KELO.CELL

The new product generation
of silicone gel with bioactive metabolites
of totipotent stem cells.

LIST OF CONTENTS

ABBREVIATIONS

bFGF	basic fibroblast growth factor
COX	Cyclooxygenase
DNA	Deoxyribonucleic Acid
ECM	Extracellular Matrix
FGF	Fibroblast Growth Factor
GSH	Glutathione
HDF	Human Dermal Fibroblasts
IL	Interleukin
INCI	International Nomenclature of Cosmetic Ingredients
MMP	Matrix Metalloproteinase
MMPs	Matrix Metalloproteinases
NF-kB	Nuclear Factor kappa B
PEG	Polyethylene glycol
SGS	Silicone-Gel Sheets
TNF-a	Tumour necrosis factor-alpha
UV	Ultraviolet

EXECUTIVE SUMMARY

KELO.CELL Silicone Gel is a novel silicone care gel that can help to prevent and improve the appearance of scars, making it noticeably softer and smoother. In its composition KELO.CELL Silicone Gel combines the gold-standard silicone formula with bioactive factors extracted from totipotent stem cells. Most claims and statements on KELO.CELL Silicone Gel are supported by the evidence provided in this review.

The current cosmetic market opened an opportunity to try and match topical silicon-based products with bioactive natural factors derived from totipotent stem cells in order to increment the overall product potential in terms of scar management. This optimized KELO.CELL Silicone Gel formulation was developed to build a semi-occlusive barrier improving hydration of the scar tissue while helping to activate the skin's own repair process and supports the remodelling of the scar. Thereby, scars become flatter, lighter, and softer. The addition of TURMERIA ZEN^{PRCF} (concentrated metabolome of totipotent stem cells from turmeric) add an extra biological power. It provides the restoration of inflammatory levels (reducing cytokine production in inflamed cells), accelerates wound healing (up to 72%) and significantly increases hydration rate.

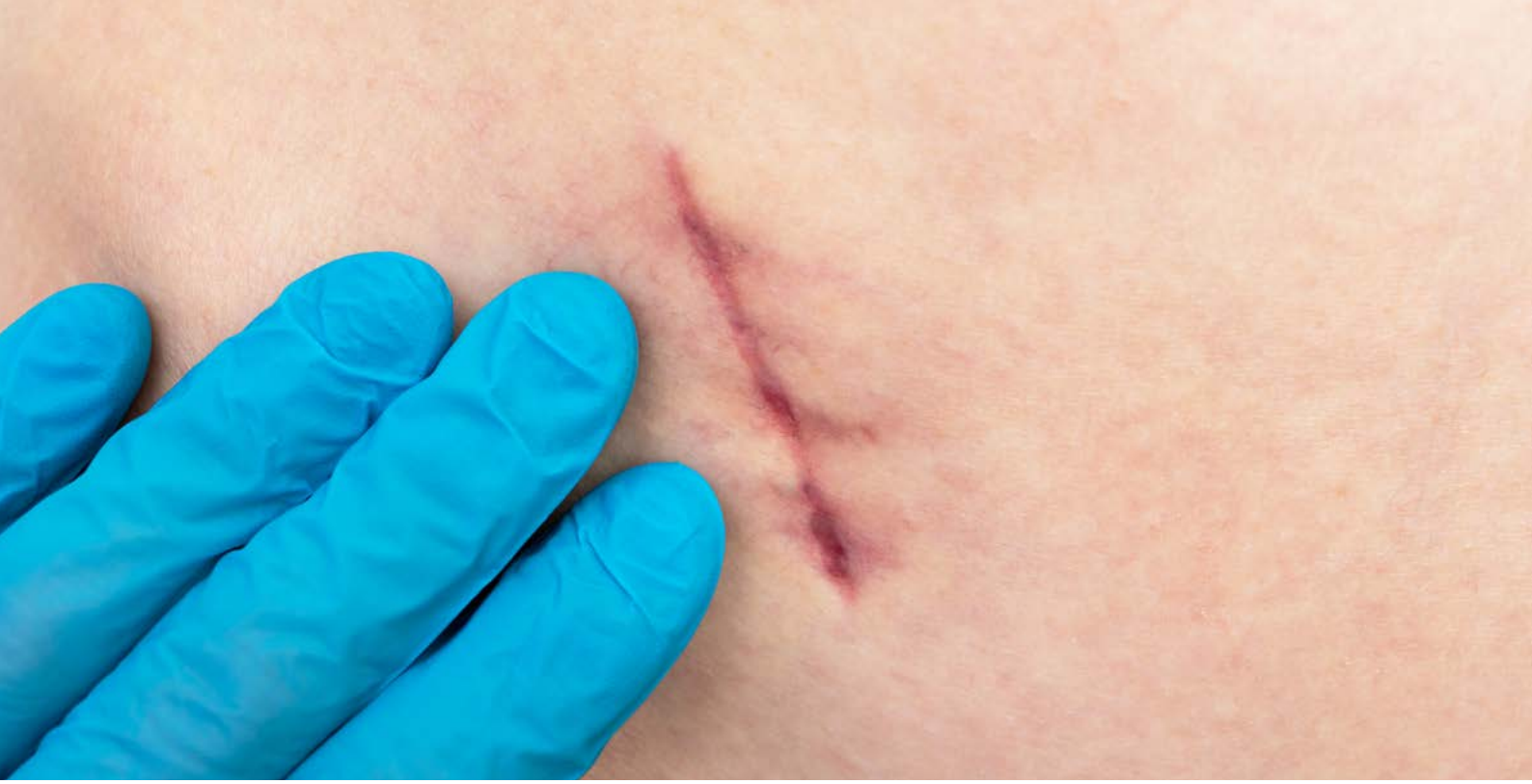
Among cosmetic formulations, KELO.CELL Silicone Gel excels by its content in stem cells extract derived from plants. Besides the term "stem cells" has become very popular in recent years, especially within the cosmetic industry, the incorporation of the bioactive ingredients derived from vegetable totipotent stem cells allows additional claims regarding inflammatory and remodelling properties. Moreover, the novel formulation may envision a broader intention of use. The incorporation of bioactive ingredients consolidates KELO.CELL Silicone Gel as a novel formulation to be applied in more than medical scenarios (scar management), allowing a broader marketing positioning as an anti-wrinkle or hydrating product. By extending the intension of use and inherent to cosmetic classification, there is the possibility to use for longer periods.

After this detailed revision, KELO.CELL Silicone Gel can assert itself as a cosmetic composition enriched in bioactive stem cells factors associated with the gold standard silicone gel technology. This formula forms a self-drying and long-lasting layer on the skin, ensuring superior hydration. The protective action that prevents dryness and the loss of skin elasticity and improves skin texture is carried out thanks to silicone polymers, while the extract from stem cells enhances hydration, decreases inflammation, while boosts skin restoration.

01. INTRODUCTION

KELO.CELL Silicone Gel is a novel silicone care gel that can help to prevent and improve the appearance of scars, making it noticeably softer and smoother. Its unique formulation helps to reduce itching and feeling of tension. KELO.CELL Silicone Gel leaves a silky soft film on the skin and absorbs quickly. It can improve the skin elasticity noticeably.

In the developed world, 100 million people acquire new scars annually and whilst global figures are unknown, they are undoubtedly much higher [1]. It is estimated that of all new scars formed, most can be attributed to everyday cuts, grazes, and minor burns. The remaining causes of new scars include hospital surgery, trauma, acne, stretch marks, elective surgery, cosmetic surgery and mole removal [2].



1.1. Understanding scars

1.1.1. Scar formation

A scar is formed by the rapid overproduction of collagen following the natural process of wound healing. Collagen is made up of naturally occurring proteins which form the main component of the body's connective tissue [3].

Any damage on the integrity of the skin may initiate a process of wound healing to restore proper skin function. This process is a complex and extremely coordinated process and involve a multitude of cellular and molecular components with a focus on survival rather than perfect healing. For the general well-being of patients, the wound healing process is efficient and complete, however, the repaired area will never attain the normal strength of the surrounding skin nor enable regrowth of skin appendages such as hair, sebaceous glands, smooth muscles, and fat tissue [2].

1.1.2. Stages of scar formation

Scar formation has the following four phases (Figure 1) [4–6]:

Haemostatic phase
Haemostasis is the first phase of wound healing, and it takes place immediately after the occurrence of injury. The most important mediators of haemostasis are blood vessels, fibrin, and platelets. Blood vessels are induced to vasoconstriction which persist for 10 to 15 minutes after injury. Fibrin and platelets are responsible for clot formation, platelet aggregation and degranulation of vesicles. Successful haemostasis will produce a fibrin clot to stop any bleeding, thereby sealing off damaged vessels and reducing blood loss. The fibrin clot is an essential structure which serve as a provisional matrix for inflammatory cells, fibroblasts, and growth factors.

Inflammatory phase
The main goal of the inflammatory phase is to create an immune barrier, by initiating a series of molecular events that protect the individual against invading micro-organisms. The inflammatory phase is characterized by physiologic changes, such as capillary vasodilation and increased permeability, that facilitate arrival of serum proteins into the wound. The cellular phase of inflammation follows and is evidenced by the migration of phagocyte white blood cells which release chemicals that cleanse the wound of debris and bacteria. The main inflammatory cells involved are neutrophils, monocytes and arising macrophages. The redness and swelling that appears for a period of three or four days after the initial trauma is a visible indicator of the immune response.

Proliferative phase
The proliferative phase of normal wound healing begins usually on the third day after the injury and lasts about three weeks. This phase is characterized by a few processes, such as formation of granulation tissue, re-epithelialization, and neovascularization.

During proliferative phase, dermal fibroblasts migrate to the wound site and over proliferate at the site of the wound to quickly create collagen to fill the wound. In this journey, fibroblasts navigate the provisional matrix along the fibronectin fibres. They may encounter a diversity of cellular and matrix compounds that can pose a problem for their migration. Thus, the expression of numerous matrix metalloproteinases (MMPs) becomes crucial. MMPs have an important role in such a wide variety of biologic processes, given that these molecules have the ability, among other, to recognize and degrade extracellular matrix (ECM), promoting fibroblast migration [7]. Wound fibroblasts substitute the provisional fibrin-fibronectin matrix by depositing collagen. Collagens have two purposes in wound healing: (i) to provide strength to the wound and (ii) to facilitate the movement of the other cells, such as endothelial cells and macrophages. on angiogenesis.

Proliferating fibroblasts and endothelial cells form a granulation tissue that serve as the foundation for scar tissue development. This tissue has a pink granular appearance due to numerous capillaries that invade the wound stroma. Granulation tissue is made up of proliferating fibroblasts, capillaries and macrophages structurally supported by a matrix of collagen, glycosaminoglycans and glycoproteins, such as fibronectin and tenascin. The granulation tissue favours the re-epithelialization process. This important process is dependent on the keratinocyte's migration across the granulation tissue and their proliferation. As the migration of fibroblasts and endothelial cells, keratinocytes migration is MMPs secretion dependent. These cells are coming from the proximity of the wound, aiming to form a new barrier between the wound and external conditions.

Remodelling phase

The remodelling phase begins after approximately three weeks and may continue for up to two years depending on the size and depth of the wound. This last phase of wound healing process has as main objective the formation of a mature scar, which over time tends to be more like undamaged skin. This phase involves wound contraction and reorganization of the granulation tissue, increasing tissue strength and reducing redness, in order to form a mature scar. While the scar covers and protects the site of the wound, it can easily be disrupted. Scar tissue never surpasses 70% of the tensile strength of normal skin [8].

Wound contraction is correlated in time with differentiation of fibroblasts into myofibroblasts. Myofibroblast is a contractile phenotype of dermal fibroblasts that helps to connect wound edges, mainly in the remodelling phase. Dermal fibroblast and myofibroblasts work in harmony, contributing to the synthesis and alignment of collagen and, thus, help the closure of the wound.

Besides wound contraction, remodelling phase implies the reorganization of granulation tissue. This process is related with remodelling of ECM, produced in proliferative phase, and involves a visible decrease of redness. ECM synthesis and remodelling are initiated concurrently with the development of granulation tissue and continue over a prolonged period. This maturation of dermis structure is accompanied by a decrease of redness of the scar. This transformation comes from the reduction of the density of capillaries in the wound, resulting from the release of several antiangiogenic mediators. In addition, over time, fibroblasts and myofibroblasts undergo apoptosis and their numbers are reduced. Ultimately, these facts result in a relatively acellular mature scar.

