Keloids: A Review of the Diseases, Causes, and Current Treatments

J. Anirudh a, T. Gomathi a*, P. L. Sujatha b, P. Devendran c and K. Anbu Kumar c

a Department of Biotechnology, Sri Venkateswara College of Engineering, Sriperumbudur, India.
b Department of Library Sciences, Madras Veterinary College, Chennai, India.
c Department of Bioinformatics, Madras Veterinary College, Chennai, India.

ABSTRACT

Keloids are benign tumors that grow as a result of excessive collagen release from overexpressed fibroblasts. Keloids and hypertrophic scars are distinguished by the fact that keloids develop beyond the site of the original lesion, but hypertrophic scars do not. It is still unclear why this mechanism operates, mainly when aberrant scarring occurs. Despite several treatments’ availability, the keloids’ recurrence rate remains high. Here, we summarize recent narrative reviews, systematic reviews, and meta-analyses to give a general overview of the condition, its underlying causes, and available therapies for keloids. To undertake a comprehensive investigation of the disease, over 100 publications were reviewed using Google Scholar and Pubmed. We also shed light on using phytochemicals as a natural alternative to prevent keloid scarring, which occurs when the body responds abnormally to external injuries by producing scar tissue. We also summarize the available current treatments.

Keywords: Keloids; hypertrophic scars; fibroblasts; phytochemicals; current treatments.

*Corresponding author: E-mail: gomathithirumurthy@gmail.com;

1. INTRODUCTION

Our skin protects our bodies from the environment and also prevents water loss. The epidermis is the outer layer of skin while the dermis is the layer beneath the epidermis, which contains a varying quantity of fat, collagen, and elastic fibers that give the skin its strength and flexibility [1]. The typical wound healing mechanism kicks in whenever our skin sustains any damage. Dysregulation of the wound healing process can occasionally occur due to certain mutations, leading to aberrant scarring [2]. Keloid or hypertrophic scarring are both examples of aberrant scarring. In contrast to keloids, which spread at the initial site of injury, hypertrophic scars do not go past the boundaries of the original wound. After surgery, there is a high recurrence risk of about 100% for keloids, which do not diminish over time [3]. Both scars are unattractive and linked to a decline in quality of life, physical condition, and mental health [4]. In the Indian community, 50 patients were diagnosed with 71 keloids, and 48% of those cases had ear keloids because ear piercing is a common custom there [5]. Keloids are equally common in both sexes, more common in persons with darker skin than in those with lighter pigmentation, and more common from the ages of 10 to 30. The high probability of identical twins acquiring keloids supports the idea that genetics plays a part in the etiology of keloids [1].

It is still unclear from a pathophysiological standpoint how keloids develop. While keloids are made up of disorganized type 1 and type 3 collagen bundles and have an abundance of blood vessels, hypertrophic scars are made up of collagen that runs parallel to the epidermis. Keloids develop months to years after the initial injury. They typically appear on the center of the chest, shoulders, cheeks, or earlobes and are painful and itchy. A keloid on a joint would restrict motion and cause psychological discomfort.

The wound healing process consists of four time-sensitive phases: hemostasis, inflammation, proliferation, and scar formation [6]. Transforming Growth Factor beta (TGF-β), Insulin-like Growth Factor (IGF-I), Platelet-Derived Growth Factor (PDGF), and Endothelial Growth Factor (EGF) are only a few of the potent cytokines that platelets secrete when they first arrive at the site of injury. These chemotactic agents recruit macrophages, mast cells, neutrophils, fibroblasts, epithelial cells, and endothelial cells. The first line of defense against cellular waste and other germs is provided by neutrophils, which phagocytize these cells. In the inflammatory phase, Natural Killer (NK) cells regulate the synthesis of important monocyte cytokines. Tumor Necrosis Factor (TNF), Interleukin-1 (IL-1), and other pro-inflammatory cytokines secreted by macrophages activate the Nuclear Factor-κB (NF-κB)-mediated release of pro-inflammatory cytokines and the release of matrix metalloproteinases (MMPs) [7]. Angiogenesis and the development of connective tissue begin 72 hours following the inflammatory phase by secretion of growth factors such as Fibroblast Growth Factor (FGF), Keratinocyte Growth Factor (KGF), TGF-β, etc. The wound also contracts during this period, known as the proliferative phase, and granulation tissue develops. The tissue is epithelialized during this phase by the migration of Keratinocytes. The extracellular matrix is rebuilt as the last stage of wound healing (ECM). This involves controlling numerous cellular populations to resemble normal tissue and organizing collagen fibrils from immature type 3 to mature type 1. The final stage of scarring requires apoptosis (programmed cell death), which is necessary for the normal skin to maintain homeostasis or a stable state.

