore proposed as the next steps towards a validated, targeted fibroblast-supporting preparation.

Keywords: *Canna indica*; fibroblast proliferation; wound healing; phytochemicals; extracellular matrix; herbal medicine.

List of Abbreviations

α-SMA Alpha-smooth muscle actin
ABTS 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
Akt Protein kinase B
DPPH 2,2-Diphenyl-1-picrylhydrazyl
ECM Extracellular matrix
EGF Epidermal growth factor
ERK Extracellular signal-regulated kinase
FGF Fibroblast growth factor
FRAP Ferric reducing antioxidant power
Keap1 Kelch-like ECH-associated protein 1
MAPK Mitogen-activated protein kinase
MMP Matrix metalloproteinase
MTT 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NF-κB Nuclear factor kappa B
Nrf2 Nuclear factor erythroid 2-related factor 2
PDGF Platelet-derived growth factor
PI3K Phosphatidylinositol 3-kinase
ROS Reactive oxygen species
TGF-β Transforming growth factor-beta
VEGF Vascular endothelial growth factor

I. Introduction

The skin is the first line of defence of the human body, and any break in its continuity sets in motion a tightly orchestrated repair programme. Classically, this programme is described as four overlapping phases, namely haemostasis, inflammation, proliferation and remodelling, each of which depends on the timely arrival, activation and withdrawal of different cell populations [1,2]. When the programme is disturbed by infection, persistent

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inflammation, poor perfusion, advancing age, metabolic disease or inadequate nutrition, a wound may stall and become chronic [3,4]. Chronic and difficult-to-heal wounds are distressing for patients and they also consume a large share of health-care resources, and their global burden is considered to be growing [5]. Diabetic wounds illustrate the problem well, because several defects in cellular behaviour accumulate in the same lesion and make healing slow and unreliable [6].

Among the cells that drive repair, the dermal fibroblast has a particularly important role during the proliferative phase. Fibroblasts migrate into the wound bed, multiply, and lay down a provisional matrix rich in collagen and other structural proteins that supports new blood vessels and, eventually, the returning epidermis [7,8]. Fibroblasts are no longer viewed as a uniform population; lineage-tracing and single-cell studies have revealed distinct subsets that contribute differently to repair, scarring and disease [9–11]. Too little fibroblast activity yields fragile granulation tissue and delayed closure, whereas excessive or prolonged activity favours fibrosis and pathological scars [12–14]. The therapeutic aim is therefore not simply to push fibroblasts to divide, but to support their proliferation and matrix synthesis at the right time, in the right place and to the right degree, and then to allow the process to resolve. This is the sense in which the word "targeted" is used in the present review.

Medicinal plants have been applied to wounds for centuries, and surveys of traditional practice together with recent experimental work continue to identify herbal preparations that appear to shorten healing time, limit infection and improve the quality of the repaired tissue [15–17]. The benefit of such preparations is generally ascribed to secondary metabolites, notably flavonoids, phenolic compounds, tannins, alkaloids, saponins and terpenoids, which act through several routes at once rather than through a single receptor [18,19]. Because a crude extract is a mixture, its activity is the combined result of many constituents. This multi-component character is both the attraction of herbal extracts and the main difficulty when standardisation and mechanism of action are considered.

Canna indica L. (family Cannaceae), commonly known as Indian shot, is a rhizomatous perennial that is widely grown as an ornamental plant in tropical and subtropical regions and has a long record of use in folk medicine [20,21]. Published reports describe antimicrobial, antioxidant, anti-inflammatory, analgesic, hepatoprotective, antidiarrhoeal and several other activities in extracts of different plant parts [20]. Extracts of the plant have also been reported to reduce the release of inflammatory mediators from monocyte-macrophage cells exposed to high glucose and lipopolysaccharide [22]. These observations, together with the phenolic and flavonoid content frequently reported for the leaf, make *C. indica* leaf extract an interesting candidate for investigation in tissue repair. However, to the best of our knowledge, direct experimental evidence on the effect of *C. indica* leaf extract on fibroblast proliferation is limited, and this article should therefore be read as a hypothesis-building review rather than a summary of established efficacy.

This narrative review has four aims: to summarise the botany, traditional use, phytochemistry and reported pharmacology of *C. indica*; to outline the cellular and molecular biology of fibroblasts in wound repair; to examine how the phytochemical classes present in the leaf could plausibly influence fibroblast behaviour; and to identify the experimental, formulation and safety steps needed to move from a plausible hypothesis to a validated preparation. Supporting literature was drawn mainly from open-access review articles that are indexed in PubMed and available in PubMed Central. Because no review dealing specifically with *C. indica* and wound repair could be identified, three Canna-specific publications were added to describe the plant itself.