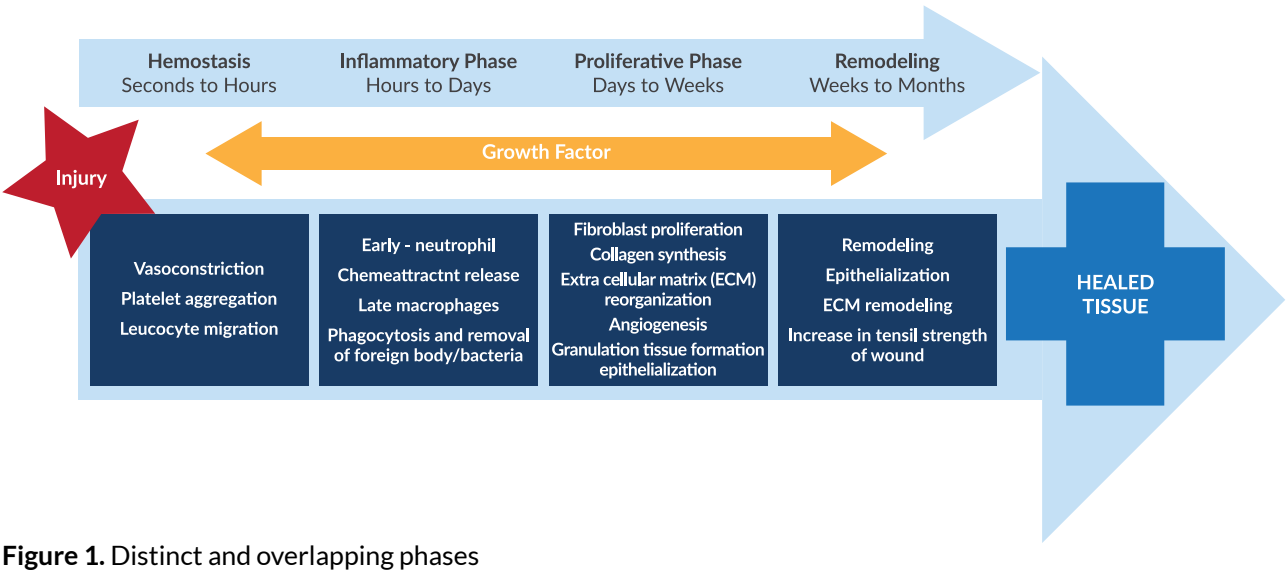


Figure 1. Distinct and overlapping phases of wound healing. Adapted from [9]

1.1.3. Physiological and psychological effects of scars

The final appearance of a scar varies from person to person. In fact, different factors such as skin type, scar location, type of injury, age of the person and even nutritional status play a determining role in scar appearance [2]. Scar types can be divided into the following categories as described in Table 1 [10,11].

Table 1. Different categories of scar types.

SCAR TYPE	DESCRIPTION
Common	These scars appear inflamed and dark in the beginning but become flatter and less noticeable over time resulting in a fine line scar.
Atrophic	These scars cause depressions or indentations below the surface of the skin. Examples are scars from acne or chickenpox.
Hypertrophic	These scars are raised above the surface of the skin. They are characterised by excessive amounts of collagen, but always remain within the boundaries of the original wound.
Keloid	Keloids should not be confused with hypertrophic scars. Although they are also raised scars, keloids are characterised by the fact that they spread beyond the boundaries of the original wound. They may continue to grow over time and usually recur after excision.
Contractures	A contracture scar occurs when the skin tightens permanently. They often develop when scars cross joints, or skin creases, at right angles. The scar tissue is resistant to stretching and can inhibit normal movement. Scar contractures often occur following burn injuries.
Stretch marks	Stretch marks occur during periods of rapid changes in weight (e.g. teenage growth spurts, pregnancy) when the body expands faster than the skin covering it, causing internal tears in the skin tissue. When these tears repair themselves, they form internal scars that are known as stretch marks.

According to scar type, scars have different appearances (Figure 2).

Figure 2. Skin scares appearance. Adapted from [12].

Scars may be perceived as a skin condition but in the majority of cases they are in fact no more than marks that are left on the skin once a wound has healed. Keloid scars are however an exception to this because they behave differently to normal scars [10]. Post-burn scars may be classified as atrophic/hypertrophic/ keloid are visible to the patient for the rest of his/her life [13].

In some instances, scars can cause physical discomfort, including pain, itchiness and tenderness. This is particularly relevant if the scar occurs across a joint, where it can limit mobility. Scars can also cause distressing psychological effects [14]. In an image-conscious society that places large importance on how we look, scars that are aesthetically unpleasant can affect an individual's confidence and cause low self-esteem. These psychological effects often vary depending on the location of the scar, how it occurred, as well as the age and sex of the scar sufferer [15].

1.1.4. Scar management

Scars are unfortunately for life. No product exists that can make them disappear completely [16]. There are, however, a number of treatments available that can help improve a scar's appearance [2]. The most used treatments for scar management are summarized on table 2.

Table 2. Description of the most used treatments in scar management.

TREATMENT	DESCRIPTION
Surgical revision and laser therapy	Surgical revision requires removing or remodelling problem scars through surgery, while laser therapy involves using cosmetic laser to resurface problem scars. Both options can yield significantly beneficial results yet remain inaccessible to most individuals because they are complex medical procedures that are relatively expensive.
Injectable substances	Collagen and other soft tissue fillers are used to elevate sunken scars, while steroid injections can flatten and soften raised scars.
Cryotherapy	This method freezes the upper layer of the scar to remove the excess skin tissue.
Radiotherapy	In severe cases low-dose, superficial radiation therapy is used to prevent the recurrence of keloid and hypertrophic scarring, post-surgery. This method of scar treatment is only used in extreme cases due to the risk of long-term side effects.
Dermabrasion	This method involves controlled surgical scraping to remove the top layers of the skin.
Chemical peels	This method, which uses chemicals to destroy the surface layer of the skin in a controlled way, can be effective for small or superficial scars.
Silicone dressings	Silicone sheets or gels are used to prevent and treat hypertrophic scarring.
Pressure bandages	These wound dressings are most often used for burn scars and can flatten and soften scars.
Topical gels, creams, ointments, and oils	The most cost-effective and least invasive means of improving the appearance of scars.

02. POSITIONING

2.1. Observation

Scar treatment has always been and still is an important topic on aesthetic, because poorly healed, clearly visible scars can have significant negative effects on cosmesis and patient self-esteem [17]. Silicone-based products are considered one of the first-line, gold standard therapy for scar management and have shown efficacy in both prevention and treatment of pathological scars [18].

Over the past two decades there has been an exponential increase in consumer interest in natural skincare products; this shift is not unique to skincare, other industries have also experienced shifts in consumer preference towards using more natural products (Figure 3) [19].

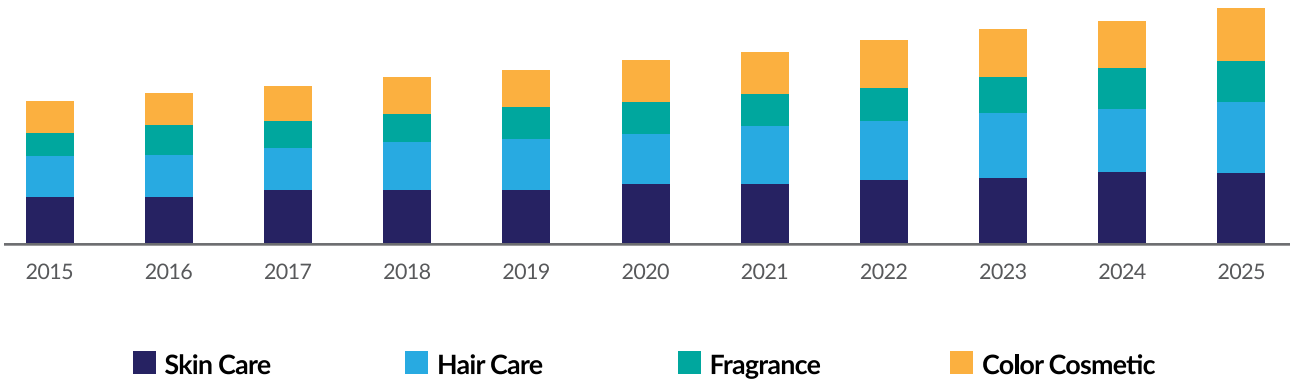
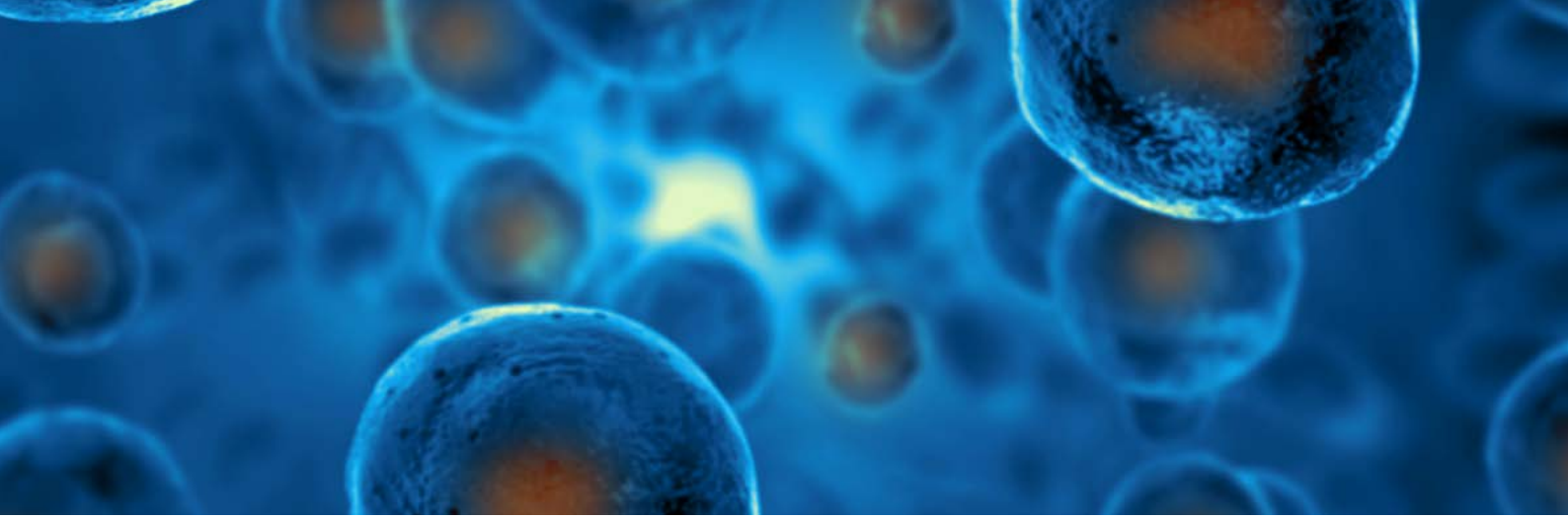


Figure 3. Natural cosmetics market size by size between 2015 and 2025 in United States of America. Adapted from [20].



Among cosmetics based on natural raw materials, various kinds of cosmetics that contain a number of biologically active substances having anti-ageing, anti-wrinkle, bleaching properties among others are commonly applied due to their ease of use and low risk of complications or adverse side effects.

In recent years to overcome some crucial problems in manufacturing more natural cosmetic products, stem cell research associated with improvements in cell culture techniques have been ensuring the growth of plant cells in the environment with microbe-free nutrients with the benefit of higher production of active concentrations through stimulating factors such as UV radiation or other substances [21]. In fact, various beneficial outcomes derive from plant stem cells. The future is bright for the field of biotechnology as vegetable stem cells are responsible for many positive cosmetic effects, such as extending the life of fibroblasts and stimulating their activity thereby rebuilding damaged epidermis, increasing the flexibility of the epidermis, activating DNA repair of the cells, protecting them from oxidative stress and protecting against UV radiation [22].

2.2. Opportunity

With over than 30 years of success and multiple clinical trials proving its efficacy and safety, silicone gel topical therapy is one of the references for the treatment of scars [23].

Moreover, since 2010, when human embryonic stem cells were used for the first time to treat a patient with a spinal injury, the term “stem cell” gained a new exposition and opened a new era [24]. Within the cosmetic industry, manufacturers and clinics started introducing new product lines and procedures with the term “stem cell” in the label, to capture the customer’s attention [25].

Extracts from stem cells have potent antioxidant and active components, however they cannot act in the same way as live stem cells [21]. Nevertheless, the use of plant stem cells itself per se overcomes restrictions, ethical and safety concerns regarding human stem cells. The use of plant stem cell extract must be seen as an extra advantage. Although some recent studies suggest a conservation in chromosome function between plants and humans [26], plant metabolome which comprised more than 200,000 small molecules are more easily processed in human skin cells thereby more effective in modulating biological processes [27]. In addition, they do not produce the response of the immune system [22].

