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SKIN PHYTOTHERAPY AND PHARMACOLOGICAL ASPECTS: A BRIEF REVIEW

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ABSTRACT

Introduction: Phytotherapy is based on the use of medicinal plants and their plant derivatives for the treatment or symptomatic relief of numerous diseases, being a widely disseminated practice in the world. The skin, as the largest organ in the body, benefits from this therapeutic system in an important way. Thus, this review aimed to prospect the possible mechanisms of action of 12 medicinal plants that have cutaneous applications.
Methods: The Scientific Electronic Library Online (SCIELO), National Library of Medicine (PUBMED) and Google Scholar/ Google Scholar databases were used, where plants were searched by their scientific names (*Aesculus hippocastanum*; *Aloe vera/Aloe vera barbadensis*; *Arnica montana*; *Libidibia férrea/Caesalpinia ferrea*; *Calendula officinalis; Cordia verbenacea/ Cordia curassavica; Equinacea purpurea*; *Equisetum arvense*; *Lippia sidoides Cham./Lippia origanoides kunth; Malva sylvestris*; *Matricaria chamomilla L./Matricaria recutita L.* e *Stryphnodendron adstringens*. **Results:** The mechanisms of action found establish a relationship with the presence of secondary metabolites, such as flavonoids; terpenes, tannins, saponins, coumarins, quinones, acids and phenolic compounds, glycosides, carotenoids, mucilages, polysaccharides, conferring anti-inflammatory, antimicrobial, antiseptic, antioxidant and healing properties. **Conclusion:** The popular use of medicinal plants is aligned with the literature mechanism of action. However, each plant has it own action pathway and active principles, requiring specific studies to understand their molecules and function in other to validate and produce new medicines.

Key words: Herbal medicines; Mechanisms of action; Integumentary system.

INTRODUCTION

The skin is the most extensive organ of the human body. Its structures are responsible for internal and external separation and maintenance along with protection against pathogenic microorganisms, chemical components, physical injuries and radiation, requiring especial care.[4,5] In folk medicine, phytotherapy, a practice encouraged by the World Health Organization (WHO), based on the use of medicinal plants and its derivatives in the treatment, prevention and symptomatic relief of several diseases, plays an important role ensuring tegumentar homeostasis as adjuvant treatment for its anti-inflammatory, antimicrobian, antiseptic and antioxidant properties.[1,5] The active components of these medicinal plants can be isolated and used in pharmacological and toxicological studies to assess its action mechanism ensuring quality and safety for the therapy as well as creation of new drugs.[2,3]

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In this scenario, this paper aims to investigate the possible mechanism present in the literature of the main species used in skin phytotherapy: *Aesculus hippocastanum*; *Aloe vera/ Aloe vera barbadensis*; *Arnica montana*; *Libidibia ferrea/ Caesalpinia ferrea*; *Calendula officinalis; Cordia verbenacea/ Cordia curassavica; Equinacea purpurea*; *Equisetum arvense; L. Lippia sidoides Cham./Lippia origanoides kunth; Malva sylvestris*; *Matricaria chamomilla L./Matricaria recutita L.* e *Stryphnodendron adstringens*, demonstrating its pharmacological relevance and enabling future studies.

METHODS

An integrative review was carried out on articles published between 2006 and 2020. The databases used in this research were the *Scientific Electronic Library Online* (SCIELO), *National Library of Medicine* (PUBMED) and *Google Acadêmico/Google Scholar* under the following descriptors: ["plant OR phytomed* OR extract OR herbal OR medicinal (OR specific name plants)"], filtered for: "human OR clinical trial OR randomized controlled trial OR meta-analysis OR review". The inclusion criteria were: reviews, randomized, comparative and double-blinded studies. The research was not limited for language in the attempt to obtain a significant amount of theoretical reference. Before article's selection, the following steps were used: exploratory reading, selective reading, analytical reading and textual analysis, and finally interpretative reading for subsequent writing. The data was grouped in categories such as scientific and popular plant's name, action mechanisms in the integumentary system and main molecules.

