REVIEW

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Natural products locally modulators of the cellular response: therapeutic perspectives in skin burns

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Abstract

Local cellular response plays a major role in restoring skin integrity, in burns with infectious complications, chronic fibrous sequelae, etc. For the study of wound-healing process, different experimental models of skin burn were developed. Mice, rats, rabbits and guinea pigs are the most used laboratory animals, kept under standard conditions of light, temperature, food and water (*ad libitum*). Commonly, by intramuscular injection, general anesthesia was induced with ketamine hydrochloride. Most times, skin burns were inflicted on the dorsal region of animals. Metal devices with different shapes and weights, heated in water at various temperatures were applied locally, for few seconds. The paper reports on 65 natural medicinal products recommended for the external and internal treatment of skin damages (first- or second-degree burns, various wounds, ulcerations). Some of them are traditionally used in the Romanian ethnopharmacology, supporting the wound-healing process mainly because of their epithelizing, astringent, emollient, demulcent, anti-inflammatory, antimicrobial, immunomodulatory and antioxidant properties.

Keywords: natural products, modulators, cellular response, skin burns, therapy.

Introduction

It is estimated that burns cause approx. 265 000 deaths per year and around the world millions of cases of skin burns are recorded. The complications of burns are one of the most difficult pathologies. The suffering is more or less severe depending on the extent and depth of the lesions [1, 2].

Active principles rutoside and citrin are used in skin burns for the improvement of capillary permeability. Associated with calcium and magnesium, vitamins A, B and C are essential for the proper functioning of the central nervous system, helping the muscles relaxation. Infusions or decoctions of some medicinal herbs are used for their diuretic properties. In the first phase of the disease are recommended fruits and vegetables juices, vegetable soups, milk and proteins [3, 4].

In minor skin burns, for external phytotherapeutic treatment are used especially medicinal herbs with flavonoids and tannins, with astringent, antiseptic, anti-inflammatory and cicatrizing effect, able to accelerate the healing of the damaged tissue. Local lavage with aqueous extractive solutions, essential oils, ointments or macerated oils prepared from medicinal herbs are indicated for the external treatment of the first- or second-degree skin burns [3, 4].

Natural products for the treatment of skin injuries

Acalypha indica, Indian nettle

In the traditional medicine of Southern India region, *A. indica* is used in the treatment of wounds. Different alcoholic extracts of Indian nettle were tested in excision and incision experimental wound models in rats. Topical application of vegetal extracts evidenced the increasing of wound healing activity in terms of epitelization, collagen synthesis, cellular proliferation and antioxidant effect (decreasing of lipid peroxidation and increasing vitamin C levels) [5–7].

Acanthus mollis, bear's breeches

The Greek physician Dioscorides recommended the roots or leaves (mucilages, tannins, flavonoids) of bear's breeches as a poultice to treat burns, because of their emollient, astringent and anti-inflammatory properties [4, 8].

Achillea millefolium, yarrow

Local lavage and dressing with infusions of yarrow flowers (flavonoids, tannins, essential oil) are indicated for the external treatment of first- and second-degree skin burns [3]. In a study of Temamogullari F *et al.*

(2009), comparing with 10% povidone iodine and 0.9% sodium chloride, daily topical application of yarrow extract accelerated wound healing of dorsal full-thickness skin defects in rabbits. Macroscopic and histologic parameters were assessed: exudation, bleeding, thickness of scar, vascular proliferation, inflammatory cell infiltrate, contraction, epithelization [9].

Actinidia deliciosa, kiwifruit

In experimental model, kiwifruit was investigated as natural remedy for eschar separation and debridement. Standard full-thickness burns were inflicted on the back of rats, under general anesthesia. Comparing with a neutral ointment and control (untreated) group, kiwifruit-treated group shows faster enzymatic debridement, good scar contraction and healthy adjacent tissue [10].

Aloe sp., aloe

Aloe vera gel treats numerous skin disorders and accelerates the healing of burns and different wounds. It is immunostimulatory, astringent, anti-inflammatory, epithelizing, emollient, demulcent, antibacterial, protective, being used in various cosmetic products [3, 4, 11, 12]. Whole-leaf fresh juice (aloin or barbaloin, tannins, resins, polysaccharides) or mucilaginous gel (glucomannan, acemannan, sterols, glycoproteins) reduce the risk of infection and accelerate wound healing by stimulating fibroblast proliferation, deposition of collagen, angiogenesis and production of growth factors. All these useful effects were highlighted by many experimental *in vitro* (NCTC2544 human keratinocytes) [13] or *in vivo* models (mice, Wistar or Sprague–Dawley rats, Hartley guinea pigs, rabbits, domestic pigs) of full-thickness skin cuts, burns and frostbites [14–21], and by randomized clinical trials, made on hundreds of volunteers [22–25].

Arctium lappa, burdock

A decoction prepared from burdock roots (lignans, inulin, polyenes, sulfurated polyacetylenes, sesquiterpene lactones) is indicated in the external (local lavage and poultices) and internal treatment of skin burns [3, 26].

Astilbe thunbergii, false spirea

Ethanol extract and active principles of false spirea rhizomes (eucryphin, bergenin and astilbin) accelerate burn wound healing in experimental model in mice. Eucryphin has the strongest wound healing effect from the three isolated compounds, mainly by stimulating angiogenesis: increasing of VEGF, TGF-β1 and HIF-1α expression in keratinocytes [27, 28].

Black Sea mollusks and gastropods

In experimental model of skin burns in Wistar rats, lipids and amino acid extracts prepared from the Black Sea mollusks (*Mytilus galloprovincialis*, Mediterranean mussel) and gastropods (*Rapana venosa*, hard-shell clam) show antioxidant and wound healing properties [29, 30].

Buddleja globosa, orange ball tree

Due to cicatrizing effect, aqueous extract prepared from the leaves (flavonoids, caffeic acid derivatives) of orange ball tree is traditionally used in Chile for wound-healing improvement. The study of Mensah AY *et al.* (2001) demonstrates that this aqueous extract has strong antioxidant activity and *in vitro* stimulates the growth of fibroblasts [31].

Bulbine sp., bulbine

In South Africa, the species *B. frutescens* (yellow bulbine) and *B. natalensis* (broad-leaved bulbine) are remedies recommended in skin ailments. In a study of Pather N *et al.* (2011), leaf gels are active in the topical treatment of excisional and incisional dermal wounds in domestic pigs. Compared with untreated wounds, an important increase in the collagen, protein and DNA content was found [32].