An opportunity therefore existed to try and match topical silicon-based products with bioactive natural factors derived from totipotent plant stem cells in order to increment the overall product potential in terms of scar management. Beyond that, this innovative product will respond to new trends found in dermocosmetic field.

2.3. Outcome

KELO.CELL Silicone Gel provides a novel formulation combining a well stablished silicone gel formulation with the immense potential of stem cells bioactive factors. In so doing, KELO.CELL Silicone Gel will set the benchmark for silicone-based product with natural derived molecules.

03. FORMULATION

3.1. Product description

KELO.CELL Silicone Gel is a silicone gel combined with bioactive factors extracted from totipotent stem cells. It is composed of the following ingredient list according to International Nomenclature of Cosmetic Ingredients (INCI) : Dimethicone, Caprylyl methicone, Dimethicone crosspolymer, PEG-12 dimethicone/PPG-20 crosspolymer, TURMERIA ZEN^{PRCF}, Tocopherol, Glycerin, Citric acid.

The manufacture process consists of the addition of all the ingredients of the formula to the main vessel and their mixture until all ingredients are mixed. After batch approval by Quality Assurance, the bulk is filled into storage containers or directly into the finished product packaging. The product is applied to the dry and clean scar twice daily, massaging the affected area.

KELO.CELL Silicone Gel is available in two pack sizes: 6 and 15 g. It is intended to use to prevent and improve the appearance of scars, making it noticeably softer and smoother. This silicone gel helps to reduce itching and feeling of tension and leaves a silky soft film on the skin and absorbs quickly. It can improve the skin elasticity noticeably. These statements are visible in the product artworks (Annex 1).

[1] The International Nomenclature of Cosmetic Ingredients (INCI) is an international system for the standardised naming of cosmetic ingredients. The system was promulgated and adopted by regulatory authorities initially in the US, followed later by the EU and Japan, and therefore makes allowance for some variances in nomenclature (example, in the naming of botanicals and colourants). INCI names are mandated to appear on the outer product packaging of every personal care product. This enables consumers to identify any ingredients to which they may be allergic. INCI protocol requires that all ingredients in a product formulation must be listed. Those ingredients whose inclusion is greater than %1 of the formulation should be listed from highest to lowest percentage. Ingredients whose inclusion is less than %1 can be listed in any order.

Based on KELO.CELL Silicone Gel composition, silicone polymers are able to build a semi-occlusive barrier which improves hydration of the scar tissue. It also increases temperature in the scar tissue. This helps to activate the skin's own repair process and supports the remodelling of the scar. The scars become flatter, lighter, and softer. In addition, TURMERIA ZEN^{PRCF} (the concentrated metabolome of totipotent cells from Curcuma longa rhizome) provides the restoration of inflammatory levels (reducing cytokine production in inflamed cells), accelerates wound healing (up to 72%) and significantly increases hydration rate [28].

Therefore, KELO.CELL Silicone can claim to be a cosmetic composition with its formula enriched in bioactive plant stem cells factors associated with the gold standard silicone gel technology. This formula forms a self-drying and long-lasting layer on the skin, ensuring superior hydration. The protective action that prevents dryness and the loss of skin elasticity and improves skin texture is carried out thanks to silicone polymers, while the turmeric stem cell extract enhances hydration, decreases inflammation, while boosts skin restoration.

3.2. List of ingredients

KELO.CELL Silicone Gel ingredient listing is categorised based on the INCI names, CAS number, function, and the relative amount in the mixture (Table 3).

Table 3. Formulation of KELO.CELL Silicone Gel.

RAW MATERIAL	RAW MATERIAL MANUFACTURER	INGREDIENTS (INCI NAME)	CAS NUMBER	INGREDIENT FUNCTION	% OF RAW MATERIAL BY WEIGHT	% OF INGREDIENT
Dowsil EL7040-Hydro Elastomer Blend	DowCorning	CAPRYLYL METHICONE	17955-88-3	Emollient, Skin Conditioning, Skin Protecting	30.0	79.9750
		PEG12- DIMETHICONE/ PPG20- CROSSPOLYMER		Skin Conditioning		20.00
		TOCOPHEROL	1406-66-2, 10191-41-0, 2074-53-5, 59-02-9, 148-03-8, 119-13-1, 54-28-4	Skin Conditioning		0.0250
Turmeria Zen-C^{PRCF}	Vytrus	CURCUMA LONGA (TURMERIC) ROOT EXTRACT	84775-52-0	Perfuming, Masking	1.0	50.000
		GLYCERIN	56-81-5	Solvent, Humectant		48.50
		CITRIC ACID	77-92-9, 5949-29-1	Chelating, Buffering		1.50
Xiameter PMX200-Fluid 1.5 CS	DowCorning	DIMETHICONE	63148-62-9, 9006-65-9, 9016-00-6	Emollient, Skin conditioning, Skin Protecting	7.0	100
Dowsil EL9241-Silicone Elastomer Blend	DowCorning	DIMETHICONE	63148-62-9, 9006-65-9, 9016-00-7	Emollient, Skin conditioning, Skin Protecting	62.0	86.5
		DIMETHICONE CROSSPOLYMER		Viscosity Controlling, Emulsion Stabilizing		13.5
				Sub-Total	**100**	**400**

3.2.1. Silicone based ingredients

KELO.CELL Silicone Gel is mainly composed by silicone polymers such as dimethicone, caprylyl methicone, PEG-12 dimethicone/PPG-20 crosspolymer and dimethicone crosspolymer.

Dimethicone is derived from silicon being a fluid mixture of fully methylated linear siloxane polymers end-blocked with trimethylsiloxy units. The potent siloxane bonds that unite silica and oxygen in these compounds account for the noted thermal and oxidizing stability of silicones. Dimethicone is a nontoxic, hypoallergenic, noncomedogenic, and nonacnegenic silicone-based polymer ideal for water-resistant formulations because it is also immiscible and insoluble in water [29]. Dimethicone derivatives such as aprylyl methicone, PEG-12 dimethicone/PPG-20 crosspolymer and dimethicone crosspolymer. present shared characteristics.

Over the past several years, a wide range of silicone-based products have become available for scar management to improve and to prevent the development of abnormal scarring [30]. The signs and symptoms of hypertrophic scars and keloids can be improved by the application of topical silicone therapy with study reporting up to 90% improvement of keloid scars following the use of silicone dressing [31].

In contrast with silicone-gel sheets (SGS), silicone gels are easier to apply and maintain than SGS. Nevertheless, while patients may wear silicone sheets for 12–24 hours per day for 3–6 months, silicone gels should be applied twice daily [32]. When a thin layer is applied to the skin, the silicone gel dries to form a thin, transparent, flexible, gas-permeable, water-impermeable silicone sheet that adheres to the skin and improves scarring [33]. No serious side effects have been reported, but folliculitis is a potential adverse effect [32]. Besides, most of the available products are expensive.

Clinical studies performed in the last two decades indicate that silicone gel is as effective as SGS in the management of abnormal scarring (Table 4) [34,35,44–49,36–43]. Recent systematic reviews demonstrated the effectiveness of silicone gel and silicone gel sheeting on the prevention of keloids or hypertrophic scars [39] and in post-operative scar [18] and validated silicone gel products as effective non-invasive treatment to prevent formation of pathologic scars and improve mature scars [50]. Similarly, the silicone gel efficacy was also demonstrated in a recent systematic review that joint evidence of improvement on scar stiffness, thickness and irregularity following topical silicone therapy [49].

A randomized, double-masked, placebo-controlled study demonstrated that wounds treated twice daily with a silicone gel (composed of dimethicone) presented less scarring than the wounds treated with a placebo gel [34].

At 3 months after surgery, the scars that developed during silicone gel treatment were significantly flatter, less red, and more pliable and associated with less pain and itching than the control scars. No side effects were associated with the silicone gel treatment, and the patients self-reported a high degree of compliance, with 98% of them reporting that they usually or always applied the gel as prescribed. Following donor site of skin grafting, silicone gels were also effective donor site of skin grafting [42].

At the second month postoperatively, the silicone gel scars were scored lower when compared with the control scars treated with placebo. The differences were statistically significant in all parameters, including pigmentation ($p= 0.001$), vascularity ($p= 0.010$), pliability ($p= 0.001$), and height ($p= 0.010$). There was no side effect of the silicone gel noted in any of the 50 patients. Another study enrolling 30 patients showed that topical silicone therapy improved score grading of all the scars [41]. Allergic reaction to silicone gel was seen in one case and mild desquamation was seen in 2 cases.

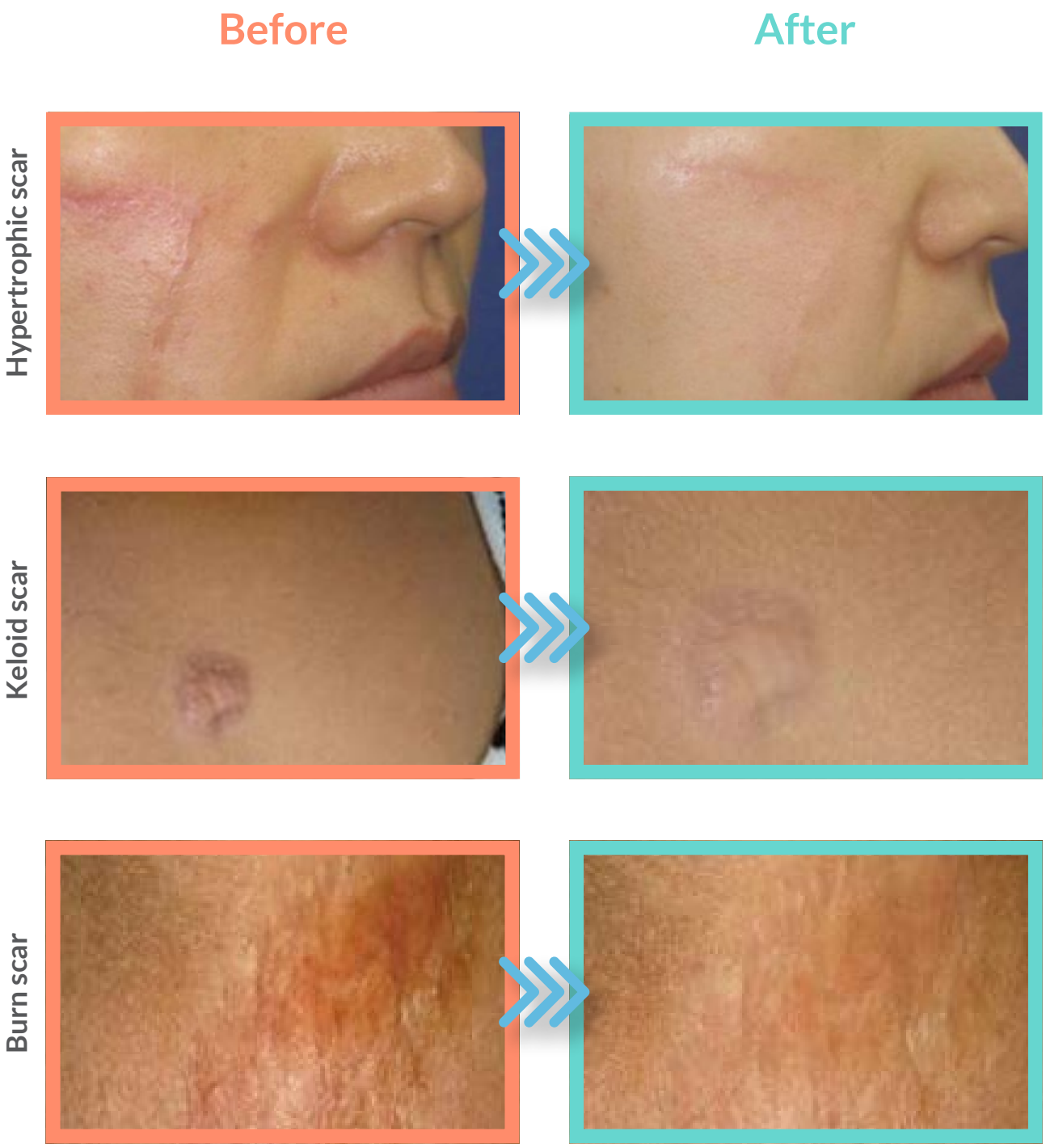
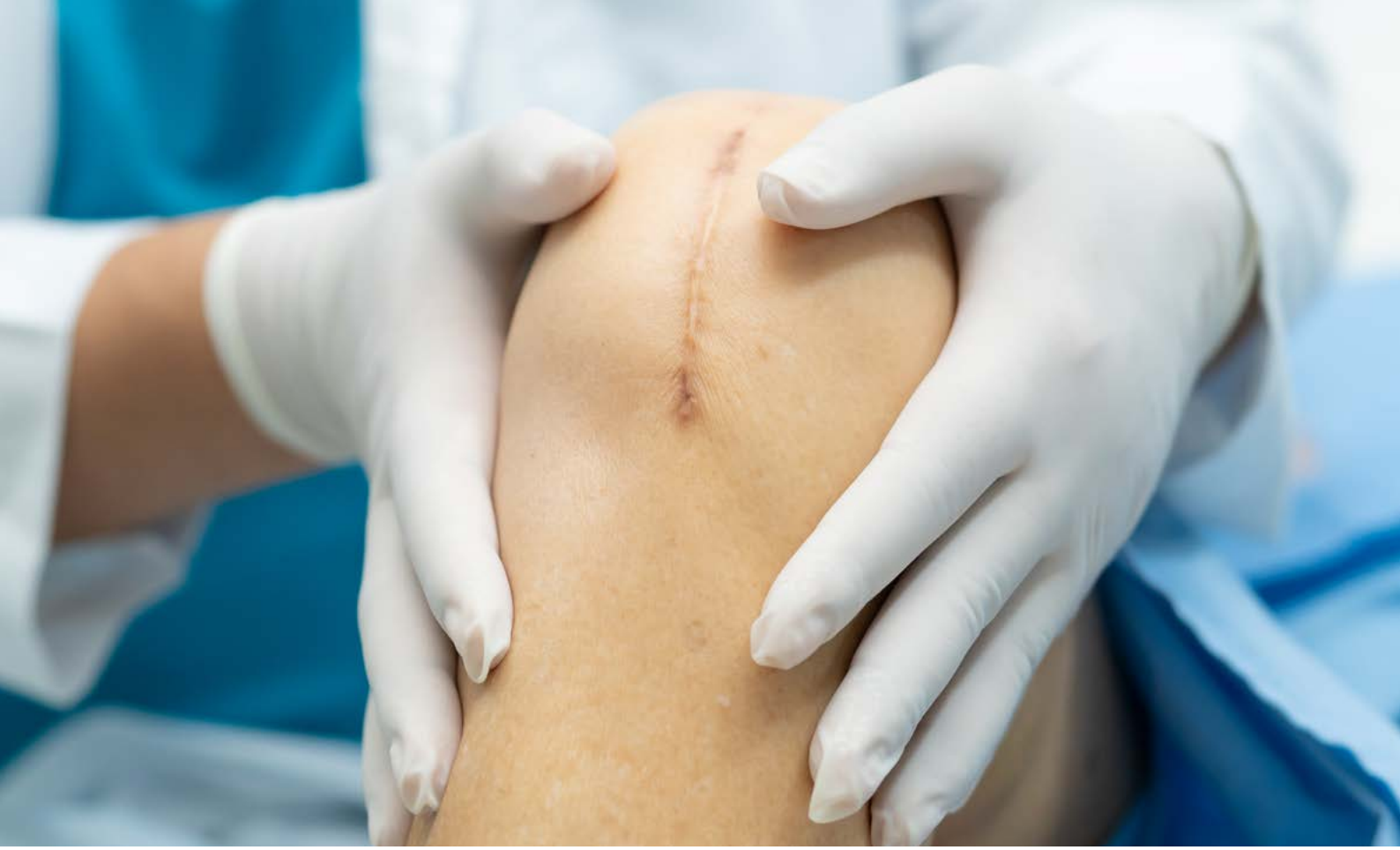


