Review Article

Keloids: A Review of the diseases, causes, and current treatments

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 utilizing 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

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 (halim et al., 2012). 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 (wang et al., 2021). 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 (gold et al., 2020). Both scars are unattractive and linked to a decline in quality of life, physical condition, and mental health (barone et al., 2021). 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 (manjunath et al., 2021). 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 (halim et al., 2012).

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 (ekstein et al., 2021). 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-(NF- κB)-mediated release of pro-inflammatory cytokines and the release of matrix metalloproteinases(MMPs) (shah et al., 2017). 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 (ladin et al., 1998). 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 (ekstein et al., 2020). 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 (unahabhoka et al., 2015). 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 in-vitro experiments by (tucci et al., 2010). 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 (supp et al., 2019).

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 (chaudhury et al., 2009). 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 (montgomery et al., 2001). The TGF-β family includes three different types of activins and more than 20 bone morphogenic proteins (BMPs) (Chin et al., 2004). 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 (derynck et al., 1996). 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 (1992), 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 (Unahabhokha et al., 2015). 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 (jagajeevan et al., 2007).Bayat et al., (2002) 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 (suarez at al.,

2013). The five integrins α1β1, α2β1, α3β1, α10β1, 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 (seifert et al., 2009). 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 (andrews et al., 2016). α2β1, and α11β1, expressed by fibroblasts, have a relatively high binding affinity to collagen type I and α1β1 to basement collagen membrane IV (eckes et al., 2006). The latency-associated peptide (LAP), which was non-covalently linked to mature TGF-β1, made up the latent form of TGF-β1 (boswell et al., 2011). TGF-β1-binding protein-1 (LTBP-1) is connected to the ECM through integrins, and it is to LTBP-1 that TGF-β1 binds [25]. Integrins are subjected to tension by mechanical stress, which induces LAP to unfold and activates TGF-β (unahabhokha et al., 2015). Inconsistencies in TGF-β signaling may modify integrin expression, which, in turn, may change collagen formation, according to (buscemi et al., 2011).

2.1.3 WNT/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 (angers et al., 2009). 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 Ca2+ pathway and the cell polarity pathway (logan et al., 2004). More and more studies link the development of keloid to the canonical Wnt/β catenin pathway (chua et al., 2011). According to igota et al (2013), 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 (baker et al., 1993). 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 (kim et al., 2017). There are over 90 tyrosine kinases, of which 58 are receptor types, and the rest are non-receptor types (robinson et al., 2000). 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. (1999) 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 (yoshimoto et al., 1999). 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. (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 intralesional cryotherapy, the condition cannot be fully cured. This treatment has a recurrence rate of roughly 24% (van leeuwen et al., 2015). There have been reports of unfavorable outcomes following intralesional cryotherapy, including postoperative pain, edema, and hypopigmentation (betarbet et al., 2020) (mourad et al., 2015).

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) (gastl et al., 1988). Interferon γ is a potential inhibitor of collagen synthesis,according to granstein et al, (1990), 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 larrabee et al. (1990). 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. (1989), 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 appearance (loordhuswamy et al., 2021).

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 (lee et al., 2017). 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. (2014) 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 (silva et al., 2016).

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 has generated interest as a potential therapeutic agent since it can inhibit specific genes in several genetic disorders (dana et al., 2017). 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. (laplante et al., 1998). Hsp27, hsp47, hsp60, hsp70, and hsp90 are known to be constitutively expressed inhealthy skin; nevertheless, their expression is elevated in stressful situations such as the wound environment (Morris et al., 2002)(dafforn et al., 2001). It is critical to comprehend how these proteins are expressed in keloid scars because, by totan et al. (2011), 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. (2011)'s study showed that hsp27, hsp47, and hsp70 were upregulated. Shin et al. (2015) 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. (Memariani et al., 2021). Patients have reported having adverse side effects such as burning, pain, itching, inflammation and wound crusting which went away with time (reddy et al., 2019). 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 (shin et al., 2016). 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. (2012) 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 (shah et al., 2016). Side effects include pain, pruritus, and a round open sore in the skin (gupta et al., 2002). 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 (andrews et al., 2016). 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 (han et al., 2000). A study by huu et al. (2019) 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 (andrews et al., 2016). With the surgical removal of the pathological scar combined with intralesional Triamcinolone injections, the recurrence rates are typically reduced by 50% (trisliana et al., 2014). Emad et al., (2010) 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 (bischof et al., 2007).

3.9.SILICONE BASED PRODUCTS

Products made of silicone have been used to treat keloids and hypertrophic scars since the 1980s (ud-din et al., 2014). Other silicone forms include liquid, gel cushions, creams, and sprays (puri et al., 2009). It is reported to be effective and reduce scars' texture, color, and height by 86%, 84%, and 68%, respectively (poston et al., 2000). 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(suetake et al., 2000). Silicone gel is easy to administer even on sensitive skin and also alleviatespruritus 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 (puri et al., 2009). Research by borgognon et al., (2000) 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 (borgognon et al., 2000). There have been a few minor side effects like pruritus, redness, and skin degradation documented (sukh et al., 2006). These can, however, be prevented if the scar region is kept clean (ud-din et al., 2014).

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 (sellin et al., 1981). Its underlying theory has not yet been fully elucidated. The greatest advantageous feature of intralesional Botulinum toxin type A is the near complete absence of adverse effects such as skin atrophy and small, dilated blood vessels (shaarawy et al., 2015). 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 (kasyanju et al., 2019). A study was conducted by zhibo et al., (2009) 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 (yoo et al., 2018). Recent studies have shown that a variety of phytochemicals are beneficial for the health of human cells (budisan et al., 2017) (aiyellabge et al., 2007). Modern medications are not ideal as these medications are expensive, have unfavorable side effects, and harm the environment (singh et al., 2020). 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(george, 2011).

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, bisdemethoxycurcumin, and volatile oils are other active ingredients (tumerone, zingiberene, and atlantone) (arora et al., 2021) (amitava et al., 2019). 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 (vasavda et al., 2019). Curcumin's effects on all stages of wound healing when applied topically were shown in a study by panchatcharam et al., (2006). 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 (dunphy et al., 1955)(sidhu et al., 1998). 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 (panchatcharam et al., 2006). The experiment performed byhsu et al., (2010) 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, curcumins play 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, 18β-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 (pastorino et al., 2018). 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 (biswas et al., 2003). The hydrophilic fraction of liquorice extracts is known to have anti-inflammatory effects (yokota et al., 1998). Glabridin's effectiveness against keloid fibroblasts was shown by zhang et al., (2022)'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 (zhang et al., 2022). 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 (albaridi et al., 2019), anti-inflammatory (ranneh et al., 2021), antioxidant (erejuwa et al., 2012), and antimutagenic (wang et al., 2002) effects of honey have all been established. It has also been discovered that honey improves wound healing (shah et al., 2017) and has anticancer (ahmed et al., 2013) and antidiabetic benefits (erejuwa et al., 2012). 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" (ahmed et al., 2013). 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 (visavadia et al., 2008). 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 (imran et al., 2011) (ahmed et al., 2013). Nurul et al., (2011) 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 (kabat et al., 2004) (chen et al., 2009) (huang et al., 2015) (bojanic et al., 2021). 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(hawash et al., 2021). 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., (2004)'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.

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.

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