Calendula officinalis, pot marigold

Marigold flowers (carotenoids, saponosides, sterols, flavonoids, mucilages, essential oil, tannins, Mn^{2+} ions) are used both internally and locally for their healing action in burns, wounds and various inflammatory skin disorders [3, 4]. Experimental models and randomized clinical trials have shown that topical preparations (especially ointments) with *Calendulae flos* extracts stimulate the wound-healing process in numerous skin problems [33–35].

Carissa spinarum, conkerberry

In the tropical regions of the Southern Hemisphere, conkerberry is traditionally used for the wound-healing properties. The epithelizing, wound contraction and antimicrobial effects of the methanolic extract from the roots were highlighted in experimental burn skin model in mice [36].

Chitosan

Chitosan is a chitin-derived polysaccharide, polymer of N-acetyl-D-glucosamine. Non-toxic, hemostatic, antibacterial, biocompatible and biodegradable bandages or films containing chitosan are recommended for burns and wounds dressing [37, 38]. Many other studies, using experimental models of burnt skin wounds in Wistar rats or New Zealand white rabbits, have shown that chitosan gel enhances tissues regeneration and wound-healing process, in combination with silver sulfadiazine cream, epidermal growth factor (EGF), heparin, calcium alginate or fucoidan [39–43]. In addition, chitosan is used in plastic surgery for the recovery of donor-site tissue damages [37].

Harpagophytum procumbens, devil's claw

Devil's claw is native to Central and South Africa. Powdered or mixed with an ointment base, tuberous roots (iridoids, sterols, flavonoids, quinones) are used to heal irritations, wounds, ulcers and burns [3, 4].

Heparinum, heparin

Saliba MJ Jr (2001) reviews the advantages of the local application of heparin in the treatment of skin burns (anticoagulant, re-epithelizing, anti-inflammatory, neo-angiogenic and collagen recovery actions), taking into account the possible adverse effects (bleeding, thrombocytopenia, allergy) [44].

Insulinum, insulin

In experimental model of skin burns on the dorsal region in rats, Madibally SV *et al.* (2003) found that insulin increases re-epithelization, reduces inflammation, stimulates wound healing and collagen fibers deposition [45].

Lavandula angustifolia, common lavender

Common lavender, native in France and western Mediterranean region, is cultivated around the world as an ornamental species and for its essence. The flowers contain essential oil, flavonoids, tannins, coumarins. The essential oil is an invaluable first aid remedy; it is antiseptic, speeds healing of burns and wounds, calms inflammation caused by insect bites [3, 4].

Leucas lavandulaefolia, leucas

L. lavandulaefolia is a species traditionally used in Indian ethnopharmacology. Comparing to nitrofurazone, in excision and incision wound models in rats, administered both in injections and in ointments, the methanol extract of leucas leaves shows a significant wound-healing potential [5, 46].

Mimosa tenuiflora, mimosa

In the traditional medicine of South America region, the aqueous extracts from the mimosa bark are used for their wound-healing effect in skin burns. For the water extract and ethanol-precipitated compounds (arabinogalactans), Zippel J *et al.* (2009) found a significant *in vitro* stimulation of activity and proliferation of human primary dermal fibroblasts [47].

Mucilages

Natural products with mucilages are used locally for the treatment of burns, different wounds or ulcerations, because of their emollient, demulcent, anti-inflammatory and protective effects [3, 4]:

- flax seeds: *Linum usitatissimum*, common flax;
- plantain leaves or fresh juice: *Plantago lanceolata* (narrowleaf plantain), *P. media* (hoary plantain), and *P. major* (common plantain);
- mullein flowers: *Verbascum densiflorum* (dense-flowered mullein), *V. phlomoides* (orange mullein), *V. speciosum* (showy mullein), and *V. thapsus* (common mullein).

Musa sp., banana

For partial-thickness burn wounds of 30 patients less than 40-year-old, Gore MA and Akolekar D (2003) used banana leaf dressing and boiled potato peel bandage with a topical agent. For the majority of patients, both products are tolerable, easily handling and less painful during every day dressing change. The surface of banana leaf is waxy, cool and non-adherent; today, in India, it is the cheapest dressing and can be obtained very easily [48].

Ribes nigrum, blackcurrant

The wound healing (cicatrizing) effect of a new topical gel based on blackcurrant buds essential oil, compared with Cicatrizin®, gel base treated and untreated groups, in experimental-induced skin burns in rats, was emphasized by Mihele D *et al.* (2010) [49].

Rosmarinus officinalis, rosemary

The healing efficacy of topical application of aqueous extract and essential oil of rosemary herb, 25 μL/excision wound, twice a day for three days, was evaluated on alloxan-induced diabetic BALB/c mice. At the level of diabetic wounds, a reduced inflammation, regeneration of granulation tissue, re-epithelization, collagen deposition and angiogenesis were observed [50].

Sambucus nigra, elder

In the Romanian ethnopharmacology, a local lavage with infusions or poultices prepared from elder flowers (flavonosides, catechic tannin, mucilages, essential oil) is indicated for the external treatment of burns [3]. In our previous studies, astringent, anti-inflammatory, antiseptic and cicatrizing effect of two topical preparations containing 10% soft extracts of elder flowers and elder leaves was assessed on the tissue regeneration in experimental model of third-degree thermal skin burns, in Wistar rats. Tinctures and soft extracts were obtained and physico-chemically characterized according to the Romanian Pharmacopoeia. The soft extracts were 10% embedded in a cold-cream type ointment base, prepared according to United States Pharmacopoeia. Thin layer chromatography analysis performed on *Sambuci flos* and *Sambuci folium* tinctures and soft extracts has revealed the presence of rutoside, luteol-7-glucoside, polyphenolic acids and coumarins [51].

Sanguisorba officinalis, official burnet

In lotions or ointments, the aerial parts and roots (tannins, flavonoids, essential oil) of official burnet are applied on burns and wounds [4, 52]. The compound tincture of *S. officinalis* herb, obtained and clinically tested in Jiangxi Hospital (China) is effective for the short-treatment duration of first- and second-degree skin burns. Silver nitrate ointment and antibiotics were used for the control group of patients [53].