Figure 4. Representative scars photographs before and after treatment with silicone gel for 6 months. The silicone gel was applied as a thin film twice a day. Adapted from [41].

A silicone gel based on polysiloxanes showed considerable effects on reduction of scars namely vascularity, pliability, and height (P□0.05) after surgical repair of hypospadias [48]. However, there was no significant difference in pigmentation (p>0.05). More recently, an advanced silicone formula based on polysiloxanes and silicon dioxide showed a significant improvement in the appearance of scars after three months of twice-daily treatment and with minimal adverse events [43,51]. In patients who have undergone prior surgery, progresses from baseline in scar height, pain, pigmentation, pliability, pruritus and vascularity of the scars as well as a significant reduction in the Vancouver scar scale from baseline were observed [43]. Importantly, only two patients reported itching as an



adverse event after application of the advanced silicone gel. In healthy subjects with an accessible linear or hypertrophic scar, the median total Vancouver Scar Scale score and median total Observer Scar Assessment Scale score decreased significantly from baseline at each visit, showing rapid and continuing improvement in the appearance of the scars [51]. No adverse events were reported.

Similar studies with silicone gel based on cyclopentasiloxane and vitamin C ester also demonstrated its effectiveness in preventing abnormal scarring after surgery [35–38,49]. In one prospective, randomized, parallel group comparison study only 7% of the patients who underwent surgery treated with silicone gel developed a hypertrophic scar or keloid developed in compared with 26% of the patients who received no treatment [35]. There were no side effects of silicone gel treatment, and all the patients reported that the gel was easy to apply.

Furthermore, a prospective study enrolling patients with bilateral immature scars, hypertrophic scars, or keloids showed that the silicone gel (cyclopentasiloxane/vitamin C ester) along with SGS or the combination of these treatments (silicone gel during the day, SGS at night) provided statistically significant improvement for symptoms of itching, irritation, and skin maceration compared with no treatment [36]. The scars in each treatment group were more pliable and less elevated and erythematous than the untreated control scars. Patient scores for the difficulty of treatment were higher with SGS, and patient scores for their willingness to comply with treatment were higher with silicone gel. A large, community-based, open-label, observational study also evaluated the efficacy this silicone gel for 1,522 patients with scars [37]. Scar parameters of colour, pliability, height, itching, and pain/tenderness were improved after at least 2 months of silicone gel treatment in 70% to 84% of cases according to physician assessments, and in 70% to 85% of cases according to patient assessments. Both patients and physicians expressed high levels of satisfaction with silicone gel treatment with respect to ease of use, duration of treatment, cosmetic outcome, and tolerability. Additional insight about this silicone gel were provided in a case series of six patients who had excessive scars [38]. After 8 weeks of treatment, all the scars showed improvement of redness, elevation, hardness, and itching after treatment, and the four scars associated with pain or tenderness also showed improvement in these symptoms. Spectrophotometric intracutaneous scope measurements obtained

for five of the six patients supported the results of the clinical assessments, showing a consistent decrease in collagen content and increased blood flow in treated scars. In comparison with SGS, clinical studies showed not only a comparable efficacy in scar prevention but also the overall patient's satisfaction in the mode of use, reporting that silicone gel are simpler and easier to use [44]. This silicone formulation (cyclopentasiloxane and vitamin C ester) also improved upper lip scar appearance in paediatric population [46] while no benefit was found in patients who had undergone bilateral direct brow lift surgery [47].

A different silicone gel composed of polysylosan was also tested in patients who had undergone outpatient surgery and the results indicated that silicone gel is able to reduce the formation of keloid and hypertrophic scars and the signs and symptoms associated with the healing process (paraesthesia, pulling sensation, alterations in colour) [40].

Although the exact mechanism of action of silicon material in scar management is still unknown, their effects are thought to be related to hydration and occlusion [32,52]. Transepidermal water loss is increased following a full thickness wound and may take over one year to return to pre-wound levels [32]. A high loss of water from the epidermis may lead to dehydration of keratinocytes. These cells may then release cytokines to activate dermal fibroblasts to increase collagen production which can lead to excessive scarring. Silicone gels are able to increase hydration of stratum corneum and thereby deactivating fibroblasts and reducing collagen production. It results into softer and flatter scar [30,53].

The thin film formed upon the application of silicone gels also promotes occlusion. This phenomenon is crucial in the regulation of dermal and epidermal behaviour thereby inhibiting scar formation. Occlusive therapy is able to decrease dermal fibrosis by hydrating the epidermis and altering the pro- and anti-fibrotic signals produced following injury [54]. In vitro research has shown that the production of basic fibroblast growth factor (bFGF) can be increased by silicone products [55]. An increase in bFGF levels in fibroblasts normalizes the collagen synthesis and increases the level of collagenases which breaks down the excess collagen. In addition, another report indicated that silicone-based products may act by downregulating the production of the fibrogenic cytokine, transforming growth factor 2 by fibroblasts that stimulates the synthesis of collagen and fibronectin [56].

Other advantages promoted by silicone gels are the protection of the scarred tissue from bacterial invasion, prevention of bacteria- induced excessive collagen production in the scar tissue, and itching and discomfort reduction associated with scars [16].

In summary, silicone-based products are well stablished both on the management of cutaneous scarring and scarring prophylaxis, being widely used in clinical practice [31]. Nevertheless, a Cochrane review pointed out some bias in the clinical studies, suggesting that further trials are required to reduce uncertainty around decision‐making in the use of these products to treat hypertrophic scars [57].

Table 4. Studies on the efficacy of silicone gel in scar management (adapted from [30]).

AUTHOR/YEAR	STUDY DESIGN	PATIENTS	INTERVENTION	SCAR OUTCOME MEASUREMENTS	MAIN RESULTS
Chan et al., 2005 [34]	Prospective, randomized, double masked, within-subject comparison study	50 Asian patients who underwent median sternotomy	Twice-daily silicone gel on half of wound compared with placebo gel on another half of wound from postoperative week 2 to month 3	Vancouver Scar Scale, scores of pigmentation, vascularity, pliability, height, pain, and itchiness	Scars that developed during silicone gel treatment were significantly flatter, less red, and more pliable and associated with significantly less pain and itching than scars that developed during placebo treatment
Murison and James, 2006 [38]	Prospective, noncontrolled study	6 patients with excessive scars (most at least 2 years old)	Silicone gel used for 8 weeks	Vancouver Scar Scale (scores of elevation, redness, hardness, itching, tenderness; collagen content and blood flow measured using intracutaneous spectrophotometry)	All scars showed improvement in redness, elevation, hardness, and itching, and pain was reduced in symptomatic scars
Sepehrmanesh, 2006 [37]	Prospective, open label, noncontrolled study	1,522 patients with scars	Silicone gel typically used twice daily for at least 2 months	Height; colour; pliability; itching; pain/tenderness	Improvement in scar colour, pliability, height, itching, and pain/ tenderness after silicone gel treatment of approximately %70 to %85 of patients
Signorini and Clementonil, 2007 [35]	Prospective, randomized, parallel group comparison study	160 patients who underwent surgery	Twice-daily silicone gel treatment compared with no treatment initiated from 10 days to 3 weeks after surgery for 4 months	Scar quality (normal mature, slightly hypertrophic, hypertrophic, or keloid scar based on colour, hardness, elevation, and relationship to wound margins)	Scar quality was significantly better in the silicone gel group than in the no treatment group at the -6month follow-up visit: the incidence of hypertrophic or keloid scarring was %7 in the silicone gel group compared with %26 in the no treatment group

AUTHOR/YEAR	STUDY DESIGN	PATIENTS	INTERVENTION	SCAR OUTCOME MEASUREMENTS	MAIN RESULTS
Chernoff et al., 2007 [36]	Prospective, within subject comparison study	30 patients with bilateral hypertrophic scars, keloids, or scars still in an erythematous and raised stage of healing	Silicone gel, SGS, or a combination of treatments for one scar compared with no treatment for the bilateral scar for 3 months	Elevation and texture measured using optical profilometry; erythema; pliability; severity of symptoms	Scars treated with silicone gel, SGS, or silicone gel/ SGS were statistically significantly less elevated. less red, and associated with fewer symptoms than untreated scars
Giorgi et al., 2009 [40]	Randomized controlled trial	110 patients who had undergone outpatient surgery	Topical Silicone Gel or zinc oxide cream twice daily for 60 days after the removal of stitches	Paraesthesia, pulling sensation, alterations in colour, pain, erythema and telangiectasia	Silicone gel is able to reduce the formation of keloid and hypertrophic scars and the signs / symptoms associated with the healing process
Puri and Talwar, 2009 [41]	Prospective, noncontrolled study	30 patients having scars	Silicone gel was applied as a thin film twice a day for 6 months	Appearance of scar, including scar type, scar size and scar colour	Improvement was noted in the treated scars.
Chittoria and Padi, 2013 [42]	Prospective randomized placebo controlled double blind study	50 patients in 100 patient scar sites	Each half site scar was treated by control (placebo) or silicone gel for 2 months	Vancouver scar scale (scores of pigmentation, vascularity, pliability, height, pain, and itchiness	Silicone gel scares presented significantly lower scores for Vancouver scar scale than placebo.
Medhi et al., 2013 [43]	Open-label prospective study	36 patients who had undergone prior surgery (10 days–3 weeks) and having recent post-surgical scars	Silicone Gel application twice daily to the affected areas for 3 months	Pigmentation, vascularity, pliability, height of scar and pain and pruritus	Significant reduction was observed in height of the scar ($P < 0.05$)., hyperpigmentation ($P = 0.0313$), vascularity ($P = 0.0313$) and pliability $P = 0.0313$) after 3 months of treatment from the baseline).