It is hypothesized that deregulation of the apoptotic system causes keloid fibroblasts to produce excess collagen and avoid senescence, resulting in an imbalance of collagen deposition and breakdown. The p53 gene has been linked to the apoptotic pathway due to its effect on BCL-2 gene expression. Apoptosis is known to be inhibited by the BCL-2 gene, which is upregulated in response to p53 gene mutations [8]. The formation of a keloid is assumed to entail numerous signaling pathways, and further research is necessary to fully comprehend the underlying mechanism.

2. FORMATION OF KELOIDS

Any disruption to the natural healing process of a wound causes abnormal scarring, such as a hypertrophic scar or a keloid. Type 1 and type 3 collagen are disordered in hypertrophic scars and keloids due to excessive fibroblast proliferation and differentiation. Keloid production has been associated with a pro-inflammatory milieu induced by dysregulated levels of three TGF-β isoforms (TGF-β1, TGF-β2, and TGF-β3) and other cytokines released by the type 2 T-helper cell (Th2) immunological response (IL-4, IL-5, IL-10, and IL-13). Increased scar elasticity has also been linked to increased elastin and...
fibrillin-1 expression [6]. A keloid is heterogenic. In contrast to the edges of the scar, which are heavily vascularized and abundant in proliferative fibroblasts, the center of a keloid is composed of disordered collagen and is avascular and acellular [9]. The mechanisms behind the formation of keloids are unclear because of this. The biological variations between fibroblasts from various areas of the keloid are seen in vitro experiments by Tucci et al. [10]. In an experiment by lu et al., 2007, keloid fibroblasts from the center were in the G0 or G1 phase, and p53 expression was higher there. Conversely, 60% of fibroblasts collected from the edges were in the proliferative phase (G2 and S phase). Moreover, the lack of animal models makes it challenging to run experiments because scientists must rely on immunodeficient patients or excised keloid tissue for mechanism research [11].

2.1 Pathways Involved in Keloid Formation

2.1.1 TGF-β pathway

TGF-β is a 25 kDa homodimer cytokine with multiple physiological and pathological functions secreted by fibroblasts and epithelial cells [12]. TGF-β is found in mammals in three different isoforms: TGF-β1, TGF-β2, and TGF-β3. Despite being on different chromosomes, all three are 80% identical in terms of the amino acid sequence [13]. The TGF-β family includes three different types of activins and more than 20 bone morphogenetic proteins (BMPs) [14]. Even though all three isoforms are nearly identical, they have different TGF-β receptor binding affinities. TGF-β interaction with type II serine-threonine kinase receptor results in transphosphorylation and activation of type I receptor, which activates the TGF-β1 receptor. By interacting with intracellular proteins known as SMADs (Suppressor of Mothers against Decapentaplegic), these activated type I receptors phosphorylate intracellular signaling pathways, which in turn stimulates gene transcription and leads to the dysregulation of wound healing [15]. TGF-β1 and TGF-β2 are believed to promote fibrosis and scar tissue development. The rate of total protein production was shown to be increased in normal fibroblasts but not in keloid fibroblasts in research by Babu et al. [16], that evaluated normal and keloid fibroblasts concerning the function of TGF-β1. Excess Extracellular matrix (ECM) components like fibronectin are caused by an aberrant breakdown of the TGF-β regulation pathway. There is no conclusive evidence that keloids are caused by or result from elevated TGF-β1 levels [9]. TGF-β1-induced augmented collagen synthesis by keloid and normal fibroblasts at the procollagen type 1 mRNA levels is a distinct response. In regions of the scar where collagen I and collagen VI are active, TGFβ1 gene transcription has been found [17]. Bayat et al. [18] examined whether there was a correlation between two novel polymorphisms in the TGF-β2 gene and the keloid. TGF-β2’s 5′-UTR end and the promoter region were cloned. The 5′-UTR runs from the capping site to the initiation codon site and is several hundred base pairs long. Most mRNAs contain a consensus sequence for translation, and when polymorphism is added, it disrupts the control of gene expression at the post-transcriptional level. They discovered a polymorphism in their study that was 109 base pairs (bp) from the start codon; this insertion would prevent it from attaching to a potential transcription factor, which results in the dysregulation of a certain pathway. Our understanding of the involvement of the TGF-β2 gene in the etiology of keloid formation may be enhanced by the discovery of novel polymorphisms in other areas of the gene.