Sanicula europaea, European sanicle

The aerial parts (saponins, allantoin, essential oil, tannins, chlorogenic and rosmarinic acids, mucilages, vitamin C) of European sanicle have been known for centuries for their ability to heal wounds and stop bleeding; allantoin promotes healing of damaged tissue and rosmarinic acid is anti-inflammatory. As a poultice, it is used to treat wounds, burns, frostbite and other skin inflammations [4, 52].

Scrophularia nodosa, woodland figwort

Mainly because of the anti-inflammatory effect, local applications with aqueous extract from the aerial parts (acylated iridoid glycosides, flavonosides, tannins, polyphenolic acids) effectively treat burns and ulcerations [4]. In the study of Stevenson PC *et al.* (2002), three acylated iridoid glycosides isolated from the dried seedpods of *S. nodosa* stimulated the growth of human dermal fibroblasts *in vitro* [54].

Sempervivum tectorum, common houseleek

The leaves and fresh juice of the leaves (tannins, mucilages) are used for their astringent and refreshing effects: applied externally, they tighten and soften many skin conditions such as burns and wounds. Common houseleek products are not recommended for internal use, because of the risk of vomiting [4, 8, 52].

Silybum marianum, milk thistle

Due to antioxidant action, in experimental model on Wistar albino rats exposed to 90^0C bath for 10 seconds, silymarin reduces the morphological alterations and oxidative damage at the burnt skin wounds level. Silymarin was delivered twice daily after the burn, in local (30 mg/kg) or in both local and systemic (50 mg/kg, *p.o.*) applications [55].

Other natural remedies

In the specialty papers, many other natural remedies are cited for the treatment of skin wounds, in different experimental models (Table 1).

Table 1 – ***Various natural remedies locally modulators of the cellular response in skin wounds***

Species	Natural products (active principles)	Effects	Experimental models	References
Apis sp., honey bee	*Cera flava*, beeswax, yellow wax (cerids, sterids, flavonoids, triacontanol, fatty acids, higher hydrocarbons)	Emollient, cicatrizing, biostimulating, healing of diabetic wounds, antipruritic.	▪ Full-thickness skin wounds on the back of diabetic male white rabbits. ▪ Beeswax and herbal oil cream on human volunteers with post-burn itch.	[56, 57]
	Mel, honey (sugars, enzymes, amino acids, vitamins)	Emollient, demulcent, antibacterial, anti-inflammatory, analgesic, cicatrizing.	▪ Topical application on open wounds in male HS/Ibg mice; ▪ Auricular burns in male white rabbits (comparing with mafenide acetate); ▪ Randomized controlled clinical trials for honey-dressed partial-thickness burns and different types of wounds or ulcers (comparing with silver sulfadiazine).	[12, 58–64]
	Propolis, propolis wax (bioflavonoids, resins, wax)	Epithelizing, antibacterial, anti-inflammatory, immunomodulatory.	▪ Burnt skin lesions in rabbits (spray or H/L-emulsion ointment with 5% propolis fluid extract); ▪ Burnt skin wounds on the back of Wistar albino male rats (50% propolis cream).	[65–67]
Astragalus gummifer *A. kurdicus* *A. microcephalus* *A. verus* goat's-thorn	*Tragacantha*, tragacanth gum (polysaccharides, starch, mineral salts)	Emollient, demulcent, cicatrizing, anti-inflammatory (6% tragacanth mucilage-saturated sterilized bandages).	▪ Burnt skin wounds on the back of New Zealand rabbits (compared with untreated and vaseline gauze treated groups).	[68]
Camellia sinensis, tea plant	Green tea leaves or buds (purine alkaloids, vitamin C, polyphenols – tannins, flavonosides, proantho-cyanidins, organic acids)	Antioxidant, astringent, cicatrizing, antitumoral, anti-inflammatory, protective in UV exposure (sunburns) and epidermal damage.	▪ Topical applications on the skin of human volunteers, after acute UV injury (erythema).	[4, 69, 70]
Carica papaya, papaya *C. candamarcensis*, mountain papaya	Pulp of fruits, dried latex hydrogels (proteinases – papain, chymopapain)	Antimicrobial, epithelizing and cicatrizing for dermal wound healing in burns.	▪ Induced wounds (third-degree burns) in Swiss albino mice; ▪ Children with full-thickness and infected burns.	[71–74]
Caryocar coriaceum, pequi	Fixed oil (fatty acids glycerides, sterols, triterpenes, vitamins A, D and E)	Anti-inflammatory, cicatrizing, accelerate cutaneous wound repair.	▪ Topical applications of ointment formulations in mice: ear edema induced by xylene; wound excision.	[75]
Cassia fistula, golden shower tree	Leaves (anthracenosides, tannins, flavonosides proanthocyanidins)	Antioxidant, antibacterial, astringent and cicatrizing in infected wounds.	▪ Ointment formulation locally applied on infected wounds of male Wistar albino rats.	[5, 76]
Centaurea sadleriana, Pannonian knapweed	Aerial parts (flavonoids, tannins, sesquiterpene lactones)	Anti-inflammatory, astringent, antimicrobial, epithelizing.	▪ Gel formulation applied on wounds inflicted on the back of female Sprague–Dawley rats.	[77]
Centella asiatica, Asiatic pennywort	Aerial parts (asiaticoside, madecassoside, flavonoids, sterols)	Cicatrizing, antimicrobial, anti-inflammatory, wound healing in burns, venous disorders and skin ulcerations.	Topical application of asiaticoside solutions or ointments: guinea pig punch wounds; streptozotocin diabetic rats; male Balb/c mice.	[5, 78, 79]
Datura alba, datura	Leaves (tropane alkaloids, flavonosides, tannins)	Antibacterial, cicatrizing, anti-inflammatory.	▪ Burnt skin wounds on the dorsal part of male albino rats.	[5, 80]
Echinacea angustifolia, narrow-leaf coneflower *E. pallida*, pale purple coneflower *E. purpurea*, purple coneflower	Roots and aerial parts (essential oil, polyacetylenes, polysaccharides, resins, echinacoside)	Immunomodulatory, antimicrobial, anti-inflammatory, cicatrizing in burns, chronic ulcerations and different wounds.	▪ Burnt skin wounds in rats; ▪ Uncontrolled clinical trials (topical application of different coneflower extracts).	[3, 4, 81]