AUTHOR/YEAR	STUDY DESIGN	PATIENTS	INTERVENTION	SCAR OUTCOME MEASUREMENTS	MAIN RESULTS
Kim et al., 2014 [44]	Prospective, randomized, parallel group comparison study	30 patients who had undergone a surgical procedure between 2 weeks to 3 months	SGS or topical silicone Gel for 3 months	Vancouver Scar Scale, scores of pigmentation, vascularity, pliability, height, pain, and itchiness, patients› questionnaire responses about any scar-related pain, pruritus, colour change, hardness, thickness, overall size, irregularity, and inconvenience of use they experienced	No significant difference in efficacy exists between the 2 products. Topical silicone gels are more convenient to use.
Goldberg et al., 2016 [51]	Single-site, observational pilot study,	15 participants with an accessible linear or hypertrophic scar	Silicone gel twice daily, cleaning and drying the target area before each application.	Vancouver Scar Scale and Observer Scar Assessment Scale	The median total Vancouver Scar Scale score and median total Observer Scar Assessment Scale score decreased significantly from baseline at each visit.
Chang et al., 2018 [46]	Mixed prospective and retrospective case-controlled clinical trial	33 consecutive age-matched patients with unilateral cleft lip	SGS or Silicone gel applied twice per day for 6 months	Vancouver scar scale, visual analogue scale and photographically assessed scar width	Silicone gel appears to be non-inferior to silicone sheeting for postoperative care of upper lip scars
Cadet et al., 2018 [47]	Randomized double-blind clinical trial	12 patients who had undergone bilateral direct brow lift surgery.	Silicone gel or placebo twice a day for 2 months	Pictures of scars and questionnaire filled out by the patient and the surgeon	Statistically significant improved appearance in scars treated with silicone gel and scars treated with the placebo after direct brow lift surgery
Shirazi et al., 2019 [48]	Randomized double-blind	64 patients who had undergone surgical repair of hypospadias	Silicone gel or placebo (Vaseline) twice a day for 2 months	Vancouver Scar Scale, scores of pigmentation, vascularity, pliability, height, pain, and itchiness	There were significant differences between the two groups in scar characteristics (p⍰0.05). No significant difference was verified in pigmentation (p>0.05).

3.2.2. Turmeria Zen-C^{PRCF}

Turmeria Zen-C^{PRCF} represents the concentrated metabolome of totipotent cells from Curcuma Longa rhizome [28]. Curcuma longa, the Turmeric, is a tropical and subtropical plant native to the Indian subcontinent and Southeast Asia characterized by the existence of very ramified, cylindrical and orange rhizomes, modified roots that act as storage and resistance organs [58].

Stem cells extract have potent antioxidant and active components, however they cannot act in the same way as the live stem cells [21]. Nevertheless, evidence compiled over the last several decades reveals that, for instance, Curcuma Longa root extract exhibits a broad array of biologic activities, such as anti-inflammatory, anticarcinogenic, antioxidant, antimicrobial, and wound healing [59–61]. These effects are mediated through the regulation of numerous signalling pathways, transcription factors, growth factors, inflammatory cytokines, protein kinases, adhesion molecules, apoptotic genes, angiogenesis regulators, and enzymes, such as cyclooxygenase (COX) and glutathione S-transferases.

Curcumin molecules impact the inflammatory process during wound healing. In vitro, human macrophages suppress cytokine production (TNF-□ and IL-1) upon treatment with 5 μM of curcumin [62]. Besides, curcumin is also a potent inhibitor of phosphorylase kinase and NF-□B activation [63,64], making of this compound a great phytochemical candidate to accelerate wound healing process, avoiding excessive scarring. Additionally, curcumin potently inhibited hydrogen peroxide-induced damage in cultured human keratinocytes and fibroblasts, demonstrating its antioxidant effect [61].

In hypertrophic scarring and keloids, there is an abundance of TGF-□1 expression, fibroblast proliferation, and excess collagen and ECM synthesis [10]. Apart from anti-inflammatory effects,, curcumin inhibits TGF-□1 signalling in keloid fibroblasts and also diminishes ECM production (Figure 5) [65]. Curcumin also suppresses the proliferation of keloids and hypertrophic scar-derived fibroblasts in vitro, showing promise in hypertrophic scar prevention [66]. The use of curcumin gel in six case reports of post-surgical patients has shown promise, with wound healing achieved with minimal scarring [67]. However, randomized controlled trials would be necessary for determining the true efficacy of these therapies.

In humans, the anti-inflammatory potency of curcumin was apparent in the randomized, double-blind trial among 96 male Iranian veterans with chronic sulphur mustard-induced pruritic skin lesions. Panahi et al. found that curcumin supplementation attenuated inflammation and pruritus in these patients, with significant increases in serum IL-8 and high-sensitivity C-reactive protein, and decreases in calcitonin gene-related peptide; substantial improvements in quality of life were also reported [68]. Similarly, in 2013, Thongrakard et al. examined the protective effects on human keratinocytes of extracts of 15 Thai herb species against UVB-induced DNA damage and cytotoxicity. Analysis revealed that the highest antioxidant activity was exhibited by the dichloromethane extract of turmeric. Further, the ethanol extract of turmeric and the dichloromethane extract of ginger demonstrated the maximum UV absorptions and stimulated the production of the antioxidant protein thioredoxin 1, as well as the capacity to protect human keratinocytes from the deleterious effects of UV exposure. The investigators concluded that their findings suggest the viability of incorporating turmeric and ginger extracts into anti-UV cosmetic formulations [69].

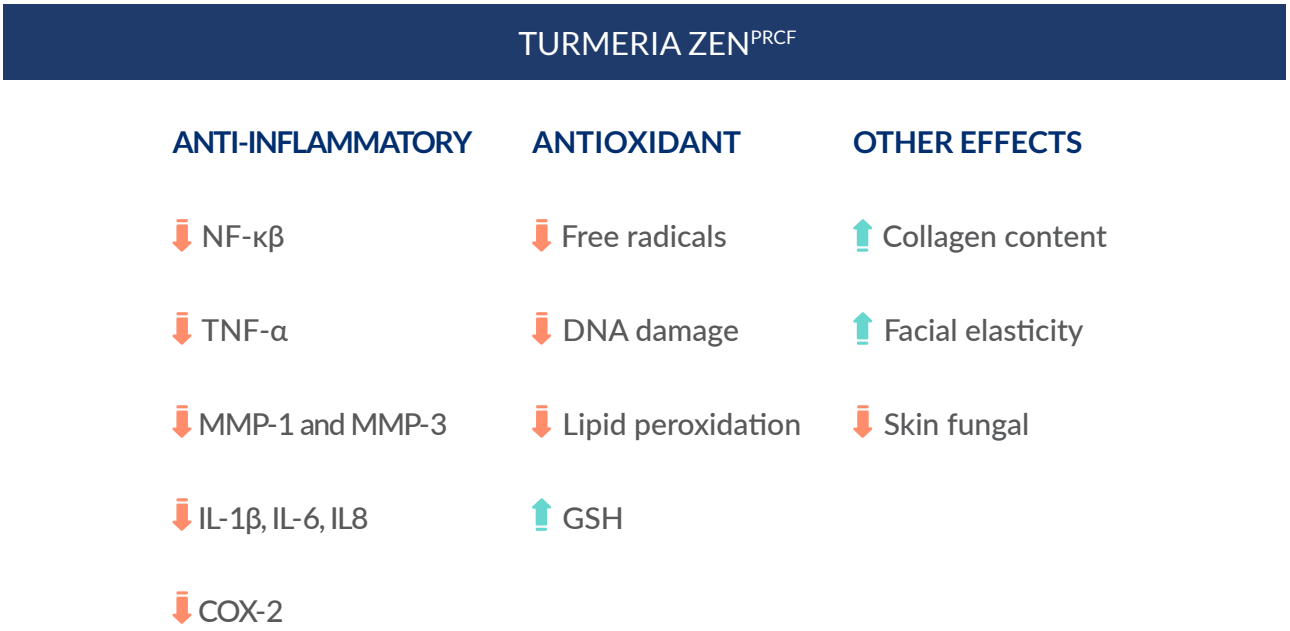


Figure 5. Summary of some of the pathways related to the therapeutic effects (anti-inflammatory and antioxidant) of TURMERIA ZEN[PRCF] in the skin. COX: cyclooxygenase; GSH: glutathione; IL: interleukin; MMP, matrix metalloproteinase; NF-kB, nuclear factor kappa B; TNF-a, tumour necrosis factor-alpha. Adapted from [70].

Specific investigation was conducted by the manufacturer Vytrus Biotech to assess the potential of the concentrated metabolome of totipotent cells from Curcuma longa rhizome (TURMERIA ZEN[PRCF]) [28].

At 0.1 µg/mL, the active metabolites extracted from Curcuma longa rhizome totipotent stem cells completely restored the basal levels of TNF-a and IL-8 in an activated human macrophages cell line (THP-1). The observed event was very pronounced in all doses tested (0.1, 1 and 20 µg/mL), reaching up to 97% decreased for TNF-a and up to 78% in IL-8 cytokines levels (Figure 6).

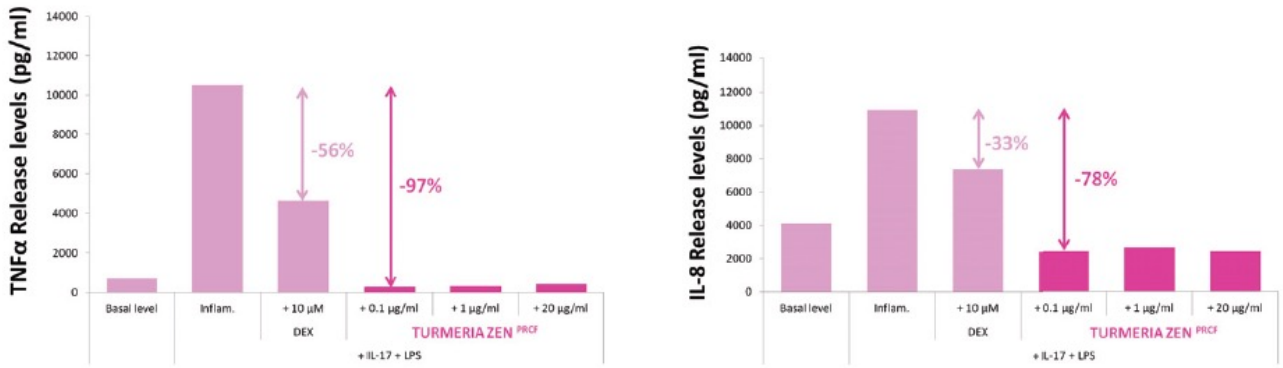


Figure 6. Anti-inflammatory activity of TURMERIA ZEN[PRCF]. THP-1 macrophages were with IL-17 (3 ng/mL) and LPS (10 µg/mL). The levels of TNF-a and IL-8 were measured. Dexamethasone (DEX) (10 µM) was used as negative control. TNF-a and IL-8 levels were quantified from cell culture supernatants by ELISA.

The wound healing properties of this extract were also assessed in a scratch assay performed in 2 mm wound monolayer culture of human dermal fibroblasts (HDF). The addition of 0.25 µg/mL of TURMERIA ZEN^{PRCF} accelerated the process at 24 and 48 hours (up to 72% and 63%, respectively) when compared with baseline conditions (Figure 7). The assay monitoring was performed for 48h through phase contrast microscopy.

In addition, the active ingredients on TURMERIA ZEN^{PRCF} contributed to a more structured and densified skin. After stimulation with 0.5, 1 and 2% of TURMERIA ZEN^{PRCF} daily, the degradation levels of collagen and elastin decreased up to 89% and up to 96%, respectively, compared to cortisol-stressed skin explants (Figure 8). Human organotypic skin explant cultures were exposed to hydrocortisone (10 µg/mL) to induce the stress condition. Histological sections were observed by optical microscopy after Masson's trichrome staining and collagen and elastin levels were quantified by colorimetric assays after 12 days.