RESULTS AND DISCUSSION

Aesculus hippocastanum

The *Aesculus hippocastanum* (Sapindaceae) has anti-exudative properties that improve venous tone. Its main components are: hydroxycoumarins (aesculin and fraxin), triterpenes, saponins, flavonoids and tannins.[6]

Its seeds contain escin, a triterpene saponin, widely used in the treatment of varicose veins. Recent data demonstrate the anti-inflammatory properties of escin in reducing vascular permeability in inflamed tissues, thus inhibiting edema formation. The ability of escin to prevent hypoxia-induced blockade of normal expression and distribution of the adhesion molecule to platelet endothelial cells-1 may help explain its protective effect on blood vessel permeability.[70]

In an experimental model of formalin-induced peritonitis, Rothkopf et. al. observed a reduction in peritonitis in the presence of escin, with a reduction of proteins in the abdominal cavity. Furthermore, the hypothesis that escin would have a sealing effect on capillaries was tested through the application of bradykinin,investigating possible antagonistic mechanism, identified by increasing the pressure of lymphatic flow to 70%.[71]

In addition, Matsuda et. al.[10] used variations of escins, called Ia, Ib, IIa and IIb, and desacilicin I and II, to investigate inflammatory effects in a murine model. It was found that, *Aesculus* not only were able to inhibit part of the vascular permeability pathway induced by acetic acid in mice, but also escins Ia, Ib, IIa and IIb (50 and 200 mg/kg) were able to inhibit the action of histamine in rats. Escins Ia, Ib, IIa and IIb (200 mg/kg) also inhibited the first phase of carrageenan-induced edema formation. In the experiments with escin Ia (200 mg/kg) and escin Ib, IIa and IIb (50 and 200 mg/kg), the inhibition of pruritus induced by the compound 48/80 in mice was observed, with a lower effect of escin Ia compared to to others.

Aloe vera (Aloe vera barbadensis)

Aloe Vera (Xanthorrhoeaceae) grows in tropical climates around it, presents a mucilage in its leaves with therapeutic indications that include burns and healing action[15] and contains about 200 active compounds, including saponins, anthraquinones, lignin and salicylic acid.[66]

Moriyama et al.[47] demonstrated *in vitro* that skin lesions are repaired more effectively when subjected to treatment with the powder obtained from Aloe vera gel (AVG) and dried leaves (CAE [Cape aloe extract]) by amplifying the potential for migration, epidermal proliferation and differentiation of keratinocytes.[47] In this study, an increase in keratinocyte migration was observed after treatment with 10 µg/mL of AVG and 10 µg/mL of CAE. Furthermore, in this same study, when comparing treated wounds and control wounds for three days, it was observed that only 25% of the wounds closed without any treatment, while those that were treated with AVG and CAE had, respectively, 50% and 75% of wounds closed in the same period. Another point evaluated was the proliferative capacity of AVG and CAE in the keratinocytes studied. The results showed an increase in the expression of the proliferation markers Ki-67 and p63, in addition to an increase in the percentage of cells in S phase of the cell cycle compared to the control group. An increase in the expression of α6-integrin (CD49f), β1-integrin (CD29), β4-integrin (CD104) and E-cadherin (CD324) was also observed on the surface of cells when submitted to the treatment with AVG or CAE. In order to confirm that AVG and CAE promote the differentiation of keratinocytes, it was observed that, only at higher concentrations, the morphology of these cells were altered, and it was also possible to detect an increase in the expression of keratinocyte differentiation markers, such as SPRR2A , SPRR1B and IVL. In addition, an *in vitro* model was found that the epidermis showed a much higher thickness in samples treated with AVG and CAE.[47]

Aloin, a compound present in *Aloe vera*, was evaluated by subjecting Hs68 fibroblasts to acute heat stress.[48] Levels of intracellular ROS were measured through assays of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and lactate dehydrogenase, and of other substances such as MDA, a marker of lipid peroxidation, 8-hydroxy-2'-deoxyguanosine (8-OH-dG), a marker of oxidative DNA damage and oxidative defense molecules such as glutathione (GSH) and the superoxide

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dismutase (SOD) enzymes. Aloin exerted protective effects on the skin, reducing ROS generation, DNA damage, IL-8 production, lipid peroxidation and increasing GSH content and SOD activity.[48] The aloesin obtained from the *Aloe vera* leaf plays an important role in the wound healing process. Wahedi et al.[49] demonstrated that, when treating endothelial cells (HUVECs) with aloesin under immunohistochemical (IHC) analysis and using ELISA, the migration of cells that assist in the tissue repair process increased significantly. The reason for this was the phosphorylation of Cdc42 and Rac1, in addition to having a greater release of cytokines and growth factors in macrophages (RAW264.7), stimulating angiogenesis, collagen deposition, granulation tissue formation and consequently the closure of wounds. It was also observed that cells that underwent treatment with aloesin had the signaling proteins Smad and MAPK activated. Such proteins are essential for angiogenesis, cell migration and tissue development.[49]