II. Botanical Profile of Canna indica L.

2.1 Taxonomy and nomenclature

Canna indica L. belongs to the family Cannaceae, which is placed in the monocot order Zingiberales together with the ginger, banana and arrowroot families. The family is monotypic and contains only the genus *Canna*, a name derived from a Greek word for a cane or reed [20]. Several names are listed as synonyms of *C. indica* in the literature, including *Canna coccinea* Mill., *Canna edulis* Ker Gawl. and *Canna lutea* Mill. [20,21]. Common English names include Indian shot, canna lily, African arrowroot and wild canna [20]. Because garden hybrids and closely related species are widely cultivated, correct botanical authentication of the plant material is an essential first step in any pharmacological study, and a voucher specimen should be deposited in a recognised herbarium.

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2.2 Distribution and habitat

The genus is native to the tropical and subtropical regions of the Americas, and *C. indica* has been introduced, cultivated and naturalised in many parts of Asia and Africa, including India, where it is common in gardens, along roadsides and canal banks and in other moist places [20,21]. The plant tolerates a range of soils but grows most vigorously in warm, humid conditions with abundant moisture. Its wide availability, rapid regrowth and low cultivation cost are practical advantages if a leaf-based preparation is ever to be developed, although the same adaptability raises questions about the environment in which the plant has grown, a point taken up in the section on safety.

2.3 Morphology

Canna indica is an erect, rhizomatous perennial herb that commonly reaches about one to two metres in height. The aerial stem is a pseudostem formed by the tightly overlapping sheaths of the leaves, which arise from a thick, starch-rich, creeping rhizome. The leaves are large, alternate and broadly ovate to elliptic with a pointed tip, with a prominent midrib and fine parallel lateral veins running towards the margin; their colour ranges from fresh green to bronze or purplish depending on the variety. The flowers are borne in terminal racemes and are asymmetrical, with showy petal-like staminodes in shades of red, orange or yellow. The fruit is a warty, three-chambered capsule that contains hard, rounded black seeds, the feature that gives the plant its common name of Indian shot [20]. The overall habit of the plant is shown in Figure 1.

Figure 1. *Canna indica* L. plant.

III. Ethnomedicinal Background

In the traditional systems of several countries, different parts of *C. indica* are used for a wide spectrum of complaints. Decoctions of the rhizome and root have been taken for fever, dropsy, dyspepsia, diarrhoea and dysentery, the flowers have been applied in disorders of the eye, and the plant has also been employed as a diuretic [20,21]. The starchy rhizome is additionally used as a food and a tonic in some communities.

For the purposes of this review, the most relevant folk practice is the external application of crushed or bruised plant material to cuts, bruises and similar skin injuries [21]. Experimental findings that the plant influences clotting time and capillary permeability in mice lend some plausibility to this practice, because control of bleeding and swelling is an early requirement of repair, but these findings have not been followed up with cell-based studies of the later proliferative phase [21].

Traditional knowledge is shaped by the choice of plant part, method of preparation, dose and local custom, and it rarely records any of these in a standardised manner. Ethnomedicinal use

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should therefore be treated as a source of leads for laboratory investigation and not as proof of efficacy. Surveys of wound-healing plants make the same point: the continued popularity of a remedy indicates that there is something to learn from it, but the lesson has to be confirmed by controlled work [15].

IV. Phytochemistry of Canna indica

Preliminary phytochemical screening of *C. indica* has repeatedly detected alkaloids, flavonoids, phenolic compounds, tannins, steroids, glycosides, carbohydrates and proteins, and the flowers are a recognised source of anthocyanin pigments [20]. Chemical investigations of the aerial parts have led to the isolation of triterpenoid and sterol-type compounds, among them betulinic acid, and the rhizome has been examined for its essential oil and non-polar constituents [21]. Seeds have also been analysed for their flavonoid content [21].

Two features of this literature deserve emphasis. First, most reports rely on qualitative colour or precipitation tests, which indicate the presence of a class of compounds but say little about the amount or the identity of individual molecules. Second, the composition of any plant extract depends on the plant part, geographical origin, season of harvest, drying conditions and, above all, the solvent and technique used for extraction [23]. A compound class reported from one sample and not from another may therefore reflect differences in method rather than in the plant. For the leaf, which is the part of interest here, quantitative profiling by chromatographic methods, together with the measurement of total phenolic and flavonoid content, is needed before pharmacological results from different laboratories can be compared with confidence.

From the point of view of tissue repair, the classes of greatest interest are the phenolic compounds and flavonoids, which are strong antioxidants and regulators of inflammatory signalling, the tannins, which are astringent and antimicrobial, and the triterpenoids and sterols, which belong to groups that have been linked with matrix synthesis and cell proliferation in other medicinal plants [18,19]. The potential contribution of each class is discussed in Section 8.

Table 1 summarises the phytochemical classes of greatest interest for tissue repair and the basis on which each is considered.