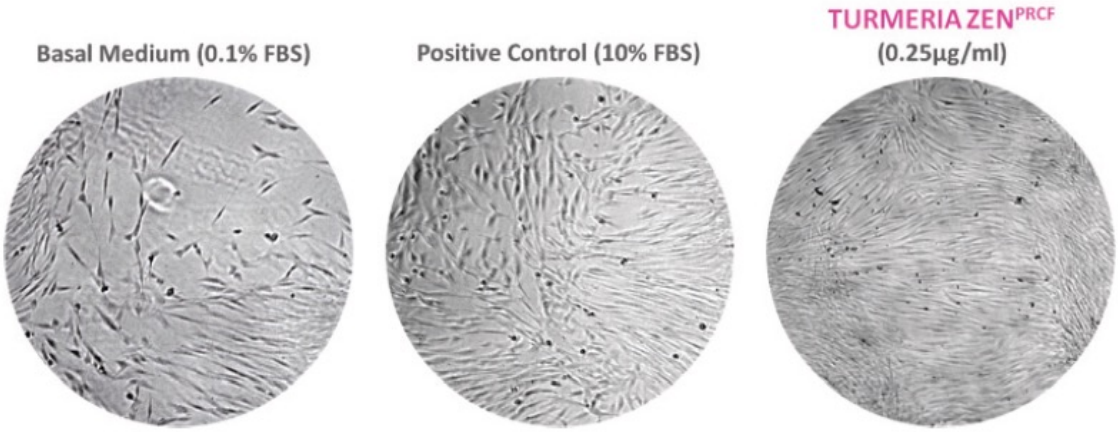


Figure 7. Wound healing properties in a scratch assay. The concentrated metabolome of totipotent cells at 0.25 µg/mL promote the faster proliferation and migration of fibroblasts in vitro.

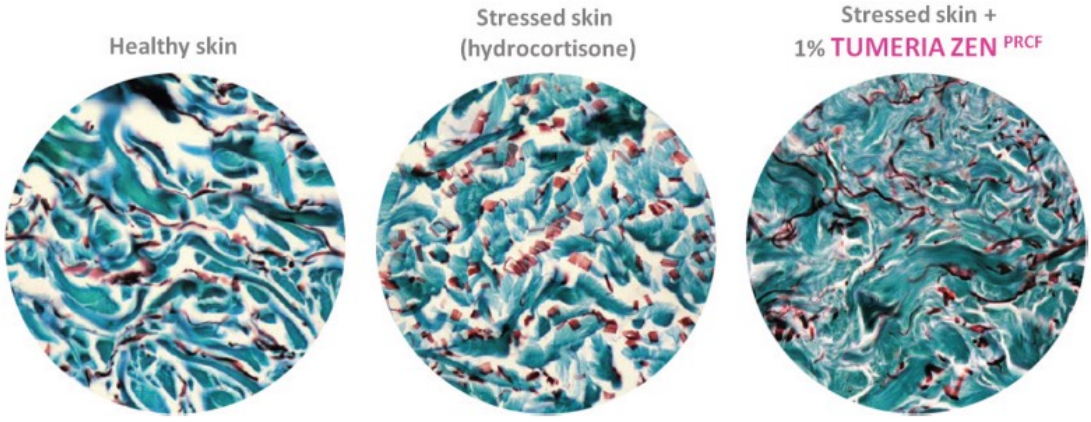


Figure 8. TURMERIA ZEN^{PRCF} protected the cortisol-stressed skin explants at 1%. The results show histological sections stained with Masson's trichrome.

In vivo, a cream formulation containing 1% of TURMERIA ZEN[PRCF] decreased deep wrinkles (Figure 9) and increased skin hydration (Figure 10). This formulation significantly reduced the wrinkle depth at 28 days. The maximum observed effect was 40% reduction while in average the depth of wrinkles decreased 9% from the start of the study. Furthermore, the face application twice daily for 28 days of cream formulation containing 1% of TURMERIA ZEN[PRCF] in a single blind placebo-controlled study significantly increase the average epidermal hydration rate. The participants enrolled were selected through a State-trait Anxiety Inventory questionnaire and cortisol test in saliva. At the end of the study, the mean hydration rate increased 13% corresponding to 4.3-fold hydration higher than placebo.

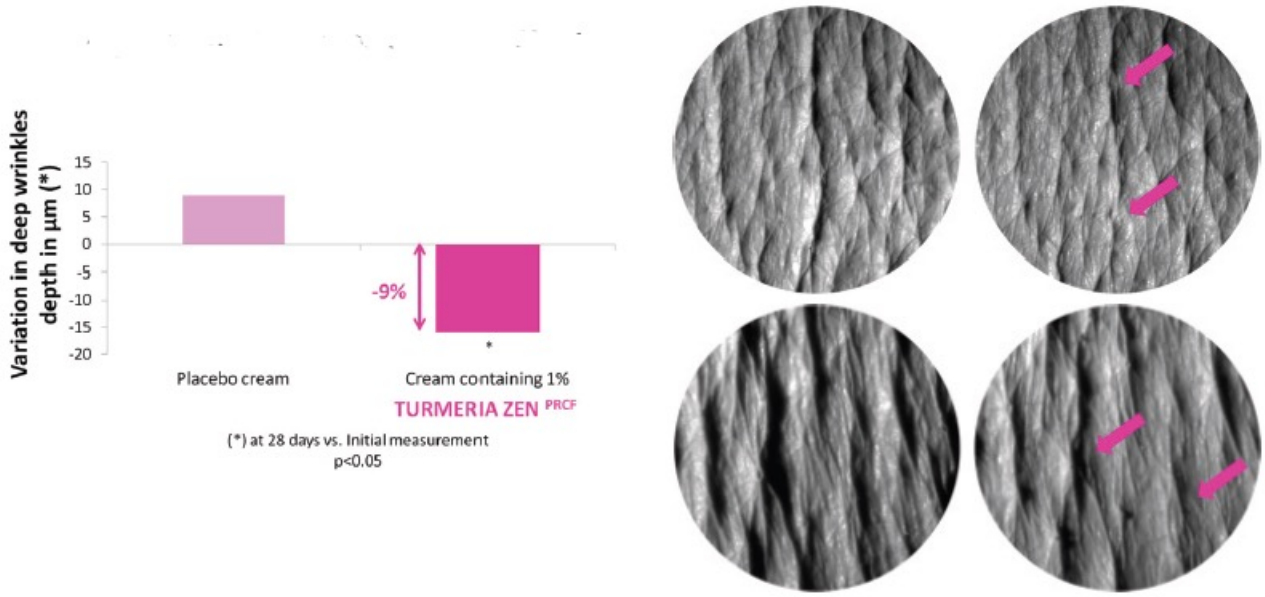


Figure 9. Anti-wrinkle effect of TURMERIA ZEN[PRCF].

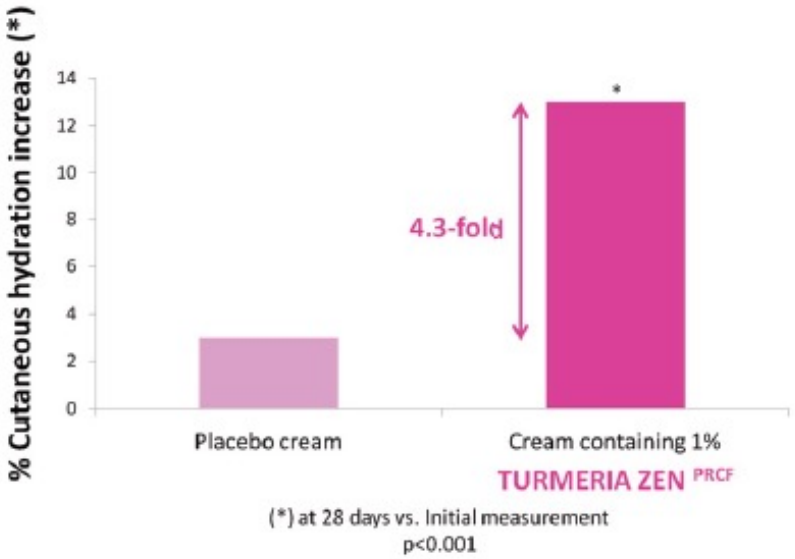


Figure 10. Skin hydration effect after 28 days of twice daily application of a cream containing 1% of TURMERIA ZEN[PRCF].

3.3. Safety assessment

KELO.CELL Silicone Gel individual ingredients (Dowsil EL-7040 Hydro Elastomer Blend, Xiameter PMX-200 Fluid 1.5 CS and Dowsil EL-9241 Silicone Elastomer Blend) have undergone a safety assessment by qualified toxicologists and has been classified as safe for its intended use by adults.

TURMERIA ZEN^{PRCF} safety profile was also presented by the manufacture [28]. No evidence of skin or ocular irritation potential was detected neither mutagenesis nor cytotoxicity in vitro. In vivo, the skin tolerance (patch test) and sensitization did not raise any safety issue.

3.4. Other information

KELO.CELL Silicone Gel contains no raw materials of animal origin. A minimal or no risk of transmitting BSE and TSE can be expected.

04.
COMPETITIVE LANDSCAPE

The competitive landscape for any product includes any solution that will achieve the goal irrespective of the constituents, mode of action or product classification. A market analysis suggests that the key competitors to KELO.CELL Silicone Gel for scar management are likely to be other silicone gels, silicone gel sheets and other scar dressings.

The principal players are outlined in Table 6 as well as product characteristics, indication of use and comments regarding advantages and disadvantages.

Among the other products in the market, KELO.CELL Silicone Gel is distinguished by:

• **Content in stem cells extract.** The incorporation of the bioactive ingredients derived from vegetable totipotent stem cells allows additional claims regarding inflammatory and remodelling properties.

• **Broader intention of use.** The incorporation of bioactive ingredients consolidates KELO.CELL Silicone Gel as a novel formulation to be applied in more than medical scenarios (scar management), allowing a broader marketing positioning as an anti-wrinkle or hydrating product. By extending the intension of use and inherent to cosmetic classification, there is the possibility to use for longer periods.

Table 6. Competitive landscape of KELO.CELL Silicone Gel.

NAME	CHARACTERISTICS/ COMPOSITION	INDICATION	DIFFERENCES FOR KELO.CELL SILICONE GEL
Dermatix®	• Medical Device • Silicone Gel (polysiloxane)	Freshly healed wounds to help prevent scars	• Clinically tested • Scientifically proven to soften & flatten scars • Does not contain stem cells extracts • Only applied to scars
Kelo-Cote®	• Medical Device • Silicone Gel (Polysiloxanes, Silicon Dioxide)	Hypertrophic scars and recent or old keloids, post-surgical scars, trauma, wounds or burns	• Clinically tested • Does not contain stem cells extracts
SVR Cicavit DM+	• Medical Device • Silicone Gel (%22 Hydrating Actives and %53 Silicone Complex)	Dermatological treatments or surgery, second-degree superficial burns, scars	• Do not use for longer than 30 days. • Does not contain stem cells extracts
Hansaplast Scar Reducer	• Medical Device • Self-adhesive patch made of polyurethane	New and old scars	• Not convenient to use in exposed areas such as face • Does not contain stem cells extracts • Only applied to scars

NAME	CHARACTERISTICS/ COMPOSITION	INDICATION	DIFFERENCES FOR KELO.CELL SILICONE GEL
Hartmann Tiritas® Medical Scar Reducer	• Medical Device • Silicone patch	Dressings for prevention and scar reduction	• Washable and reusable. • The same dressing can be used for up to 7 days • Does not contain stem cells extracts • Only applied to scars • Not convenient to use in exposed areas such as face
Cicalfate+ Scar Gel	• Cosmetic • Formulated based on thermal water, dimethicone, hyaluronic acid and C+ restore component.	Recent and up to -6 months-old scars	• Does not contain stem cells extracts
Cicaplast Gel B5	• Cosmetic • Formulated based on water, glycerine and dimethicone.	Recent scars	• Tested in face, lips and body • Mineral complex that protects against bacterial proliferation • Does not contain stem cells extracts • Only applied to recent scars
Bio-Oil® Oil	• Cosmetic • Formulated with base oils, specialist oils, vitamins, plant extracts, essential oils, anti-inflammatory and antioxidant ingredients	Scar, stretch marks, uneven skin tone, ageing and dehydrated skin	• Does not contain stem cells extracts