Species	Natural products (active principles)	Effects	Experimental models	References
Equisetum arvense, horsetail	Aerial parts (natural silica, saponosides, flavonosides)	Restore damaged tissues, anti-inflammatory, stimulate collagen synthesis.	▪ Dermal wound healing model in male albino Wistar rats (5% or 10% ointment); ▪ Full-thickness skin wounds on the dorsal part of rabbits.	[3, 82, 83]
Hippophaë rhamnoides, sea buckthorn	Fixed oil from berries or seeds (fatty acids glycerides, sterols, triterpenes, flavonoids, vitamins A, D and E) Lyophilized aqueous leaves extract (flavonosides, carotenoids, triterpenes, vitamins, tannins, proantho-cyanidins)	Epithelizing, antioxidant, anti-inflammatory, wound healing in skin burns, frostbites, ulcerations, corneo-conjunctival burns, corneal grafts, plastic and reconstructive ocular surgery.	▪ Full-thickness burn wounds on the dorsal surface of male Sprague–Dawley rats (comparing with silver sulfadiazine ointment).	[3–5, 84–86]
Hypericum perforatum, St. John's wort	Aerial parts infusion or macerated oil – *Hyperici oleum* (naphtodianthrones, phloroglucinols, flavonosides, xanthones, tannins, proantho-cyanidins, essential oil)	Cicatrizing, antimicrobial, anti-inflammatory, antidepresive, restore the damaged skin in first- or second-degree burns.	▪ Burnt skin models in male Sprague–Dawley rats and Swiss albino mice (*Hyperici oleum* ointment formulations comparing with Madécassol®).	[3, 4, 87]
Ipomoea batatas, sweet potato	Peels or fibers from tubers (polysaccharides, polyphenols, vitamins)	Emollient, epithelizing, antioxidant, dressing material in skin burns and wounds.	▪ Incision or excision wound models in Wistar rats (gel containing peel extract).	[88, 89]
Linum usitatissimum, common flax	Fixed oil (fatty acids glycerides, sterols)	Cicatrizing, emollient, anti-inflammatory, regenerative, epithelizing (*Linimentum calcii*).	▪ Incision or excision wound models in Wistar rats (flaxseed oil); ▪ Uncontrolled clinical trials.	[3, 4, 90]
Matricaria recutita, German chamomile	Flowers aqueous extract or macerated oil – *Matricariae oil* (essential oil, sesquiterpene lactones, flavonoids, polyacetylenes, sterols, carotenoids)	Emollient, demulcent, cicatrizing, antimicrobial, anti-inflammatory, in first- and second-degree burns (lavage, poultice or dressing).	▪ Excision, incision, dead space, and burnt skin wound models on the back of male albino Wistar rats (compared with olive oil, triamcinolone acetonide and clobetasol propionate).	[4, 91–97]
Melaleuca alternifolia, Australian tea tree	Essential oil (terpenes) Leaves and small branches aqueous extract (essential oil, flavonoids, tannins)	Antiseptic, anti-inflammatory, epithelizing, effective against infected burns, wounds, insect bites.	▪ Clinical trials for methicillin-resistant *Staphylococcus aureus* (MRSA) decolonisation regimens in acute or chronic wounds of mixed etiology (essential oil); ▪ Fresh deep partial thickness hot water burns in a porcine model (essential oil hydrogel treated burns compared with water-cooled burns).	[3, 98–100]
Murraya koenigii, curry leaf	Leaves (flavonoids, tannins, alkaloids, essential oil)	Cicatrizing, antibacterial, astringent, anti-inflammatory, stimulates the wound healing process.	▪ Excision and incision wounds in male albino rats.	[4, 101, 102]
Nasturtium officinale, wartercress	Leaves macerated oil (glucosinolates, flavonosides, tannins)	Antimicrobial, anti-inflammatory, epithelizing.	▪ Male rabbits burned by concentrated hydrochloric acid or by a hot glass rod (80^0C) for three times (compared with bacitracin zinc or neomycin).	[103]
Olea europaea, olive	Olive oil (fatty acids glycerides, iridoids, triterpenoids, lignans, phenylpropane derivatives)	Emollient, cicatrizing, anti-inflammatory, antibacterial.	▪ Partial-thickness burns inflicted on the dorsum of domestic female pigs (comparing with silver sulfadiazine).	[3, 4, 104]
Opuntia ficus-indica, Indian fig	Cladodes (lyophilized polysaccharide extracts)	Epithelizing, antibacterial, anti-inflammatory, immunomodulatory.	▪ Large full-thickness circular wounds in male Sprague–Dawley rats.	[105]
Phyllanthus niruri, stonebreaker	Aerial parts (acidic arabinogalactan, flavonoids, tannins, lignans, terpenes, alkaloids)	Cicatrizing, antibacterial, anti-inflammatory, analgesic, antioxidant.	▪ Topical and oral administrations of ethanolic extract formulations in partial thickness-burn wounds or in dexamethasone-suppressed burn wounds in male albino Wistar rats.	[106]
Polygonum cuspidatum, Japanese knotweed	Aerial parts (tannins, flavonosides, anthraquinones)	Epithelizing, analgesic, anti-inflammatory, immunomodulatory.	▪ Burns inflicted on the back of Wistar rats.	[107]
Rheum officinale, rhubarb	Roots (anthraquinones, flavonoids, tannins)	Astringent, antibacterial, cicatrizing.	▪ Emodin gel applied on full-thickness wounds excised on the dorsal skin of male Sprague–Dawley rats.	[4, 108]

Species	Natural products (active principles)	Effects	Experimental models	References
Solanum tuberosum, potato	Pulp, peels or fresh juice of tubers (starch, vitamins, minerals)	Emollient, demulcent, moisturizer, epithelizing.	▪ Full-thickness skin defects in Wistar rats (dressing with boiled potato peels); ▪ Clinical trials in superficial partial thickness skin loss burns (boiled peels dressing compared with silver sulfadiazine).	[4, 109–114]
Symphytum asperum, rough comfrey *S. caucasicum*, Caucasian comfrey *S. officinale*, comfrey	Roots or leaves (allantoin, tannins, carotenoids, saponosides, polysaccharides)	Demulcent, emollient, cicatrizing, anti-inflammatory, regenerative of damaged tissues.	▪ Open-wound model in female Wistar rats: allantoin incorporated in soft lotion L/H emulsion; three topical formulations with leaves extract; ▪ Excisional wound and burnt skin models in mice.	[4, 5, 115–118]
Terminalia chebula, yellow myrobalan *T. bellirica*, beleric myrobalan *Phyllanthus emblica*, Indian gooseberry	Dried fruits – *Triphala rasayana*, "three fruits" (mucilages, pectins, flavonoids, carotenoids, vitamins)	Antibacterial, wound healing and antioxidant for the treatment of infected wounds.	▪ Full-thickness wounds on the dorsal side of male Wistar albino rats (alcoholic extract and ointment).	[5, 119]
Trigonella foenum-graecum, fenugreek	Seeds (galactomannans, fibers, saponosides, flavonoids, essential oil, proteins, lipids)	Wound healing properties in abscesses, ulcers and burns.	▪ excision, incision and dead space wound models in Wistar rats (aqueous suspension and seeds extract).	[4, 5, 120–122]
Vitis vinifera, common grape vine	Grape seeds extracts (proanthocyanidins, tannins, resveratrol)	Antioxidants, accelerators of dermal wound healing.	▪ Dermal excisional wounds inflicted on the back of mice.	[123]