Table 1. Phytochemical classes of interest in *C. indica* leaf and their possible relevance to fibroblast-mediated repair

Class	Basis in the literature	Possible relevance to tissue repair	Ref.
Flavonoids	Detected in screening; seeds analysed for flavonoid content	Antioxidant and anti-inflammatory; may favour proliferation and migration of skin cells, collagen synthesis and angiogenesis; effects depend on concentration	19–21, 49
Phenolic acids and polyphenols	Phenolic compounds repeatedly detected in screening	Antioxidant, anti-inflammatory and antimicrobial; modulate oxidative stress and inflammatory signalling	20, 50, 51
Tannins	Detected in screening	Astringent and antimicrobial; may form a protective surface layer and reduce microbial load, but may inhibit cell growth at high concentrations	20, 24, 52
Alkaloids	Reported in screening studies	Some are anti-inflammatory or antimicrobial, others cytotoxic; call for careful cytotoxicity testing	18, 20, 53
Terpenoids, triterpenoids and sterols	Betulinic acid and sterol-type compounds isolated from the aerial parts	Antimicrobial, antioxidant and anti-inflammatory; triterpenoids linked to collagen synthesis and proliferation in other medicinal plants	18, 21, 54

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V. Reported Pharmacological Activities

Reviews of *C. indica* list anthelmintic, antibacterial, antiviral, antidiabetic, antidiarrhoeal, anti-inflammatory, analgesic, immunomodulatory, antioxidant, cytotoxic, haemostatic, hepatoprotective and molluscicidal effects, mostly in studies on crude extracts of different plant parts [20,21]. Several of these actions bear directly on the conditions that a healing wound requires, and they can be considered in turn.

Antimicrobial activity. Bacterial colonisation and biofilm formation are among the commonest reasons why wounds stall. Plant phenolics, tannins, flavonoids, terpenoids and alkaloids are known to injure microbial cells through several mechanisms, such as damage to membranes, inhibition of enzymes and deprivation of essential substrates [24]. Reports of antibacterial and antifungal activity in *C. indica* extracts are therefore consistent with its chemical profile [20].

Antioxidant activity. Excessive reactive oxygen species damage cells and matrix in the wound environment and contribute to the failure of chronic wounds to progress [25]. Antioxidant compounds have been proposed as supportive agents in wound care, although the evidence from clinical studies remains limited and mixed [26]. Radical-scavenging activity is one of the most consistently reported properties of *C. indica* extracts [20].

Anti-inflammatory activity. An orderly transition from the inflammatory to the proliferative phase is a prerequisite for fibroblast activity, and persistent inflammation is a hallmark of chronic wounds [27,28]. The ability of *C. indica* extracts to lower inflammatory mediators in activated macrophage-type cells [22], and the anti-inflammatory and analgesic effects summarised in reviews [20,21], therefore suggest a way in which the plant might create a more favourable environment for fibroblasts. It must be stressed that these studies were not designed as wound models.

Haemostatic activity. Shortened clotting and bleeding times and reduced capillary permeability have been described in mice treated with plant preparations [21], which would be compatible with the traditional use of crushed leaves on fresh cuts.

Taken together, these data indicate that *C. indica* possesses properties that could remove some of the obstacles to the proliferative phase of healing. Nevertheless, most studies used non-standardised crude extracts, a variety of plant parts and widely differing doses, many relied on chemical assays rather than on cells relevant to skin repair, and few separated the contribution of the leaf from that of other organs. These limitations must be kept in view when the plant is considered as a fibroblast-supporting agent.

VI. Skin Wound Healing and the Place of the Fibroblast

6.1 Phases of repair

Immediately after injury, platelets aggregate and the coagulation cascade forms a fibrin clot that stops bleeding and acts as a temporary scaffold; the platelets and the damaged tissue release growth factors and cytokines that call in inflammatory cells [1,2]. Neutrophils arrive first to clear debris and microbes, and they are followed by monocytes that mature into macrophages. The macrophage is a pivotal cell, because its shift from a pro-inflammatory to a reparative phenotype helps to switch the wound from inflammation to proliferation [27,29]. If this switch fails, inflammation persists, proteases and reactive oxygen species accumulate and the wound becomes chronic [28].

During the proliferative phase, keratinocytes migrate and multiply to restore the epidermal barrier [30], endothelial cells form new vessels under the influence of vascular endothelial growth factor and related signals [31], and fibroblasts build granulation tissue, a vascular and cell-rich connective tissue that fills the wound space [7]. In the final remodelling phase, the provisional matrix is progressively replaced and reorganised, collagen is cross-linked and aligned, many cells are removed by apoptosis, and the wound matures into a scar of increasing tensile strength [1,32]. The phases overlap in time and space, and a defect in one phase is usually transmitted to the next.

6.2 Fibroblast origin and heterogeneity

The dermis contains fibroblast lineages that differ in location, gene expression and function, for example those of the papillary and the reticular dermis, and different subsets contribute in distinct ways to matrix deposition, hair follicle support and scarring [9,10]. In wounds, fibroblasts are recruited chiefly from resident populations and respond to local cues, and the idea that a single, uniform fibroblast type heals the skin is no longer tenable [11]. This heterogeneity has a practical consequence for herbal research. Most in vitro studies employ a single primary or immortalised cell type, such as

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normal human dermal fibroblasts or murine 3T3 cells, which may not represent the subsets that matter most in a wound. Results should therefore be interpreted with this limitation in mind and, where possible, confirmed in more than one model.