05. TESTING

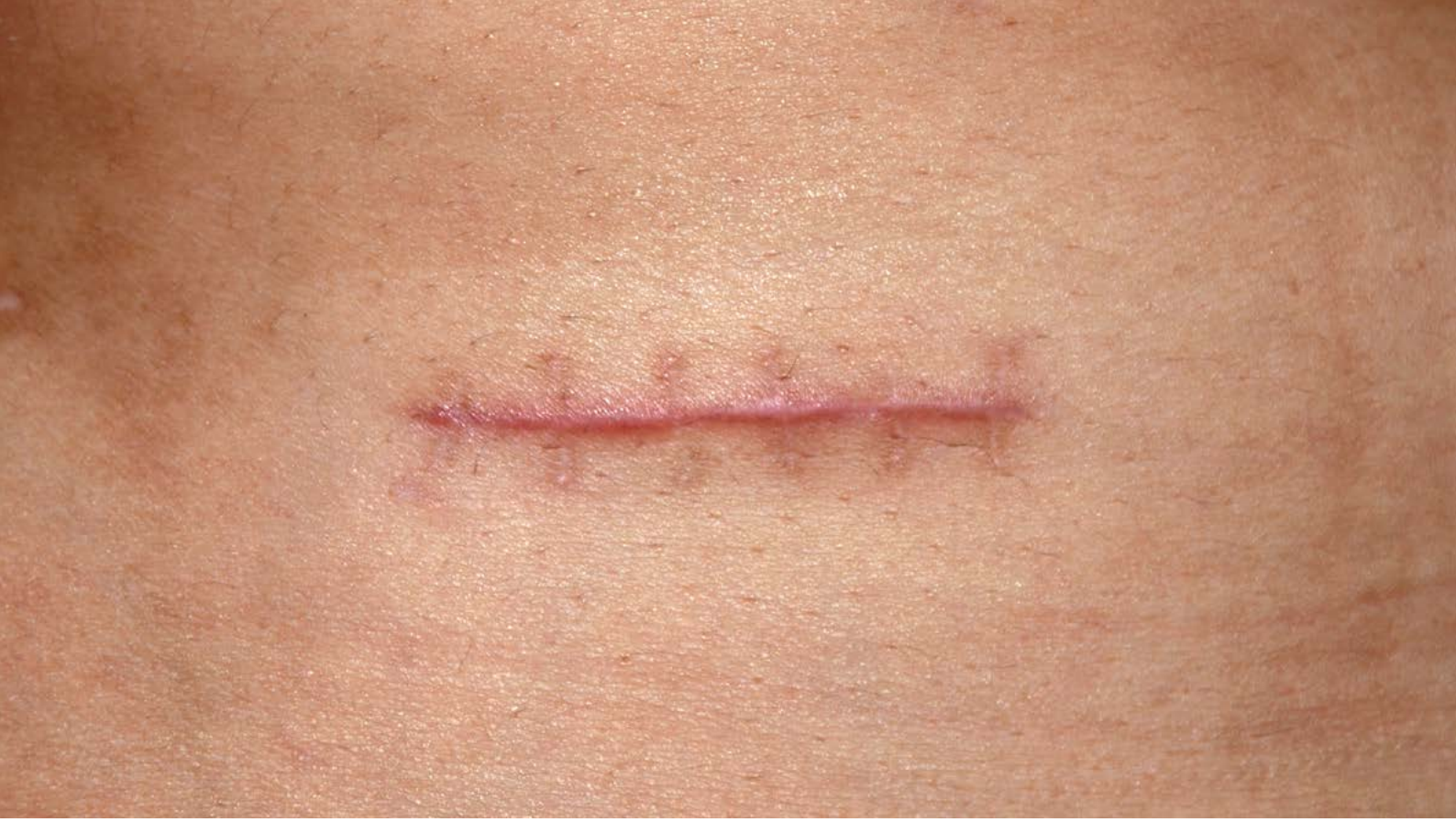
5.1. KELO.CELL Silicone Gel Perception Study

Understanding clinicians' perspectives and motivations is essential to rate and validate the product's key attributes as physicians decide to use/offer a product based on their overall performance. Therefore, this perception study was performed to evaluate the physician's experience and motivation regarding the use of KELO.CELL Silicone Gel, clinical's perception of the benefits associated with KELO.CELL Silicone Gel application and, ultimately, to assess satisfaction with KELO.CELL Silicone Gel and the probability of recommending it to other physicians.

This study consisted of the application of a questionnaire to physicians with distinct specialties. The questionnaire was composed of 6 closed questions and intended to evaluate the physician's perception of the use of KELO.CELL Silicone Gel with reference to the probability of recommending in different situations and by rating the ease of use, drying time, improvement in the scar appearance, and an assessment of general satisfaction. The questionnaire was applied over a period of 4 months.

This study enrolled 13 physicians whose answers correspond to 56 Kelo.Cell Silicone Gel users. The studied sample had heterogeneous competences in terms of medical speciality, being that 31% (4) were obstetricians, 31% (4) were plastic surgeons, 23% (3) were general surgeons and 15% (2) were dermatologists. All the physicians had more than 10 years of speciality and their place of work was mainly in Oman (9 in 13, ~70%).

Of note, 92% (12 out 13) of the recruited physicians usually recommend a topical treatment for scar management, reinforcing their contribution evaluating and comparing KELO.CELL Silicone Gel with the currently available options in this area. The majority of the inquired physicians reported that they would frequently recommend the application of KELO.CELL Silicone Gel in all the considered situations, being the visible and exposed scars the most unanimous condition (Figure 1). The non-responders usually do not manage those types of scars. Importantly, more than 90% (92,3%) of the inquired physicians would often or always recommend the application of Kelo.Cell in visible/exposed scars.



Approximately 85% of the physicians would routinely recommend KELO.CELL Silicone Gel for trauma scars or old ones. The percentage of "always" recommending KELO.CELL Silicone Gel in stretch and old scars was 53.8% and 38.5%, respectively. More than 6 out of 10 of the physicians reported that they would always recommend KELO.CELL Silicone Gel in the cases of visible/exposed scars, trauma scars or burn scars. Only one physician reported rarely recommending KELO.CELL Silicone Gel for post-acne scars while 60% would often or always recommend this product. 53,8% (approximately 5 out of 10) of the physicians answered that they would often or always recommend KELO.CELL Silicone Gel application in c-section scars.

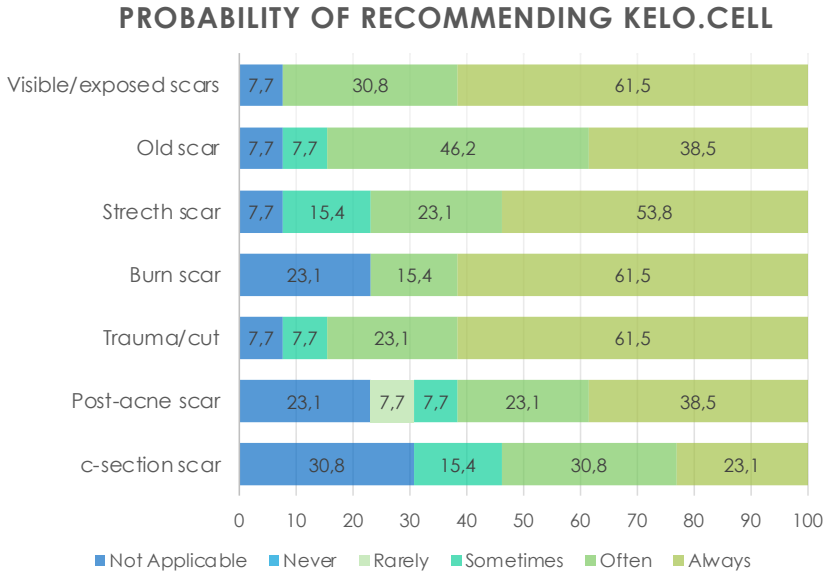


Figure 12. The probability of recommending KELO.CELL Silicone Gel for each scar.

Physicians were asked to rate in "never, "rarely, "sometimes", "often" or "always" the probability of offering KELO.CELL Silicone Gel in those scars. This graph represents the percentage of physicians by answer category. N=13 for each scar type. Not applicable corresponds to non-answers.

Looking in depth at the results, it is possible to conclude that, on average, the probability of recommending KELO.CELL Silicone Gel was high in all conditions. Burn scars were the condition with a higher score of recommendation (4.8) followed by visible/exposed scars (4.7). Even the lowest score – 4.1 for c-section scar – reveal that on average the physician would frequently recommend KELO.CELL Silicone Gel in this situation.

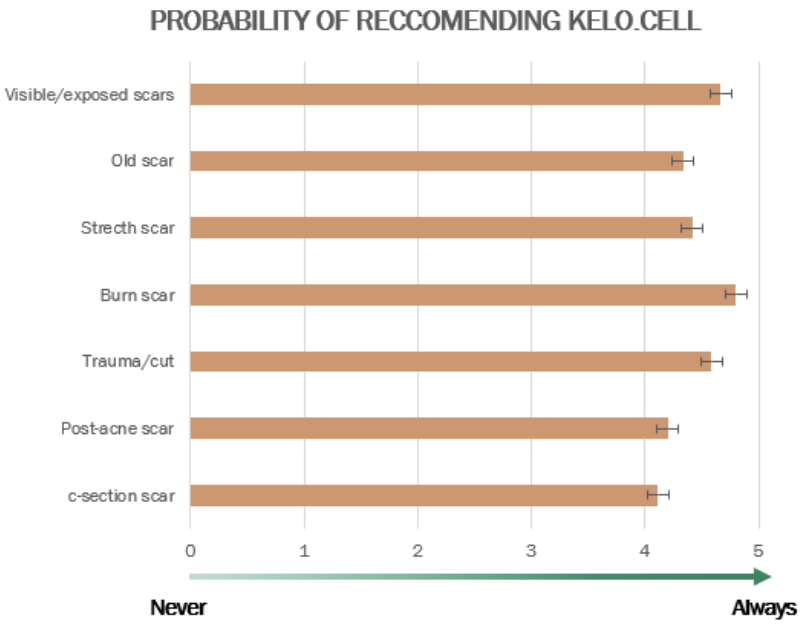


Figure 13. The probability of recommending KELO.CELL Silicone Gel for each scar.

For each class, it was attributing a numerical number in which 0 corresponds to "never" and 5 to "always". This graph represents the average categorization of the probability of recommending KELO.CELL Silicone Gel in each scar type. On average, the score was always superior to 4, which corresponds to "often". Non-answers were not included in this calculation.

In addition, the recruited physicians were asked to rate how beneficial KELO.CELL Silicone Gel is when compared with the other current available scar management options (Figure 14.). Among the physicians who answered, all considered the KELO.CELL Silicone Gel cost-efficacy ratio is either "beneficial" or "very beneficial" after using KELO.CELL Silicone Gel in comparison with other scar management options. KELO.CELL Silicone Gel application regimen was also considered by all the physicians as "beneficial" or "very beneficial" in comparison with other scar management options. The drying time was thought appropriate by 38.5% of the physicians and very appropriate by 69.2% in comparison with other available scar management options.

All the physicians considered KELO.CELL Silicone Gel is easy or very easy to use and beneficial or very beneficial for promoting skin hydration. Finally, more than 80% of physicians rated the overall improvement of scar appearance as either "beneficial" or "very beneficial" after using Kelo.Cell in comparison with other scar management options.

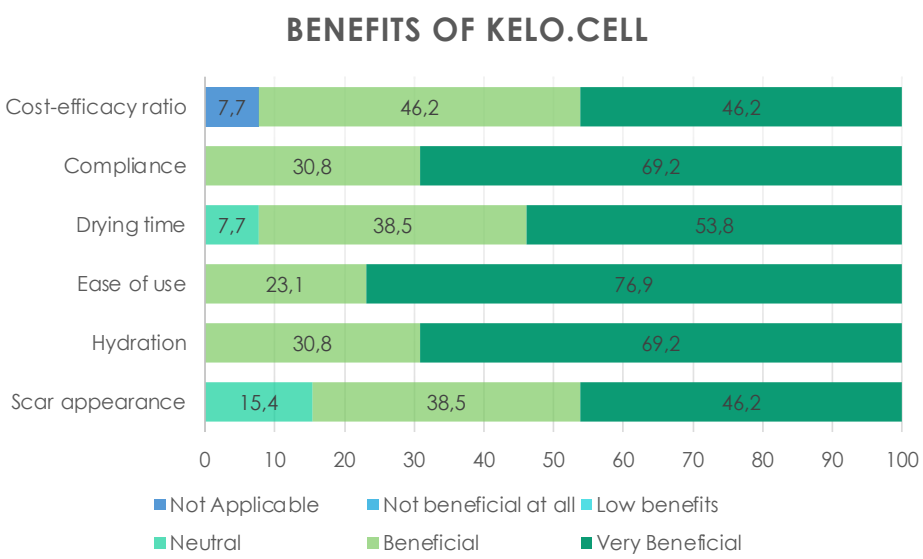


Figure 14. The benefits of KELO.CELL Silicone Gel in comparison with the other current available scar management options.

Physicians were invited to classify each KELO.CELL Silicone Gel attribute as "not beneficial at all", "low beneficial", "neutral", beneficial" and "very beneficial" when in comparison with the state-of-the-art. Only one physician did not answer in the cost-efficacy ratio.