2.1.2 Integrin pathway

Integrins are heterodimeric transmembrane receptors that bind to ECM ligands in conjunction with cadherins, selectins, and syndecans. Keloids are hypothesized to develop in regions where there is skin tension. Butterfly-shaped keloids, for example, form in the chest region. Under mechanical stress, fibroblasts secrete stress-related proteins like Heat shock proteins (HSPs), integrins, and cytokines, which leads to an overproduction of ECM components [19]. The five integrins α1β1, α2β1, α3β1, α1β1, and α11β1 bind to laminins (α1β1), fibronectin (α3β1), and collagen. TGF-β and other cytokines can regulate integrin expression in an autocrine and paracrine mechanism [20]. This means that with the aid of integrins, the fibroblasts in a keloid will recognize the aberrant production of ECM components, resulting in a phenotypical change [21]. α2β1, and α11β1, expressed by fibroblasts, have a relatively high binding affinity to collagen type I and α1β1 to basement collagen membrane IV [22]. The latency-associated peptide (LAP), which was non-covalently linked to mature TGF-β1, made up the latent form of TGF-β1 [23]. TGF-β1-binding protein-1 (LTBP-1) is connected to the ECM through integrins, and it is to LTBP-1
that TGF-β1 binds [24]. Integrins are subjected to tension by mechanical stress, which induces LAP to unfold and activates TGF-β [9]. Inconsistencies in TGF-β signaling may modify integrin expression, which, in turn, may change collagen formation, according to Buscemi et al. [24].

2.1.3 WNT and β-catenin pathway

The Wnt family of signaling molecules regulates a wide range of processes and is being linked more to tissue homeostasis in animals. Wnt signals exhibit pleiotropic activity (Nusse, 2005). This pathway needs to be tightly regulated because it is so complex. Diseases including cancer, keloids, and other conditions are brought on by mutations or dysregulation [25]. Wnt proteins, which bind to the frizzled family of receptors, cause the start of Wnt signaling. By preventing glycogen-synthase kinase-dependent phosphorylation of β-catenin, the receptor activation stabilizes cytosolic β-catenin and increases the levels of β-catenin protein. The accumulating β-catenin binds to the target genes' transcription factors and activates transcription. Canonical (i.e., β-catenin-dependent) and non-canonical (i.e., β-catenin-independent) Wnt signaling are two different types of Wnt signaling. Among the non-canonical pathways are the Ca\(^{2+}\) pathway and the cell polarity pathway [26]. More and more studies link the development of keloid to the canonical Wnt/β catenin pathway [27]. According to Igota et al. [28], the Wnt5a/β-catenin canonical pathway is important in defining the keloid fibroblast phenotype. When Wnt5a binds to FZD receptors and LRP5/6 (Low-density lipoprotein receptor-related protein) in Keloid fibroblasts, Dvl (disheveled signaling relay) is activated. As a result of increasing GSK3-β's (Glycogen synthase kinase-3) phosphorylation at Ser 9 position (GSK3-β's inactivation), Dvl inhibits the β-catenin destruction complex (APC, GSK3-β, and Axin). Working with transcription factors from the TCF and LEF families causes the suppression of β-catenin phosphorylation and build-up of β-catenin in the cytoplasm, which is subsequently translocated into the nucleus to control the target gene's transcription. As a result, keloid development is caused by the gradual, recurrent multiplication of fibroblast cells and the synthesis of collagen. The development of new keloid treatment techniques may be facilitated by targeting Wnt5a/β-catenin signaling.

2.1.4 Insulin Like Growth Factor- 1 (IGF-I) pathway

Growth factors resembling proinsulin structurally are called insulin-like growth factors. IGF-1 may play a dual role in mediating the many postnatal effects of growth hormones by acting as both a mitogen and a differentiation factor [29]. Growth factors such as platelet-derived growth factor (PDGF), Fibroblast Growth Factor (FGF), and Transforming growth factor-β (TGF-β) bind to receptors of the Protein Tyrosine Kinase (PTK) family. PTKs are enzymes that catalyze tyrosine phosphorylation of specific target proteins. PTKs activate key signaling pathways, which regulate various cellular functions like growth, metabolism, motility, and differentiation [30]. There are over 90 tyrosine kinases, of which 58 are receptor types, and the rest are non-receptor types [31]. It is still not understood which PTK is involved in keloid development. Given that PTK is closely related to abnormal cell proliferation and migration, it's assumed that PTK functions in keloid fibroblasts. An experiment performed by Yoshimoto et al. [32] demonstrated the role of IGF-I in keloid formation. They compared the expression of PTK on normal and keloid fibroblasts. IGF-IR was found to be overexpressed in keloid fibroblasts and may contribute to the development of ECM in keloids. IGF-I/IGF-IR pathway may prolong the wound-healing process and promote keloid formation [32]. IGF-IR has been found to have tyrosine kinase activity and bind IGF-1 with a high affinity. It is highly over-expressed in most malignant tissues where it functions as an anti-apoptotic agent by enhancing cell survival. From their study, the IGF-I/IGF-IR pathway might be involved in the regulation of the invasiveness of keloid fibroblasts.