6.3 Proliferation, migration and matrix synthesis

Fibroblasts are activated by platelet-derived and macrophage-derived growth factors, migrate along the fibrin-fibronectin provisional matrix, multiply in the wound bed and begin to secrete large amounts of extracellular matrix, chiefly collagen, together with fibronectin, proteoglycans and hyaluronan [7,8]. The matrix is not an inert filler; it provides a scaffold for cell movement, stores growth factors and transmits mechanical and biochemical signals back to cells [33]. Collagen is the principal structural protein of the dermis, and the amount, type and organisation of collagen laid down in the wound determine how strong the repaired tissue will be [34].

Matrix synthesis is always balanced by matrix degradation. Matrix metalloproteinases, produced by fibroblasts, macrophages and keratinocytes, remove damaged matrix and allow cell migration and remodelling, while their natural tissue inhibitors prevent excessive breakdown [35]. Imbalance in either direction impairs healing: too much protease activity destroys growth factors and new matrix in chronic wounds, whereas too little favours the accumulation of dense, disorganised collagen [32,35]. A fibroblast-directed preparation should therefore be judged not only by cell number but also by the quality of the matrix that the cells produce.

6.4 Myofibroblasts and the resolution of repair

Under the influence of transforming growth factor-β and mechanical tension, a proportion of wound fibroblasts differentiate into myofibroblasts. These cells express alpha-smooth muscle actin, generate contractile force that draws the wound edges together and secrete matrix very actively [8,36]. In normal healing, myofibroblasts disappear when closure is complete, either through apoptosis or through loss of their activated state. When they persist, as in fibrosis and pathological scarring, matrix accumulates and tissue function is lost [12,36,37]. The behaviour of fibroblasts therefore has two sides: their activation is essential for repair, yet their failure to switch off is harmful. Any strategy that aims at fibroblast proliferation must respect this duality.

VII. Molecular Regulators of Fibroblast Proliferation

7.1 Transforming growth factor-β and Smad signalling

Transforming growth factor-β (TGF-β) is present from the earliest to the latest stage of healing. It attracts fibroblasts and inflammatory cells, stimulates collagen and other matrix genes, drives myofibroblast differentiation and also influences re-epithelialisation, with its isoforms differing in effect [38]. At the receptor level, ligand binding activates a pair of serine-threonine kinase receptors that phosphorylate Smad2 and Smad3, which then combine with Smad4 and move into the nucleus to regulate gene transcription; non-Smad routes, including mitogen-activated protein kinase and phosphatidylinositol 3-kinase cascades, run in parallel [39]. Excessive or sustained TGF-β signalling is a central driver of fibrosis [12,40]. A candidate extract should therefore be examined for its effect on TGF-β signalling, with the aim of avoiding over-activation.

7.2 Growth factor receptors

Platelet-derived growth factors are potent mitogens and chemoattractants for mesenchymal cells, including fibroblasts, and are released early from platelets and macrophages [41]. The fibroblast growth factor family, acting through its tyrosine kinase receptors, regulates proliferation, migration and survival in many tissues and takes part in several steps of skin repair [42]. The epidermal growth factor system acts mainly on keratinocytes and epithelial migration but has wider effects on cutaneous repair [43], and vascular endothelial growth factor sustains the blood supply on which proliferating cells depend [31]. Because these receptors converge on shared intracellular cascades, a plant constituent that modifies those cascades, directly or through antioxidant action, could in principle alter the response of fibroblasts to endogenous growth factors.

7.3 PI3K/Akt and MAPK/ERK cascades

Receptor tyrosine kinases of the platelet-derived and fibroblast growth factor families signal largely through the phosphatidylinositol 3-kinase (PI3K)/Akt cascade and the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) cascade [41,42]. Akt promotes cell survival, growth and cell-cycle progression through a large network of substrates

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[44], while the ERK cascade relays proliferative signals to the nucleus. Activation of these two routes is a common mechanism by which mitogens increase the number of fibroblasts, and phosphorylation of Akt and ERK is a convenient, measurable indicator of whether a test substance acts as a mitogen in cultured cells.

7.4 Wnt/β-catenin signalling

Wnt signalling is activated after injury in many tissues, where it contributes to cell proliferation and tissue repair, and its regulation is important because inappropriate or prolonged activity is associated with fibrotic outcomes [12,45]. In skin, Wnt/β-catenin activity has been linked to the behaviour of dermal fibroblasts during repair, which makes it a pathway that deserves attention when the effects of a botanical preparation on fibroblast number and matrix output are studied [45].