Complex preparations

In the treatment of burns, good results are obtained using a local dressing with an infusion of equal parts mixed herbs, which speeds up the wound healing process: *Arnicae flos*, *Chamomillae flos*, *Juglandis folium*, *Lavandulae flos*, *Menthae folium*, *Querci cortex* [3, 4].

For the first- and second-degree burns with various expansion areas, but also in accidental injuries and post-surgical wounds, is recommended a complex cicatrizing ointment based on pot marigold, St. John's wort and poplar buds extracts, associated with beeswax, sea buckthorn oil and yarrow or chamomile essential oils. In skin ailments – scratches, bruises, blisters, minor burns, sunburn, insect bites –, simple local applications or diluted compresses with essential oils mixtures (common lavender, rosemary, sage, thyme, eucalyptus, cypress, geranium, Australian tea tree) promotes healthy and quickly regeneration of the epidermis [3, 4].

Moghimi HR *et al.* (2009) shown the increasing of silver sulfadiazine permeation flux through third-degree burn eschar, using topical agents containing four terpenes (limonene, geraniol, 1,8-cineole, and α-pinene oxide) as skin permeation enhancers for antimicrobial therapy of burn wounds [124].

Along with external treatments, modern phytotherapy recommends the internal use, 500 mg three times daily, of standardized extracts from burdock roots associated with devil's claw and *Yucca* sp. [3].

Experimental models of skin burns

Experimental models of skin burns are used for the pharmacodynamic testing of therapeutic agents and for the deciphering of the mechanisms of thermal injury. In which concern the study of the wound-healing process modulation, different experimental models of skin burn were developed. The most used animal species are mice, rats, rabbits and guinea pigs. General anesthesia was induced by intramuscular injection of different doses of ketamine hydrochloride. Most times, skin burns were inflicted on the dorsal region applying, for 5–10 seconds, metal devices with different shapes and weights, heated in water at various temperatures (75–100^{0}C) [125–131]. For example, Kaufman T *et al.* (1990) used a reproducible deep-partial skin-thickness burn model on female albino Hartley-derived guinea pigs, for the study of the wound-healing process (epithelizing, contraction and scar formation). The skin thickness of guinea pig is almost constant when its weight exceeds 450 g. The animals were anesthetized by intramuscular injection of 150 mg/kg ketamine hydrochloride and the burnt wounds were produced on the dorsal skin with cylindrical aluminum templates, heated to 75^{0}C, in a water bath, and applied locally for five seconds. For the confirmation of the depth of the burn wound, India ink injection technique was used [125].

Animals

Our study was performed on four groups of adult male Wistar rats, each of ten animals, weighing between 290 and 330 g. Under standard conditions of light, temperature, food and water (*ad libitum*), the rats were kept in the animal facility of the University of Medicine and Pharmacy of Craiova, both before and after the burns. Ethics Committee of the University approved the experimental protocol according with the European Council Directive 86/609/EEC, the European Convention on the Protection of Vertebrate Animals (2005) and the Government Ordinance 37/2002 [51, 132, 133].

Procedures

In our study, by intramuscular injection of 85 mg/kg ketamine hydrochloride (Ketalar®, Parke-Davis) and 6 mg/kg xylazine hydrochloride (Rompun®, Bayer), general anesthesia was induced then the hair was removed from the higher dorsal region of the rats. On an

area of about 1.5 cm^2, burns were inflicted using a special cone-shaped stainless steel device (350 g weight, 1 cm diameter) equipped with a control thermometer. Heated in boiling water (100^0C), the metallic device was applied locally to each rat for five seconds [51, 132, 133].

Skin burns from the dorsal region of the rats were treated with four creams, applied daily in the form of thin films: cold-creams with 10% *Sambuci flos* (S1) and *Sambuci folium* (S2) soft extracts for the first and second group, respectively; 1% silver sulfadiazine cream (SDA) for the third group (reference); cold-cream base (CCB) for the fourth group (control). Daily, for three weeks, the evolution of the skin burns was monitored. In terms of macroscopic appearance of the lesions, all rats had initially third degree skin burns with epithelial and underneath connective tissue necrosis, until the muscle layer, perilesional edema (approx. 4 mm) and intense erythema [51].

Histological study

Techniques and equipments

At 7, 14 and 21 days, burnt skin was sampled from each group of animals, under general anesthesia, with about 3 mm of perilesional area, in order to dynamically track the evolution of the wound healing process. The burnt skin pieces were fixed immediately after sampling in 10% buffered neutral formalin, for 72 hours, at room temperature, and then embedded in paraffin. On a Microm HM350 rotary microtome, equipped with a waterfall based section transfer system (STS, Microm), 4-μm thick serial sections were cut for the histological study. After Hematoxylin–Eosin (HE) and Masson's trichromic routinely staining, cross-sections were assessed under the light microscope and photographed using a Nikon Eclipse 90i microscope (Apidrag, Romania), equipped with a QImaging Rolera cooled CCD camera. Image ProPlus 7 AMS software (Media Cybernetics Inc., Buckinghamshire, UK) was used to capture and archive the images [51, 132, 133].

Macroscopic assessment

Initially highlighted by white-gray area of coagulation necrosis, the macroscopic appearance of the wound changed during the next days, becoming light brown-blackish with raised edges surrounded by a reddish zone of hyperemia and edema. The evolution of burnt skin wounds was variable, as a result of the application of creams (Figure 1): rats treated with S1 and S2 cold-creams had a good epithelization, for 21 days the wound healing being almost complete; SDA (reference) and CCB (control) groups showed a delay of wound healing, for 21 days the epithelization being incomplete, compared with S1 or S2 groups [51].