3. CURRENT THERAPIES FOR KELOID TREATMENT

There are numerous therapeutic approaches for keloids currently available, but none of them provide a long-lasting cure due to the condition's high recurrence rate.

3.1 Cryotherapy

Cryotherapy involves freezing keloids to reduce their size and likelihood of recurrence. The scar is subjected to temperatures of less than -20°C. (Harshai et al., 2003). Cryotherapy using a curved hypodermic needle with a greater internal freezing area, as suggested by Harshai et al.
following the
id therapy, albeit it is unclear to
ole in decreasing fibrosis. IFN γ

xibility, and extends
s of unfavorable outcomes
portant
–
xpressed in keloid scars
stripped molecular

addition to its potential to enhance the shape and
atrophic scars and contour deformities. In

excision, improving the appearance of keloids
effective in reducing keloid recurrence after
resulting in lower production
and absence of keloid recurrence. Shin et al.
[48] observed the downregulation of hsp70
expressions of hsp27 and hsp47. When
synthesis because, by
mediated Hsp70
expression, resulting in lower production
of collagen-I, collagen-III, MMP14, TIMP-1, and
TIMP-2, and that the siRNA-mediated Hsp70
knockdowns did not influence the vitality of
the keloid fibroblasts, suggesting a probable function
for Hsp70 in keloid development. There is a

(2003), is a viable method that enables the
treatment of the base scar. Fewer cycles are
needed for this treatment. Following the
procedure, the collagen fibers were organized
and resembled a regular scar. Despite the
beneﬁts of intrallesional cryotherapy, the
condition cannot be fully cured. This treatment
has a recurrence rate of roughly 24% [33]. There
have been reports of unfavorable outcomes
following intrallesional cryotherapy, including
postoperative pain, edema, and hypopigmentation [34,35].

3.2 Interferons

A class of polypeptides known as interferons has
antiviral and anti-proliferative properties. There
are three different forms of interferon protein
products: interferon α (IFN- α), interferon β (IFN-
β), and interferon γ (IFN-γ) [36]. Interferon γ is a
potential inhibitor of collagen synthesis,
according to Granstein et al. [37], and it may be
used to treat keloid therapy, albeit it is unclear to
what extent. Interferon therapy is administered at
low concentrations over 8–10 weeks. Adverse
symptoms such as fever, chills, nocturnal
sweats, and headache were reported in studies
by Larabee et al. [38]. Another form of interferon
called IFN- α2β is used for treating keloid
lesions. Due to its anti-proliferative properties
and ability to either directly lessen cutaneous
fibrosis or counteract the effects of TGF-β and
histamine, IFN-α2β is frequently utilized in the
treatment of keloids. In a study by Berman et al.
[39], interferon α-2β was administered in vivo for
a brief period at a low dose, and it caused a
quick, persistent reduction in the area of the
keloid. Fibroblasts generated from the interferon
α2β-treated keloid maintained a normal
phenotype when cultivated in vitro without
interferon α2β. However, the keloid started to
grow again and was resistant to further interferon
therapy. By initially activating Jak1, which
increases the collagen’s negative regulator YB-1
(Y-box protein-1), stimulating Smad7, and
ultimately suppressing TGF-β, IFN γ plays a
significant role in decreasing fibrosis. IFN γ
intralesional injection has been shown to be
effective in reducing keloid recurrence after
excision, improving the appearance of keloids
and hypertrophic scars, and enhancing their [40].

3.3 Fat Grafting

Autologous fat grafting can now be used to treat
atrophic scars and contour deformities. In
addition to its potential to enhance the shape and
fill in areas of insufficiency, its power to
regenerate and remodel surrounding tissues is
receiving more attention [41]. Regarding the
underlying pathophysiology and mechanism,
multiple in vitro and in vivo studies discovered
various immunohistochemical pathways where
fat grafting may have beneficial effects on keloids
and hypertrophic scars. Spiekman et al. [42]
demonstrated that stromal cell-conditioned
medium produced from adipose tissue reduced
TGF-β1-induced proliferation of adult human
dermal fibroblasts. Adult human dermal
fibroblasts treated with TGF-β1 simultaneously
had their expression of the SM22 gene and
protein and contractility lowered by the medium.
Additionally, the medium significantly decreased
the transcription of the genes for collagen I and
III and the proteins they encode. Additionally,
autologous fat grafting improves scar quality,
reduces pain, increases ﬂexibility, and extends
the range of motion [43].