7.5 NF-κB and inflammatory signalling

Nuclear factor kappa B (NF-κB) is a family of transcription factors that controls the expression of inflammatory cytokines, chemokines and adhesion molecules, and sustained NF-κB activation is characteristic of chronic inflammation [46,47]. In chronic wounds, high levels of inflammatory mediators and proteases create a hostile environment in which fibroblasts become less responsive to growth stimuli [28]. Reduction of excessive NF-κB-driven inflammation is therefore one indirect way by which an anti-inflammatory plant extract may favour fibroblast proliferation.

7.6 Redox balance and Nrf2

Reactive oxygen species play a dual role in healing. At low concentrations they act as signalling molecules that support cell migration, proliferation and defence against microbes, whereas at high concentrations they damage lipids, proteins and DNA and delay repair [25]. The transcription factor Nrf2, normally held in check by its inhibitor Keap1, is a master regulator of the cellular antioxidant response; when oxidative stress rises, Nrf2 moves to the nucleus and activates genes that encode antioxidant and detoxifying proteins [48]. Many polyphenols are believed to act, at least in part, by engaging this pathway, and the potential of antioxidant strategies in wound care has been reviewed [26].

These pathways do not operate independently. TGF-β, growth factors, Wnt, NF-κB and redox signals interact at several points, so that a change in one is likely to alter the others. A well-designed study of a plant extract should therefore measure more than one endpoint and avoid attributing an effect to a single pathway on the basis of a single marker.

Table 2 summarises the regulators discussed above and the points that deserve attention when a plant extract is studied.

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Table 2. Molecular regulators of fibroblast proliferation and points of attention for herbal extract studies

Pathway	Principal role in repair	Point of attention for extract studies	Ref.
TGF-β/Smad	Attracts fibroblasts and inflammatory cells, stimulates collagen and matrix genes, drives myofibroblast differentiation	Excess or sustained signalling drives fibrosis; over-activation should be avoided	12, 38–40
Growth factor receptors (PDGF, FGF, EGF, VEGF)	Mitogenic and chemotactic signals for mesenchymal cells; FGF supports proliferation, migration and survival; VEGF sustains blood supply	Converge on shared cascades; constituents that modify these cascades could alter the response to endogenous growth factors	31, 41–43
PI3K/Akt and MAPK/ERK	Relay proliferative and survival signals to the nucleus	Phosphorylated Akt and ERK are measurable indicators of mitogenic action in cultured cells	41, 42, 44
Wnt/β-catenin	Activated after injury; contributes to proliferation and repair	Inappropriate or prolonged activity is associated with fibrosis	12, 45
NF-κB	Controls inflammatory cytokines, chemokines and adhesion molecules	Sustained activation characterises chronic inflammation; reducing it may indirectly favour fibroblast proliferation	28, 46, 47
Nrf2/Keap1	Master regulator of the cellular antioxidant response	Many polyphenols are believed to act partly through this pathway	25, 26, 48

VIII. Phytochemicals as Modulators of Fibroblast Activity

8.1 Flavonoids

Flavonoids are polyphenolic compounds built on a fifteen-carbon skeleton and are divided into several subclasses such as flavonols, flavones, flavanones, isoflavones and anthocyanidins; they occur widely in leaves, flowers and fruits and are credited with antioxidant, anti-inflammatory and antimicrobial properties [49]. A review of their role in healing concluded that they can influence pathways in the inflammatory, proliferative and remodelling phases, for example by limiting oxidative stress and inflammatory cytokine release, promoting the proliferation and migration of skin cells, and favouring collagen synthesis and angiogenesis [19]. Their effects are, however, dependent on concentration, and the same compound can stimulate cells at low doses and inhibit them at higher ones, which is why dose-response studies are indispensable.

8.2 Phenolic acids, polyphenols and tannins

Phenolic acids, divided into hydroxybenzoic and hydroxycinnamic derivatives, are simple polyphenols with antioxidant, anti-inflammatory and antimicrobial activities [50]. Polyphenols as a group have been associated with the modulation of oxidative stress and inflammatory signalling in many experimental systems [51]. Tannins, which include condensed proanthocyanidins and hydrolysable tannins, bind proteins and metal ions, which accounts for their astringency and antimicrobial action [52]. In wounds, this property may help to form a protective surface layer and to reduce microbial load, but at high concentrations tannins may inhibit cell growth, so that their role must be defined experimentally rather than assumed [24,52].

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8.3 Alkaloids

Alkaloids are a chemically diverse group of nitrogen-containing compounds, many of which are pharmacologically potent, and they form the basis of a number of important medicines [53]. In the context of wound repair, some alkaloids are described as anti-inflammatory or antimicrobial, whereas others are cytotoxic [18,53]. For a plant such as *C. indica*, in which alkaloids have been reported in screening studies [20], the presence of this class is therefore a reason for careful cytotoxicity testing and not an assurance of benefit.