Day	S1	S2	SDA	CCB
	Burnt skin wound area (mean±SD) [cm^2] / Wound healing rate [%]			
7	1.25±0.14 / 16.66**	1.34±0.16 / 10.66**	1.42±0.15 / 5.33**	1.45±0.17 / 3.33**
14	0.58±0.08 / 61.33**	0.65±0.09 / 56.66**	0.74±0.09 / 50.66**	0.81±0.11 / 46**
21	0.14±0.02 / 90.66*	0.23±0.04 / 84.66*	0.35±0.03 / 76.66*	0.48±0.05 / 68*

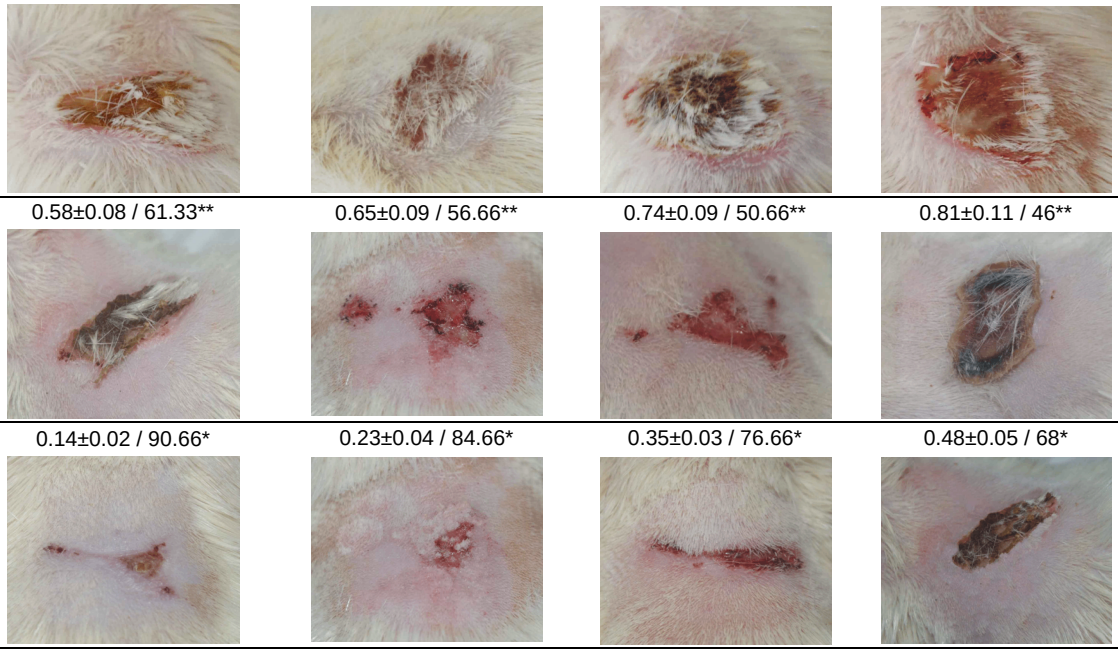

Figure 1 – ***Evolution of burnt skin wounds, after the application of creams: S1 – cold-cream with 10% Sambuci flos soft extract; S2 – cold-cream with 10% Sambuci folium soft extract; SDA – 1% silver sulfadiazine cream (reference group); CCB – cold-cream base (control group); SD – standard deviation; * – p<0.01; ** – p<0.05.***

Microscopic assessment

A thick coagulation necrosis area, composed mainly of deformed collagen fibers, with variable staining capacity, was highlighted at the surface of burnt skin wound, seven days after the injury.

An inflammatory infiltrate band of polymorpho-nuclear neutrophils cleaved the viable area from the collagen fibers. Remnants of degenerated pilosebaceous follicles were also found. The inflammatory reaction was much lower and the post-combustion edema was much reduced for S1 and S2 groups (Figure 2, a and b).

For SDA group, between the necrosis area and the muscular plan, the microscopic lesions are distinguished by vacuoles of edema (Figure 2, c and d). The inflammatory reaction was much stronger for CCB group, compared with S1, S2 or SDA groups (Figure 2, e and f) [51].

After 14 days, at the necrosis zone and into the underlying viable conjunctive tissue, the skin injuries treated with S1 or S2 cold-creams showed a thinned coagulation area of necrosis and many cellular elements of the immune system. The limit between the viable tissue and necrosis area is marked by a thin layer of polymorphonuclear neutrophils and lymphocytes. The angiogenesis rich vascular network can be seen into the depth of the burnt wound (Figure 3, a and b). For SDA group, the vacuoles of edema are visible at the level of the fairly thick coagulation necrosis area and into the underlying conjunctive tissue. The necrosis area and the viable underlying conjunctive tissue are separated by a thick band of polymorphonuclear neutrophils and lymphocytes (Figure 3, c and d). Compared with SDA group, CCB group shows the same coagulation necrosis area but the inflammatory infiltrate was more abundant and extensive. A small number of neoformation vessels was observed comparing with S1 or S2 groups (Figure 3, e and f) [51].

Twenty-one days after burn, for S1 or S2 groups, we can see a relatively well-shuffled granulation tissue and a much-reduced inflammatory infiltrate. A remodeling process outlined for the neoformation blood vessels. The re-epithelization process was well expressed (Figure 4, a and b). At the wound surface, the coagulation necrosis area and an abundant inflammatory infiltrate persist for SDA group. Comparing with S1 or S2 groups, the re-epithelization process of the burnt skin wound was lower (Figure 4, c and d). The coagulation necrosis area and abundant inflammatory infiltrate persist for CCB group; the re-epithelization process was difficult (Figure 4, e and f) [51].

Natural medicinal products locally modulators of the cellular response support the wound-healing process mainly because of their epithelizing, astringent, emollient, demulcent, anti-inflammatory, capillaroprotective, anti-microbial, immunomodulatory and antioxidant properties (flavonoids, tannins, essential oils, mucilages, allantoin, saponosides, anthracene derivatives, lipids, carotenoids, vitamins).