3.4 siRNA Transfection

The discovery that siRNA (small interfering RNA)
can control gene expression through a process
known as RNAi (RNA interference) is one of the
most signiﬁcant developments in biology. siRNA
generated interest as a potential therapeutic
agent since it can inhibit speciﬁc genes in several
genetic disorders [44]. Heat Shock Proteins
(HSPs), which are widely distributed molecular
chaperones and exude a protective response
when a cell is under stress, are important
regulators of apoptosis [45]. Hsp27, hsp47,
hsp60, hsp70, and hsp90 are known to be
constitutively expressed in healthy skin;
nevertheless, their expression is elevated in
stressful situations such as the wound
environment [46,47]. It is critical to comprehend
how these proteins are expressed in keloid scars
because, by Totan et al. [48], collagen synthesis
and the expression of hsp27 and hsp47 are
intricately linked. Inflammation and inflammatory
cytokines are tightly connected to tissue
expressions of hsp60, hsp70, and hsp90. When
comparing normal and keloid tissue, Totan et al.
[48]’s study showed that hsp27, hsp47, and
hsp70 were upregulated. Shin et al. [49]
transfected keloid cells with hsp70 siRNA and
observed the downregulation of hsp70
expression, resulting in lower production
of collagen-I, collagen-III, MMP14, TIMP-1, and
TIMP-2, and that the siRNA-mediated Hsp70
knockdowns did not influence the vitality of
the keloid fibroblasts, suggesting a probable function
for Hsp70 in keloid development. There is a
scope for RNA therapies in the treatment of keloids.

### 3.5 Imidazoquinolines

Imidazoquinolines, including imiquimod and resiquimod, are strong immune modulators binding toll-like receptors 7 and 8 agonists. Resiquimod has up to 100 times the potency of imiquimod, both in vitro and in vivo. Imiquimod 5% cream (Aldara), a topical immunomodulatory drug, increases the expression of tissue necrotic factor alpha (TNF-α), gamma and alpha interferons (IFN-γ and -α), and interleukin 1, 6, 8, and 12 [50]. Patients have reported having adverse side effects such as burning, pain, itching, inflammation and wound crusting which went away with time [51]. However, more research is required to elucidate the impact of 5% imiquimod cream in inhibiting keloids.

### 3.6 5-Fluorouracil (5-FU)

5-Fluorouracil is an antineoplastic drug that resembles the structure of metabolic pyrimidines and inhibits the proliferation and differentiation of myofibroblasts [52]. Additionally, by permanently inhibiting the enzyme thymidine synthase, which converts uridine into thymidine, it blocks the production of DNA. Moreover, 5-FU is believed to inhibit the expression of the type I collagen gene and the effects of tumor growth-beta 1. A study by Saha et al. [53] injected 5-FU intralesionally over 4-5 sessions. About 85% of patients had a very good outcome and for about 35% of the patients, the keloid lesions reoccurred six months post-treatment with 5-FU [54]. Side effects include pain, pruritus, and a round open sore in the skin [55]. Smaller keloid lesions prone to recurrence after some time can benefit from 5-FU.

### 3.7 Triamcinolone Acetonide

Triamcinolone Acetonide (TAC) is the most effective intralesional corticosteroid injection for keloid treatment. A series of injections are given every four to six weeks for several months or until the scar flattens. TAC should be injected at the proper depth in the mid-dermis to prevent the irreversible atrophy of the epidermis [21]. Corticosteroids impact many important pathways in the development of keloids by reducing inflammation throughout the wound-healing process. Moreover, it decreases the growth of fibroblasts, inhibits collagen synthesis, and increases collagen breakdown [56]. A study by Huu et al. [57] established the effects of TAC on keloids. 90.7% of patients experienced quite positive treatment outcomes, while 86.6% and 95.5% of patients reported post-treatment pain relief and an end to itching, respectively. Possible side effects include irregular menstruation, acne, skin atrophy, hypopigmentation, and ulcers.