8.4 Terpenoids, saponins and sterols

Terpenoids form the largest group of plant secondary metabolites and include monoterpenes, sesquiterpenes, diterpenes and triterpenes, many with antimicrobial, antioxidant and anti-inflammatory properties [54]. Triterpenoids and saponins from several wound-healing plants are credited with stimulating collagen synthesis and cell proliferation [18], and plant sterols are frequently part of the lipophilic fraction of leaf extracts. The occurrence of triterpenoid and sterol-type compounds in the aerial parts of *C. indica* [21] makes this fraction worthy of attention, although whether it is present in the leaf at an active level has not been shown.

8.5 Evidence from studies on wound-healing plants

Surveys of herbal wound-healing research show that many plants have been tested for effects on fibroblast viability and migration in cell culture and for wound contraction, epithelialisation, collagen content and histology in animals [17,18]. Certain species, among them *Centella asiatica*, *Curcuma longa* and *Paeonia suffruticosa*, stand out in such surveys as particularly well documented [15]. The proposed mechanisms include anti-inflammatory, antimicrobial and antioxidant actions together with stimulation of collagen synthesis, cell proliferation and angiogenesis [18]. Comprehensive discussions of traditional therapies and of selected natural products point in the same direction, while also noting the variable quality of many of the underlying studies [16,17].

8.6 Multi-target action and synergy

A crude extract contains many constituents that may act at different points of the same network. One compound may scavenge radicals, another may reduce inflammatory signalling and a third may stimulate proliferation, and together they may produce an effect that none would give alone [18,19]. This possibility of synergy is often cited as an advantage of whole extracts over isolated compounds. It is, however, difficult to prove, and it makes standardisation and the identification of marker compounds more important rather than less.

IX. Mechanistic Rationale for Canna indica Leaf Extract

The case for investigating *C. indica* leaf extract rests on three lines of reasoning, none of which is yet a demonstration of effect. The first is chemical: the classes reported for the plant, namely phenolics, flavonoids, tannins, terpenoids and sterols, overlap with the classes that review authors associate with wound-healing activity in other species [18–20]. The second is pharmacological: antioxidant, anti-inflammatory, antimicrobial and haemostatic activities have been described, and these address the very conditions that, if unfavourable, prevent fibroblasts from entering and sustaining the proliferative phase [20–22,25,27]. The third is ethnomedicinal: crushed plant material has been applied to cuts and bruises [21].

On this basis, at least three mechanisms can be proposed as hypotheses to be tested. A direct mitogenic effect might arise if constituents of the leaf enhance signalling through the PI3K/Akt or MAPK/ERK routes in fibroblasts or sensitise them to endogenous growth factors [41,42,44]. An indirect, permissive effect might result from the lowering of oxidative stress and inflammatory signalling in the wound milieu, enabling fibroblasts to respond to normal growth cues [25,28,46]. A matrix effect might involve increased synthesis or better organisation of collagen, as reported for other plant extracts [18,34]. A fourth contribution, protection of the wound from infection, would be expected to support all of these [24].

The word "targeted" in the title implies that the effect should be selective in time, place and degree. Time-selectivity means that the preparation should act mainly during the proliferative phase and should not keep fibroblasts in an activated state afterwards. Place-selectivity depends on topical formulation and on controlled release at the wound surface, discussed in Section 12. Degree-selectivity means a dose range in which proliferation and matrix deposition are enhanced without cytotoxicity on the one hand or myofibroblast persistence on the other. Markers such as alpha-smooth muscle actin, TGF-β, the ratio of type I to type III collagen and the balance of matrix metalloproteinases and their

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inhibitors can be used to monitor this balance [32,35,36].

X. Extraction, Standardisation and Quality Control

The first practical decision in preparing a leaf extract is the choice of extraction technique and solvent. Classical methods such as maceration, percolation and Soxhlet extraction are simple and inexpensive, whereas ultrasound-assisted, microwave-assisted and supercritical fluid extraction can shorten the process and reduce solvent use, although each has advantages and limitations in selectivity, scale and possible degradation of heat-sensitive compounds [23]. Solvent polarity determines which classes are recovered: water and aqueous alcohols tend to extract polar phenolics, flavonoid glycosides and tannins, medium-polarity solvents recover aglycones and some terpenoids, and non-polar solvents extract sterols and lipophilic components [23]. Since the hypothesis under discussion centres on phenolic and flavonoid constituents, hydroalcoholic extracts merit priority, but this should be confirmed by comparing yield and activity across solvents.

Standardisation is the step that turns a plant extract into a reproducible material. It begins with botanical authentication and a record of the collection site, season and plant age, and continues with defined drying and storage conditions, determination of extractive value and moisture, and measurement of total phenolic and total flavonoid content. A chromatographic fingerprint, obtained by thin-layer or high-performance liquid chromatography, and the quantification of at least one marker compound allow different batches to be compared. Tests for microbial load, heavy metals, pesticide residues and residual solvents belong to the same quality framework. Quality and safety monitoring have long been recognised as weak points in the use of herbal medicines, and they should not be postponed until late in the development process [55].