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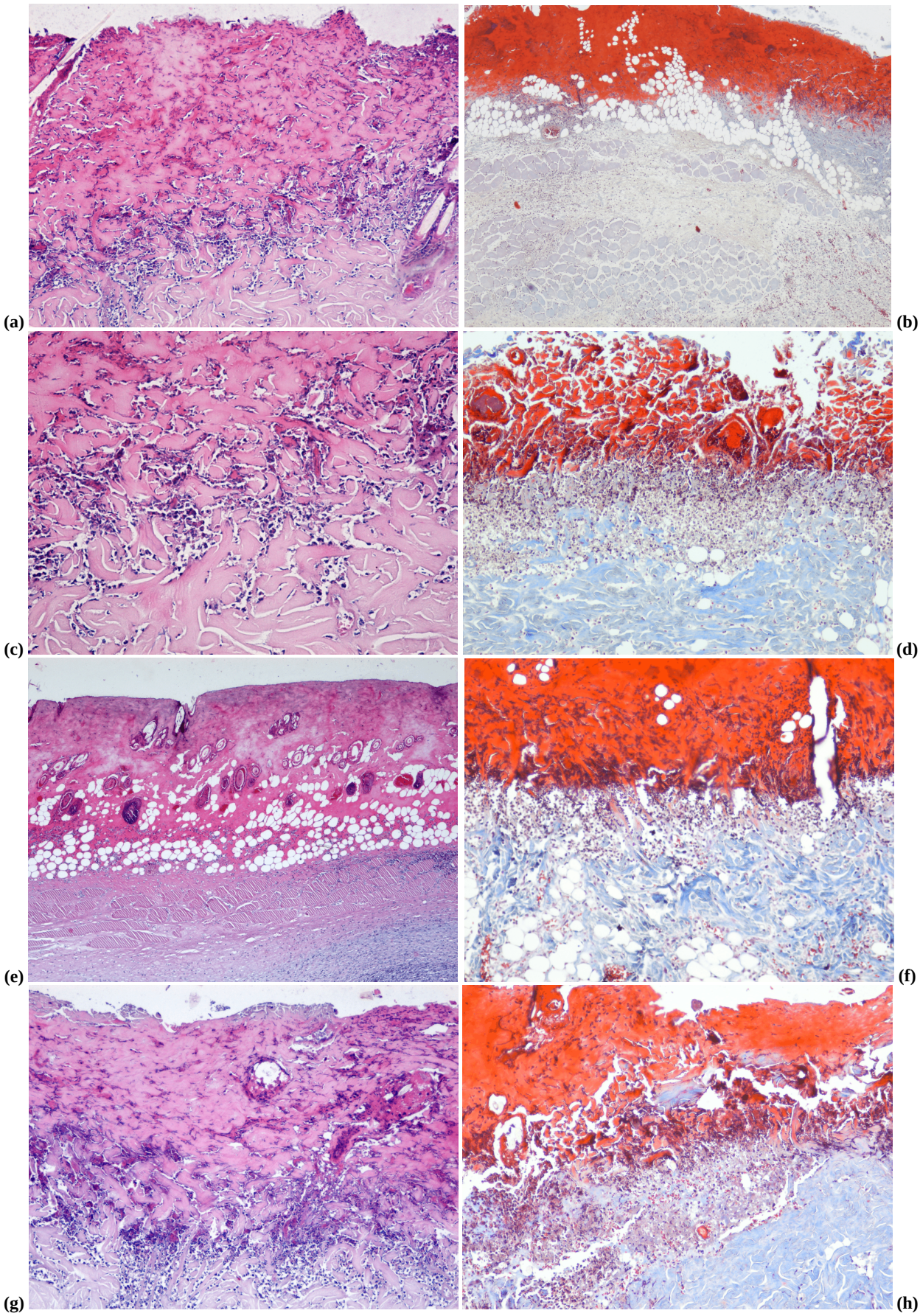

Figure 2 – ***Microscopic evolution of burnt skin wounds, seven days after the application of creams: (a, b) cold-cream with 10% Sambuci flos soft extract (S1); (c, d) cold-cream with 10% Sambuci folium soft extract (S2); (e, f) 1% silver sulfadiazine cream – reference group (SDA); (g, h) cold-cream base – control group (CCB). HE stain: (a), (c) and (g) ×100; (e) ×40. Masson's trichromic stain: (b) ×40; (d), (f) and (h) ×100.***