Regarding re-epithelialization, *Aloe vera barbadensis* was remarkable when analyzed and compared in a study with a control group. In one study, skin wounds in the back of mice, treated with topical *Aloe vera* gel, showed a proliferative effect in keratinocytes, increasing factors related to the healing process and epidermal formation. These results were associated with the glycoprotein fraction G1G1M1DI2 of *Aloe vera*. This fraction of proteins bound to oligosaccharides increased the expression of the epithelial growth factor (EGF) receptor and, consequently, the DNA synthesis. In addition, in the group treated with *Aloe vera*, an average number of fibroblasts was observed higher than those not treated, because there are IGF-2 receptors on the surface of these cells, and the mannose-6-phosphate component binds to these receptors and induces the proliferating activity of fibroblasts and their differentiation into myofibroblasts or production in large amounts of extracellular matrix proteins, such as collagen. Fibroblast infiltration is also related to the production of transforming growth factor beta-3 (TGF-β) by macrophages, neutrophils and platelets, sensitizing fibroblasts to connective tissue growth factor (CTGF). In view of this, CTGF together with EGF further stimulate the proliferation of fibroblasts. Concomitant to these factors, a greater expression of vascular endothelial growth factor A (VEGF-A) was observed, therefore a greater number of blood vessels, confirming the angiogenic response of β-sitosterol from *aloe*, previously observed in other studies as a result of the recruitment of essential proteins, such as VEGF, von Willebrand factor and laminin, in order to this process to take place.[50]

Several studies have shown improvement in epidermal thickness and collagen deposition with topical application of *Aloe vera* to wounds in animal models, reducing excessive inflammatory cell infiltration.[51,52,53,54] Moreover, prevention of pressure ulcers in the hip, sacrum and heel areas was effective when *Aloe* gel was applied twice daily for ten days in a randomized, triple-blind clinical trial with 80 patients admitted to the orthopedic ward.[55] In a randomized clinical trial with 30 patients admitted to a burn treatment center in Iran, the hydrocolloid, moisturizing and anti-inflammatory effect of *Aloe* gel was evidenced, promoting epithelialization and granulation tissue in superficial second-degree burns.[56] The wound healing after cesarean section using an *Aloe vera* gel was evaluated in a prospective, double-blind, randomized clinical trial conducted in 90 post-cesarean women at Amir-al-Momenin Hospital (Gerash, Iran), dividing them in two groups, and those treated with *Aloe vera* gel showed better healing after eight days of treatment.[57] The rapidity of wound healing in skin graft donors subjected to topical *aloe* gel was demonstrated in a double-blind, randomized, controlled clinical trial. Accelerated healing of the skin graft donor site was significant in those using *Aloe vera* gel.[58]

Arnica montana

Arnica montana (Asteraceae) has been used for centuries for the treatment of various pathological conditions such as bruises, wounds, rheumatism and inflammation. The plant has very significant anti-inflammatory potential, where the molecular mechanism of sesquiterpene lactones differs from non-steroidal anti-inflammatory drugs.[59]

In a study investigating the effect of healing without and with the use of arnica and with the microcurrent added in the use of arnica gel in dorsal region surgical wounds performed in rats, the application of microcurrent of 10 μA for 2 minutes associated with administration of arnica gel produced a healing effect associated with a lower amount of inflammatory infiltrate.[60]

Silva et. al.[61] studied the relationship between arnica and inflammatory reactions caused by UVB radiation. It was shown that, after UVB induction of edema formation in the ear of mice, *Arnica montana* was able to reduce it ($p<0.05$) similarly to treatment with dexamethasone ($p<0.05$; con positive), and was able to partially reduce the inflammatory process ($p < 0.05$).[61]

Libidibia ferrea

The lotion containing the glycolic extract of the fruits from *Libidibia ferrea* (Fabaceae), which is synonymous with *Caesalpinia ferrea*, has antiseptic and healing properties when used topically, as well as anti-inflammatory and analgesic action.[11,12]