Antioxidant capacity is commonly estimated with radical-scavenging and reducing-power assays such as DPPH, ABTS and FRAP. Each assay has its own chemistry and none of them reflects the full behaviour of an extract in a living system, so that using several complementary assays gives a more reliable picture than any single one [56]. Antioxidant values should be treated as supporting data and not as a substitute for experiments on fibroblasts.

XI. Preclinical Evaluation Strategies

11.1 In vitro studies with fibroblasts

A logical first step is a dose-ranging study in normal human dermal fibroblasts, with a second fibroblast line such as NIH 3T3 or L929 as a confirmatory system. Cell viability and proliferation can be measured by tetrazolium-based (MTT) or resazurin assays, by DNA synthesis assays or by direct cell counting. The scratch assay provides a simple model of cell migration into a gap, but because closure of the gap reflects both migration and proliferation, a proliferation inhibitor or low-serum conditions should be included to separate the two processes. A cytotoxicity window should be established first, so that the doses used in functional assays are non-toxic.

Beyond cell number, the quality of the response should be examined. Collagen output can be estimated by hydroxyproline or Sirius red assays, and expression of collagen types I and III, alpha-smooth muscle actin, TGF-β, matrix metalloproteinases and their inhibitors can be measured at gene and protein level [57]. Mechanistic work may include immunoblotting for phosphorylated Akt and ERK, Smad2/3 phosphorylation, NF-κB activation and Nrf2 activity [39,44,46,48]. Experiments carried out under oxidative-stress or high-glucose conditions can model features of chronic and diabetic wounds more closely than normal culture conditions [6,25].

Table 3 lists suggested in vitro assays and the purpose of each.

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Table 3. Suggested in vitro assays for evaluating the response of fibroblasts to a plant extract

Parameter	Suggested method	Purpose	Ref.
Cell viability and proliferation	MTT or resazurin assays, DNA synthesis assays or direct cell counting	Define a non-toxic dose range before functional assays	57
Cell migration	Scratch assay with a proliferation inhibitor or low-serum conditions	Separate migration from proliferation	57
Collagen output	Hydroxyproline or Sirius red assays	Judge the quality of the matrix produced	57
Gene and protein expression	Collagen types I and III, α-SMA, TGF-β, matrix metalloproteinases and their inhibitors	Monitor beneficial and harmful aspects of fibroblast activation	57
Signalling	Immunoblotting for phosphorylated Akt and ERK, Smad2/3 phosphorylation, NF-κB activation, Nrf2 activity	Explore mechanism of action	39, 44, 46, 48
Disease-like conditions	Culture under oxidative stress or high glucose	Model features of chronic and diabetic wounds	6, 25

11.2 In vivo studies

Animal models remain necessary to examine the complexity of the whole wound. Excision, incision, burn and impaired-healing models are the most widely used, and the progress of healing can be followed by the rate of wound contraction, time to epithelialisation, photographic analysis, biophysical measurements such as tensile strength, and histological, immunological and biochemical analysis of the tissue [57]. Studies on animals require prior approval from the Institutional Animal Ethics Committee, as the institute's guidelines for project work also specify. Good practice includes the use of a vehicle control and a reference treatment, randomisation, blinded assessment of outcomes and sufficient animals per group. Diabetic or otherwise impaired models are particularly informative because fibroblast function is compromised in such wounds [4,6].

XII. Formulation and Delivery Considerations

For a wound, a topical preparation is the obvious route. Traditional formulations such as ointments and creams are easy to make, but modern wound dressings are designed to keep the wound moist, to protect against infection, to allow gas exchange and, increasingly, to release active agents in a controlled manner [58]. Hydrogels, films, foams and nanofibrous mats are all candidates for carrying a plant extract, and incorporation of an extract into such a dressing could provide a sustained supply of phenolic constituents during the several days of the proliferative phase [16,58].

Nanocarriers, including liposomes, polymeric nanoparticles, nanoemulsions and nanofibres, have been investigated as a means of improving the stability, solubility, skin penetration and release profile of natural products used for wounds [18,59]. This is relevant to *C. indica*, because polyphenols are prone to oxidation, light sensitivity and low stability in aqueous media. Practical issues include the staining of dressings by coloured extracts, the loading capacity of the carrier, sterility, and compatibility between the extract and the other excipients. Formulation work should proceed only after the extract itself has been standardised and its activity on fibroblasts has been established, as a delivery system cannot compensate for an inactive or variable extract. Extraction efficiency of bioactive plant compounds depends on solvent selection, heat, mechanical agitation, and matrix characteristics across conventional and non-conventional methodologies [60].