### 3.8 Surgical Excision

Many keloid lesions are still only treatable through surgical excision. When utilized as the only type of treatment, keloid lesions have been shown to return in 70–100% of patients, frequently resulting in more resilient collagen build-up and greater lesion formation, much to the chagrin of both doctors and patients. However, the recurrence rate is decreased when paired with adjuvant treatments [21]. With the surgical removal of the pathological scar combined with intralesional Triamcinolone injections, the recurrence rates are typically reduced by 50% [58]. Emad et al. [59] experimented with the effectiveness of immediate radiotherapy and surgical excision on keloids. Before receiving adjuvant radiation, a group of patients underwent extralesional surgical excision. Irradiation following surgery began 48 hours after surgery. A superficial X-ray therapy equipment delivered a total radiation dose of 12 Gy in three fractions for three weeks. Their study’s findings demonstrated that immediate radiotherapy combined with surgery was more effective and safer for treating keloids. Due to the increased risk of cancer formation with radiotherapy in their developing tissue, children shouldn't be exposed to radiation [60].

### 3.9 Silicone Based Products

Products made of silicone have been used to treat keloids and hypertrophic scars since the 1980s [61]. Other silicone forms include liquid, gel cushions, creams, and sprays [62]. It is reported to be effective and reduce scars' texture, color, and height by 86%, 84%, and 68%, respectively [63]. Silicone gel improves stratum corneum hydration, which helps to regulate fibroblast proliferation and reduce collagen formation. Additionally, to produce a softer and flatter scar, it induces mild hydration in which it behaves as though it were a component of the underlying stratum corneum, shielding the skin's surface from numerous external stimuli that heighten pruritus and the ensuing
unintentional scratching of the scars without interfering with the stratum corneum's normal operation [64]. Silicone gel is easy to administer even on sensitive skin and also alleviates pruritus and discomfort of the scar. Long-chain silicone polymer (polysiloxanes), silicon dioxide, and volatile components are all present in silicone gel. With silicone dioxide, long-chain silicone polymers can cross-link. It operates around the clock and stretches out like an incredibly thin sheet [62]. Research by Borgognon et al. [65] looked at the efficiency of silicone sheets in preventing recurrences after keloid excision. A higher percentage of complete remissions (60%) were seen in keloids treated with surgical excision and silicone sheet application than in keloids treated simply with surgery. There were no cases of recurrence even after 18 months of follow-up [65]. There have been a few minor side effects like pruritus, redness, and skin degradation documented [66]. These can, however, be prevented if the scar region is kept clean [61].

3.10 Botulinum Toxin Type A

Botulinum Toxin Type A is a powerful neurotoxin produced by the gram-positive bacterium Clostridium botulinum. It functions by rigidly adhering to the neuromuscular junction and so preventing presynaptic acetylcholine release [67]. Its underlying theory has not yet been fully elucidated. The greatest advantageous feature of intralosional Botulinum toxin type A is the near complete absence of adverse effects such as skin atrophy and small, dilated blood vessels [68]. Numerous studies have shown that Botulinum toxin type A can be used to treat keloids since it improves keloids' pruritus, and pain, softens their texture, and reduces their size [69]. A study was conducted by Zhibo et al. [70] to assess the effectiveness of botulinum toxin type A in the treatment of keloids. Botulinum toxin type A was used to treat 12 patients, and all 12 showed positive results and responded to all forms and sizes. Additionally, there were no instances of side effects or recurrences one year later. However, further research is still needed to elucidate the mechanism of the neurotoxin on keloids.

4. USE OF PHYTOCHEMICALS FOR KELOID TREATMENT

Plants provide essential nutrients for life, as well as bioactive phytochemicals that support health and disease prevention. While it has long been believed that the macro- and micronutrients found in plants are essential components for human health, phytochemicals have more recently come to light as important cellular signaling pathway modulators [71]. Recent studies have shown that a variety of phytochemicals are beneficial for the health of human cells [72,73]. Modern medications are not ideal as these medications are expensive, have unfavorable side effects, and harm the environment [74]. A staggering 5.2 million injuries are reported in India each year as a result of medical mistakes and unfavorable outcomes. Of these, medication errors, hospital-acquired infections, and blood clots that form in the legs from being immobilized in the hospital are the main causes. Similarly, nearly 3 million years of healthy life are lost in India each year due to these illnesses (Agarwal, https://www.ima-india.org/ima/left-side-bar.php?pid=210). India is renowned for its ancient herbal sciences, which depend on the long-term, safe, ongoing use of several herbal medications to preserve good health. In many circumstances, herbal medicines would focus on supporting other systems and functions strained by the primary symptom rather than treating the main presenting ailment. Due to the medicinal properties of the herbals medicines, this enables the body to heal. These abilities are intended to improve the presenting condition [75].