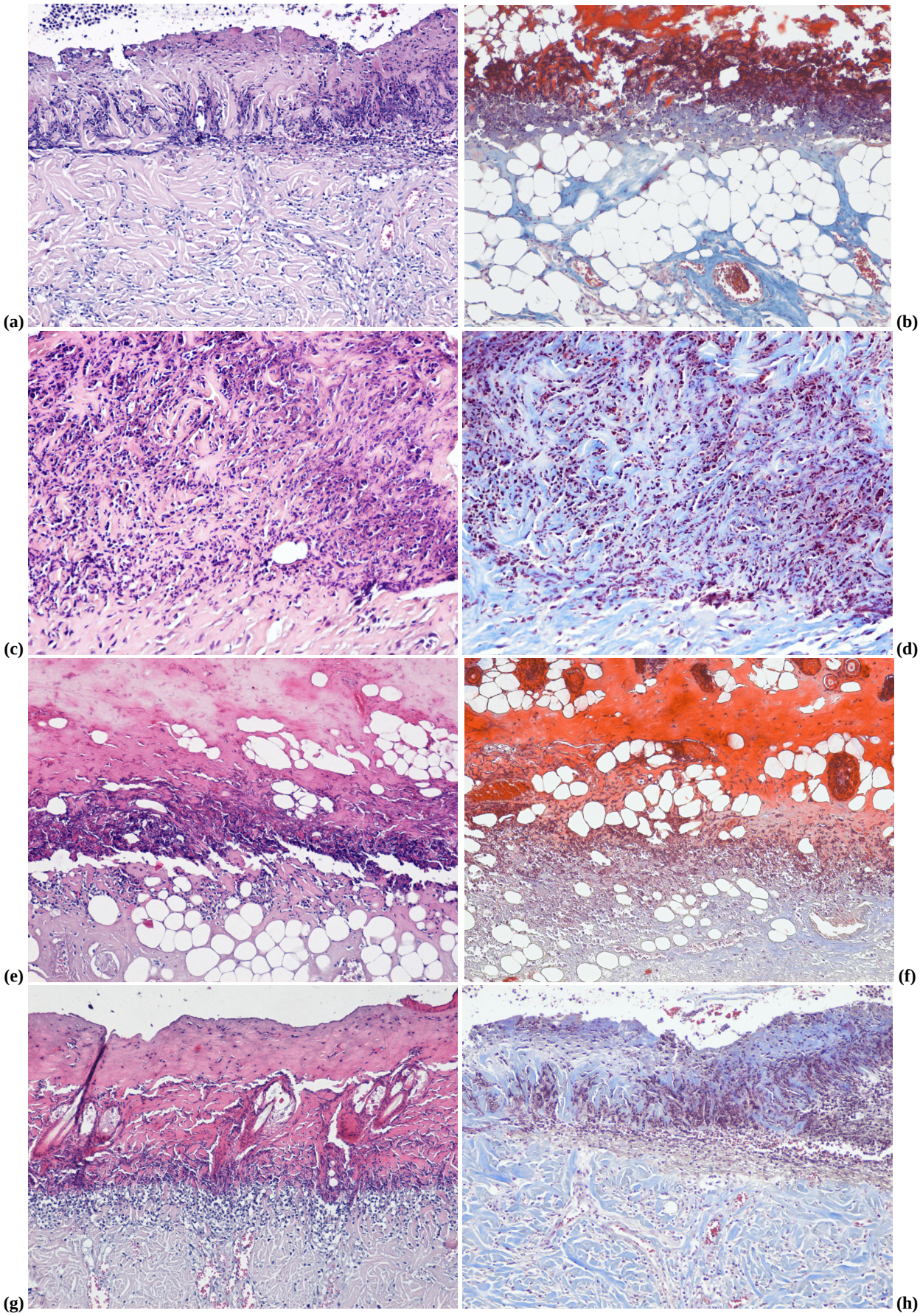

Figure 3 – ***Microscopic evolution of burnt skin wounds, 14 days after the application of creams: (a, b) cold-cream with 10% Sambuci flos soft extract (S1); (c, d) cold-cream with 10% Sambuci folium soft extract (S2); (e, f) 1% silver sulfadiazine cream – reference group (SDA); (g, h) cold-cream base – control group (CCB). HE stain: (a), (e) and (g) ×100; (c) ×200. Masson's trichromic stain: (b), (f) and (h) ×100; (d) ×200.***

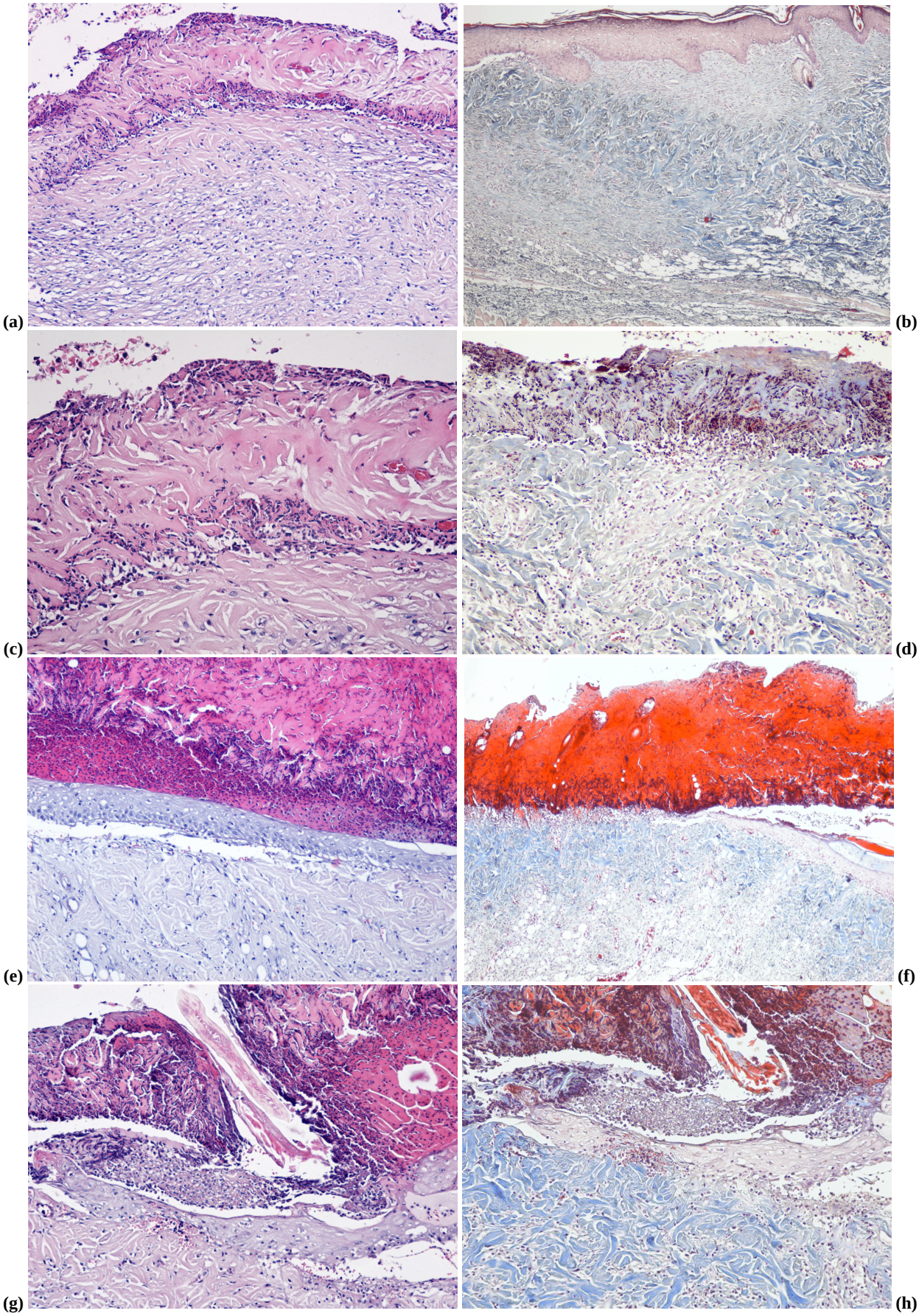

Figure 4 – ***Microscopic evolution of burnt skin wounds, 21 days after the application of creams: (a, b) cold-cream with 10% Sambuci flos soft extract (S1); (c, d) cold-cream with 10% Sambuci folium soft extract (S2); (e, f) 1% silver sulfadiazine cream – reference group (SDA); (g, h) cold-cream base – control group (CCB). HE stain: (a) ×40; (c), (e) and (g) ×100. Masson's trichromic stain: (b) and (f) ×40; (d) and (h) ×100.***

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