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XIII. Safety and Toxicological Considerations

A natural origin is not a guarantee of safety. Herbal products can cause adverse reactions through intrinsic toxicity, allergy, adulteration, contamination and interaction with other treatments, and surveillance of these problems is difficult [55]. For a topical leaf preparation, the principal concerns are irritation, skin sensitisation and, if the wound is large or the product is absorbed, systemic exposure to bioactive compounds. Alkaloids and other constituents reported in preliminary screening may be cytotoxic at higher concentrations, and some screening studies have also reported cardiac glycosides [20,53]. These findings call for cytotoxicity testing in skin cells, dermal irritation and sensitisation studies, and, if development proceeds, acute and repeated-dose toxicity studies.

Environmental quality of the raw material is a further issue. *Canna indica* is also studied for phytoremediation, that is, for its capacity to grow in contaminated soil and water [20], and plants that take up heavy metals or pesticides from their surroundings could carry those contaminants into an extract. Leaves intended for pharmacological work should therefore be collected from uncontaminated sites and tested for heavy metals and pesticide residues.

XIV. Balancing Proliferation and Scarring

The aim of promoting fibroblast activity must always be weighed against the risk of excessive scarring. Hypertrophic scars and keloids arise when inflammation is prolonged and fibroblast activity and collagen deposition continue beyond the needs of repair [13,14], and fibrotic disease in general is sustained by persistent myofibroblasts and sustained profibrotic signalling, especially through TGF-β [12,40]. A preparation that merely increases proliferation could, in theory, aggravate these outcomes.

There is, however, a rationale for expecting that a polyphenol-rich, anti-inflammatory and antioxidant extract might do better than a simple mitogen. Persistent inflammation is itself a driver of pathological scarring [13], and reducing it could limit the stimulus for excess matrix production. At the other end of the spectrum, fibroblasts in chronic and diabetic wounds are often hypo-responsive and fail to proliferate and synthesise matrix adequately [4,6], so that there is a genuine need for agents that restore a degree of fibroblast activity in such wounds. Whether *C. indica* leaf extract can achieve a balanced response, with support for early proliferation and without persistent myofibroblast activation, is an experimental question. Studies should therefore include markers of both the beneficial and the harmful side of fibroblast activation, and a long enough observation period to see whether the response resolves.

XV. Research Gaps and Challenges

The central gap has already been stated: to the best of our knowledge, there are few peer-reviewed studies in which *C. indica* leaf extract has been tested directly on fibroblasts or in wound models. Other limitations follow from this. The plant material used in published work is seldom authenticated and standardised, which makes results difficult to reproduce. Crude extracts have rarely been fractionated, so the compounds responsible for any activity are unknown. Mechanistic information is almost entirely absent, and the available pharmacological data are derived from assays that are only indirectly related to skin repair. There are no clinical data. The wider literature on herbal wound healing suffers from similar problems, including heterogeneity of extracts, doses and models, and a tendency to report positive findings [15,17,18]. Safety documentation is incomplete, and quality control of herbal products remains a challenge in general [55].

XVI. Future Perspectives

A realistic research pathway can be outlined as a series of steps, each of which should be completed before the next is started. The plant should first be authenticated, collected from an uncontaminated site and processed into well-characterised leaf extracts prepared with solvents of different polarity, with phytochemical fingerprints and marker compounds defined [23,55]. Bioassay-guided fractionation, supported by modern chromatographic and mass-spectrometric profiling, could then identify the constituents responsible for any activity. Dose-response studies in human dermal fibroblasts, including conditions of oxidative stress and high glucose, and co-culture with keratinocytes or macrophages, would show whether the extract has direct or indirect effects on cell number, migration and matrix output [18,57].

Mechanistic studies of the Akt, ERK, TGF-β/Smad, Wnt, NF-κB and Nrf2 routes would explain how any effect arises and would indicate whether the response is likely to be self-limiting [39,44–46,48]. Promising extracts could then be tested in excision and diabetic wound models, with attention

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to the quality of collagen and to markers of scarring [57]. In parallel, formulation research on hydrogels, nanofibrous dressings or nanocarriers could define the way in which the extract is best delivered to the wound [58,59]. Toxicological and dermal safety studies should accompany these stages, and small, well-controlled clinical studies would be justified only after a favourable preclinical profile has been established.

XVII. Conclusion

The fibroblast is a central cell of wound repair, and its coordinated proliferation and matrix synthesis are required for the formation of strong, functional tissue. Many medicinal plants appear to support these processes, and the phytochemical classes reported in *Canna indica* leaf, together with its recorded antioxidant, anti-inflammatory, antimicrobial and haemostatic properties and its folk use on cuts and bruises, provide a reasonable basis for investigating it as a fibroblast-supporting agent. At present, however, this is a hypothesis and not an established fact: direct experimental evidence of fibroblast proliferation by the leaf extract is scarce, standardised preparations are lacking and safety data are incomplete. Progress will depend on authenticated and standardised extracts, carefully designed cell-based and animal studies that measure both beneficial and potentially harmful aspects of fibroblast activation, and formulation approaches that deliver the extract to the wound in a controlled way. If these conditions are met, *C. indica* leaf extract may deserve a place among the plant-derived candidates for targeted support of tissue repair.

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