4.1 Curcuma Longa

Curcuma longa is one of the most demanding spices to work with in Indian cooking. Curcumin is the component that makes Curcuma longa active, demethoxycurcumin, bisde-methoxycurcumin, and volatile oils are other active ingredients (tumerone, zingiberene, and atlantone) [76,77]. It is renowned for its astounding ability to treat many ailments. It has anti-inflammatory, antioxidant, diabetes-prevention, infectious-disease-fighting, healing, antiviral, and hypolipidemic properties [78]. Curcumin's effects on all stages of wound healing when applied topically were shown in a study by Panchatcharam et al. [79]. Compared to untreated wounds, wound tissues treated with curcumin had many invading cells, like macrophages, neutrophils, and fibroblasts. As contraction continues and resistance rises during the creation of granulation tissue, fibroblasts transform into myofibroblasts. Myofibroblasts are thought to be a defining feature of tissue that is contracting. The apparent increase in
myofibroblasts in wounds treated with curcumin may be a factor in quick wound contraction [80,81]. Another function of curcumin is in the deposition of collagen in wounds. Curcumin treatment causes a significantly higher level of type III collagen than type I collagen, and local fibroblasts are responsible for this rise [79]. The experiment performed by Hsu et al. [82] showed the effect of curcuminoids administered along with bleomycin. By co-administering curcuminoids along with bleomycin, elevated levels of TGF-β1 were suppressed, preventing the synthesis and transactivation of autocrine TGF-β1 in the Keloid Fibroblasts. The addition of curcuminoids to the Keloid Fibroblasts also prevented the synthesis of SMAD 2 and phosphorylation. Based on these data, curcumin plays a major role in wound healing and could be a potential cure for keloids.

4.2 Glycyrrhiza Glabra (Liquorice)

The Fabaceae family member Glycyrrhiza glabra Linn. has been valued for its medicinal properties since antiquity. Several phytocompounds found in this plant, including glycyrrhizin, 1β-glycyrrhetinic acid, glabrin A and B, and isoflavones, have shown a variety of pharmacological effects. Through pharmacological studies, it has been demonstrated that several extracts and pure compounds from this species exhibit a wide range of biological activities, including antibacterial, anti-inflammatory, antiviral, antioxidant, and antidiabetic effects [83]. Its application in the treatment of wounds is mentioned in several Ayurvedic scriptures. The plant aids in the retention of Na⁺ and Cl⁻ and the excretion of K⁺, acting as a treatment for Addison's illness. It is also renowned for its efficacy against peptic ulcer syndrome [84]. The hydrophilic fraction of liquorice extracts is known to have anti-inflammatory effects [85]. Glabridin’s effectiveness against keloid fibroblasts was shown by Zhang et al. [86]’s experiment. Glabridin is a flavonoid obtained from the plant Glycyrrhiza glabra that possesses a variety of biological characteristics. It was discovered that glabridin caused apoptosis, which inhibited keloid fibroblasts from proliferating. Glabridin was also found to inhibit the production of collagen. The cause was shown to be the suppression of the PI3K/Akt and TGFβ-1/SMAD pathways [86]. Liquorice could be a potential therapeutic agent for keloid treatment with further research.

4.3 Tualang Honey

Honey has been used to treat a wide range of ailments since ancient times. The antibacterial [87], anti-inflammatory [88], antioxidant [89], and antimutagenic [90] effects of honey have all been established. It has also been discovered that honey improves wound healing [7] and has anticancer [91] and antidiabetic benefits [89]. One form of honey produced by the rock bee (Apis dorsata), which constructs hives on the branches of towering Tualang trees mostly in the northwest of Peninsular Malaysia, is referred to as “Tualang honey” [92]. Since honey has so many beneficial qualities, its effectiveness concerning wound healing is well acknowledged. Honey aids in the healing process by reducing the swelling, inflammation, and pus discharge typical of all wound types and promoting the growth of fibroblasts, which secrete collagen [93]. Due to the relaxing nature of the treatment, the reduced discomfort, and the pleasant scent of the dressing, patients choose Tualang Honey hydrogel dressings over normal dressings [91,94]. Nurul et al. [95] experimented to find out whether Tualang honey has any effect on keloid fibroblasts. On keloid fibroblasts, crude tualang honey was extracted using methanol. The keloid fibroblasts' ability to proliferate was shown to be inhibited by the volatile components of the methanol extract of honey, and the size of the scar was also found to be reduced as a result. Research on the effects of tualang honey on keloid fibroblasts is still in its infancy, and more thorough research is required to ascertain the underlying mechanism.