At the end of the questionnaire, physician's overall perception was evaluated (Figure 15). Approximately 85% of the physicians considered the user satisfaction rate as "high" or "very high" and more than 8 out of 10 of the physicians perceived an elevated user receptivity, rating as "high" or "very high". Of note, more than 90% of the physicians would recommend KELO.CELL Silicone Gel to another health care professional.

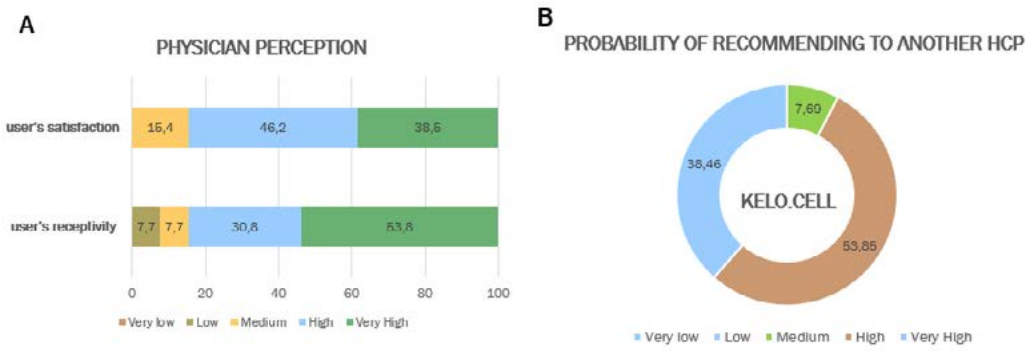


Figure 15. Physician overall perception of KELO.CELL Silicone Gel. User satisfaction and receptivity about KELO.CELL Silicone Gel was rated by physicians in five categories. The assessment of the probability of recommending KELO.CELL Silicone Gel to another healthcare professional was determined in an identical way.

In sum, this study allows us to conclude that:

- **More than 90% of the physician would recommend KELO.CELL Silicone Gel to another healthcare professional.**
- **The physicians, in this study, trust KELO.CELL Silicone Gel is an effective product for scar management, even in old ones.**
- **All physicians considered that KELO.CELL Silicone Gel is beneficial in terms of hydration, ease of use and compliance when compared to the other available solution in the scar management field.**

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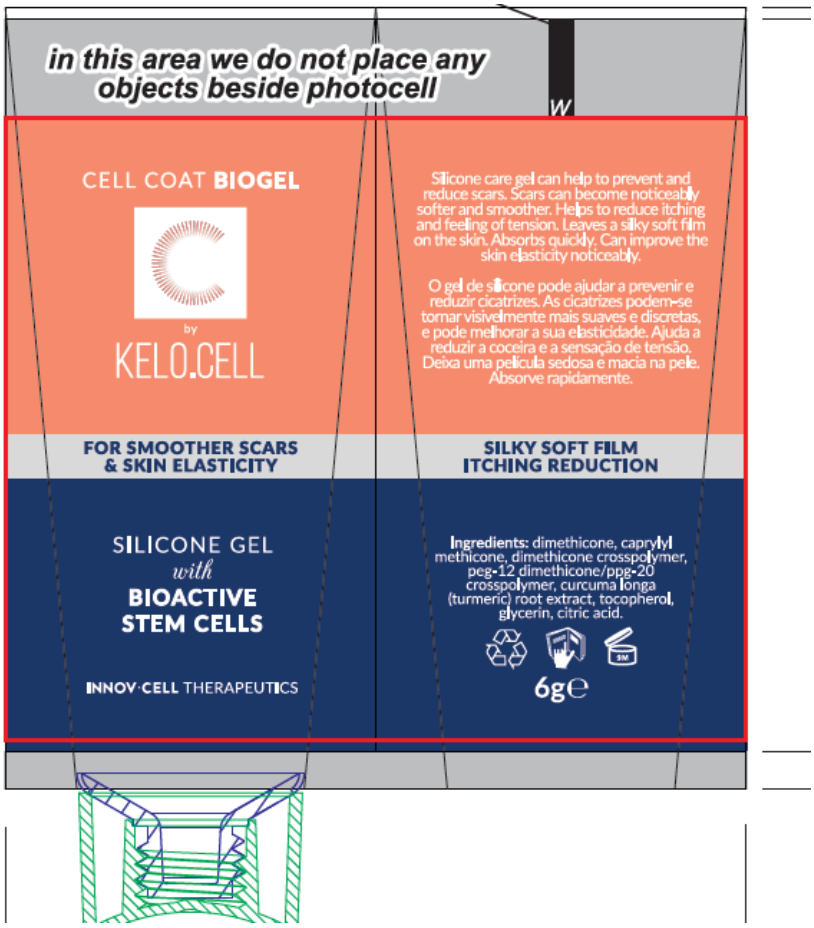
07.
ANNEXES

Annex 1 - KELO.CELL Silicone Gel Folding box and tube design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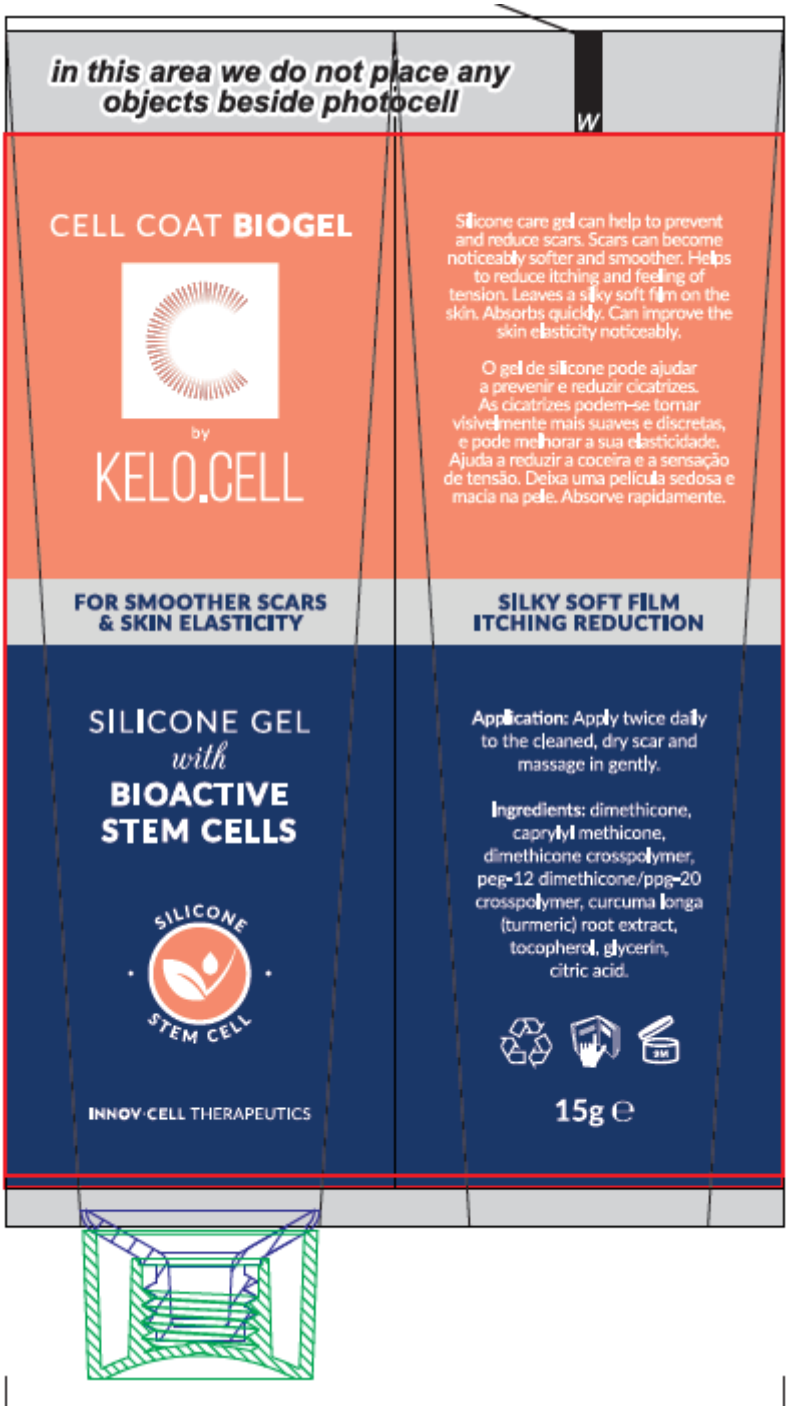
CELL COAT BIOGEL
by
KELO.CELL
Silicone care gel can help to prevent and reduce scars. Scars can become noticeably softer and smoother. Helps to reduce itching and feeling of tension. Leaves a silky soft film on the skin. Absorbs quickly. Can improve the skin elasticity noticeably.
O gel de silicone pode ajudar a prevenir e reduzir cicatrizes. As cicatrizes podem-se tornar visivelmente mais suaves e discretas, e pode melhorar a sua elasticidade. Ajuda a reduzir a coceira e a sensação de tensão. Deixa uma película sedosa e macia na pele. Absorve rapidamente.
FOR SMOOTHER SCARS & SKIN ELASTICITY
SILKY SOFT FILM ITCHING REDUCTION
SILICONE GEL
with
BIOACTIVE STEM CELLS
INNOV-CELL THERAPEUTICS
Ingredients: dimethicone, caprylyl methicone, dimethicone crosspolymer, peg-12 dimethicone/ppg-20 crosspolymer, curcuma longa (turmeric) root extract, tocopherol, glycerin, citric acid.
6g℮


KELO.CELL
El gel de silicona puede ayudar a prevenir y reducir las cicatrices, que pueden tornarse visiblemente más suaves y discretas, y con mayor elasticidad. Ayuda a reducir el picor y la sensación de tensión. Deja una película suave y sedosa sobre la piel. Se absorbe rápidamente.
KELO.CELL
O gel de silicone pode ajudar a prevenir e reduzir cicatrizes. As cicatrizes podem-se tornar visivelmente mais suaves e discretas, e pode melhorar a sua elasticidade. Ajuda a reduzir a coceira e a sensação de tensão. Deixa uma película sedosa e macia na pele. Absorve rapidamente.
CELL COAT BIOGEL
by
KELO.CELL
KELO.CELL
Silicone care gel can help to prevent and reduce scars. Scars can become noticeably softer and smoother. Helps to reduce itching and feeling of tension. Leaves a silky soft film on the skin. Absorbs quickly. Can improve the skin elasticity noticeably.
SILKY SOFT FILM
SKIN ELASTICITY
FOR SMOOTHER SCARS
ITCHING REDUCTION
Manufacturer:
SanderStrothmann,
Brüsseler Str. 2, 49124
Georgsmarienhütte.
Made in Germany
Distributor:
Kelocell Lda.
Quinta das Varandas,
Av. Cónego Urbano Duarte
nº65, Coimbra, Portugal
Ingredients: dimethicone, caprylyl methicone, dimethicone crosspolymer, peg-12 dimethicone/ppg-20 crosspolymer, curcuma longa (turmeric) root extract, tocopherol, glycerin, citric acid.
Store at room temperature.
Armazenar a temperatura ambiente.
Almacenar a temperatura ambiente.
在常温下储存。
15g℮
60-90
SILICONE GEL
with
BIOACTIVE STEM CELLS
SILICONE STEM CELL
INNOV-CELL THERAPEUTICS
硅胶护理凝胶可以帮助预防和减淡疤痕。疤痕会变得更着柔软和平滑。有助于减少瘙痒和绷紧感。在皮肤上形成丝般柔软的薄膜。吸收快。可显著改善皮肤弹性。
Application: Apply twice daily to the cleaned, dry scar and massage in gently.
Aplicação: Aplicar duas vezes ao dia sobre a cicatriz limpa e seca, e massagear suavemente.
Aplicación: Aplicar dos veces al día sobre la cicatriz limpia y seca, y masajear suavemente.
使用方法：每天两次涂抹于清洁、干爽的疤痕并轻轻按摩。
4 044518 000516


in this area we do not place any objects beside photocell
CELL COAT BIOGEL
by
KELO.CELL
Silicone care gel can help to prevent and reduce scars. Scars can become noticeably softer and smoother. Helps to reduce itching and feeling of tension. Leaves a silky soft film on the skin. Absorbs quickly. Can improve the skin elasticity noticeably.
O gel de silicone pode ajudar a prevenir e reduzir cicatrizes. As cicatrizes podem-se tornar visivelmente mais suaves e discretas, e pode melhorar a sua elasticidade. Ajuda a reduzir a coceira e a sensação de tensão. Deixa uma película sedosa e macia na pele. Absorve rapidamente.
FOR SMOOTHER SCARS & SKIN ELASTICITY
SILKY SOFT FILM ITCHING REDUCTION
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15g e

MADE IN GERMANY