5. DISCUSSION

Keloid formation's mechanism continues to be a conundrum. This disease is not explained by a single, all-encompassing hypothesis, which is very concerning. As keloids are limited to humans, researchers must rely on in-vivo and in-vitro studies. There were numerous ambiguities in the collection of keloid fibroblasts in in-vitro research, according to a review of more than 100 papers. Therefore, keloid fibroblasts from the scar should be collected using a standard model for objective cell culture research. Keloid management is still a multimodal process for the time being. There is still no one treatment that consistently has a low recurrence rate available. More research looks at how existing medicines can be combined for a synergistic effect. Incorporating stem cells to prevent keloids is another intriguing treatment. Adult multipotent
stromal cells known as mesenchymal stem cells (MSCs) can be easily extracted from a variety of tissues, including bone marrow, adipose, and umbilical tissue. MSCs release chemokines and microvesicles, which have anti-inflammatory and anti-fibrotic paracrine actions. There is data to support that transplanted MSCs can support a return to homeostasis and decrease inflammation. Additionally, MSCs may promote a T-cell response that leads to the dysregulation of TGF-β1, a crucial regulator of collagen production, to impair ECM deposition [96-99].

Psychotherapy for really itchy keloids is another factor for future therapy. Although there is no evidence supporting the use of psychological psychotherapy to treat keloid-associated pruritus, there is evidence connecting personality characteristics and coping techniques to the persistence of pruritus in post-burn patients [100]. Moreover, there are a lot of pathways, cytokines, and growth factors that are found to be upregulated or downregulated in keloids compared to normal tissues. In Messadi et al. [101]'s study, cDNA microarray analysis of the NF-κB pathway revealed that 15% of genes were upregulated in keloid fibroblasts compared to normal fibroblasts. The majority of these upregulated genes are proinflammatory cytokines like IL-1α, IL-1β, TNF-α, and IL-6, as well as anti-apoptotic genes like TRAF1, TRAF2, IAP-1, IAP-2, and xIAP. Because of this, it is challenging to comprehend the underlying mechanism. Studies should focus more on determining the underlying cause to develop a potential cure for this disease [102-106].

6. CONCLUSION
The recurrence rate for keloid is still very high and there is no established treatment for it. Although adjuvant therapies are beneficial because they reduce the likelihood of recurrence, they can also cause adverse effects like pruritus, discomfort, and movement restrictions depending on the location and how big the keloid is. These therapies might not be totally helpful because the process of keloid development is not well known. The use of phytochemicals has grown recently, and research indicates that they have numerous targets in different signaling pathways, making them a viable therapeutic alternative for keloid disease.

CONSENT
It is not applicable.


ISSN:0305-4179. DOI: 10.1016/j.burns.2006.02.014, PMID 16782279.


DOI: 10.1007/s40200-021-00830-2, PMID 34900824, PMCID PMC8630252.


ISBN: 9780128138328

DOI: 10.1016/B978-0-12-813832-8.00004-2


DOI: 10.1056/NEJM195511172532002, PMID 13272801.


DOI: 10.1046/j.1524-475x.1998.00211.x, PMID 9776860.


DOI: 10.1007/s00403-010-1075-y, PMID 20717830.


DOI: 10.1002/tr.21787, PMID 30117204, PMCID PMC7167772.


DOI: 10.1117/1534734603002001006, PMID 15866825.


DOI: 10.1021/acs.jafc.2c02045. PMID 36005946.


DOI: 10.1155/2019/2464507, PMID 31281362, PMCID PMC6589292.


DOI: 10.1186/s12906-020-02170-9, PMID 33441127, PMCID PMC7807510.


DOI: 10.3390/molecules17044400, PMID 22499188, PMCID PMC6268297.


DOI: 10.1021/jf025641n, PMID 12405798.


DOI: 10.1155/2013/2464507, PMID 24363771, PMCID PMC7840505.


PMID 23966819, PMCID PMC3474796.

93. Visavadi BG, Honeysett J, Danford MH. Manuka honey dressing: an effective

DOI: 10.3896/IBRA.4.03.1.06.

DOI: 10.1007/s14068-010-00487-y. PMID 21943200.

DOI: 10.1002/sc tm.19-0202. PMID 31804767. PMCID PMC6954709.

DOI: 10.1371/journal.pone.0007119, PMID 19771171, PMCID PMC2743192.

DOI: 10.1016/j.jcyt.2015.03.690. PMID 25939802.

DOI: 10.1007/s00441-020-03361-z, PMID 33386995.

DOI: 10.2340/00015555-3923. PMID 34518894.

DOI: 10.1007/s00403-004-0487-y. PMID 15278366: 15.


DOI:10.1097/01.PRS.0000056868.42679.05, PMID 12711943.

DOI:10.1097/01.PRS.0000270293.93612.7b, PMID 17700113.

DOI: 10.1038/sj.cr.7290260, PMID 15686623.

DOI: 10.1097/PRS.0b013e3181c82dd5, PMID 20124841.