Total polysaccharides (TPL), as well as their major polysaccharide fractions (FI, FII and FIII), showed anti-inflammatory and analgesic activity when administered intravenously in Winstar rats weighing 150 to 200 g.[12] These animals were submitted to edema induced by subcutaneous injection of carrageenan or dextran (300 μg), histamine (100 μg), serotonin (20 μg), bradykinin (30 μg), prostaglandin E_2 (30 μg) and L-arginine (15 μg). The edema was measured and monitored by means of a paw plethysmometer 30, 60, 180 and 300 minutes before and after the administration of the aforementioned edematogenic agents, TPL and its major polysaccharide fractions. The administration of TPL at a concentration of 1 mg/mL showed a maximum inhibition of 60%, being able to inhibit 48% in the initial phase (60-180 minutes) and 76% in the final phase (180-300 minutes) of inflammation induced by carrageenan, when compared to the control group, in which the rats were treated with methysergide via intraperitoneal (5 mg/kg),

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indomethacin via subcutaneous injection (5 mg/kg) and with L-NG-methyl-ester-nitroarginine (L- NAME), an inhibitor of the enzyme nitric oxide synthase (NOS), intravenously (30 mg/kg). Among the major fractions of TPL, FIII, at a concentration of 1 mg/mL, showed the highest anti-inflammatory activity, being able to significantly inhibit carrageenan-induced edema between 60 (51%) and 300 minutes (49%), as well as edema induced by prostaglandin E_2 (63%), L-arginine (61%), bradykinin (60%), histamine (65%) and serotonin (62%). Such anti-inflammatory effect seems to be associated with negative modulation of the mentioned pro-inflammatory cytokines (prostaglandin E_2, L-arginine, bradykinin, histamine and serotonin).[12]

The antimicrobial activity of the hydroalcoholic extract of *Libidibia ferrea* was evaluated by microdilution tests and determination of minimum inhibitory concentrations. Thus, the results showed antimicrobial activity against *Streptococcus mutans* and *Streptococcus oralis*, in solutions of 100 µL/mL; 50 µl/ml; 25 µl/ml; 12.5 µL/ml; 6.25 µl/ml; 3.125 µL/mL and 1.5625 µL/mL, although their mechanism of action has not been described in the study.[13]

The healing activity of *Libidibia ferrea* was evaluated in surgical lesions performed by trichotomy, in which the skin and subcutaneous tissue of rabbits anesthetized with ketamine and xylazine were removed.[14] These lesions would be treated with 4 formulations: Jucá pod powder (formula 1); Jucá pod powder with 2:1 granulated sugar (formula 2); the ointment from the powder of the jucá pod in glycerin (formula 3) and the ointment of the powder of the jucá pod with granulated sugar 2:1 in glycerin (formula 4), administered 24 hours after the aforementioned surgical procedure. The healing process was monitored through macroscopic (hyperemia, exudation and crust formation) and histopathological (acute inflammation, non-specific chronic inflammation, fibroblast proliferation, collagenization and wound re-epithelialization) evaluation of the lesions, as well as measurement of the area of the wound 3, 10 and 17 days after surgery with the aid of a caliper. As a result of the study, less exudation was observed in the groups of animals treated with the powders and formation of a protective crust over the entire lesion, forming a physical barrier against tissue dehydration and the entry and proliferation of pathogenic microorganisms and infections, probably due to the presence of tannins, one of the secondary metabolites of *Libidibia ferrea*. In addition, the groups treated with the formulations, mainly with the ointment 1, in view of the macroscopic and histopathological evaluation, had a greater fibroblastic and vascular proliferation (angiogenesis), re-epithelialization and reduction of the lesion area in relation to the control groups. The administration of ointments 1 and 2 also reduced hyperemia, exudation and promoted a greater formation of collagen fibers, which were arranged in the healing tissue in a more organized way.[14]

Calendula officinalis

Calendula (Asteraceae) is used as treatment of the skin and mucous membranes due to its anti-inflammatory, antiseptic and healing properties. Its preparations, such as infusions, extracts, tinctures, gels and ointments, are administered topically and produced from its inflorescences (flowers). The therapeutic properties are associated with the presence of alpha-bisabolol (BISA), triterpenes, flavonoids, carotenoids, saponins, anthocyanins, steroids and phenolic acids in its composition, secondary metabolites of marigold.[15]

According to Preethia et. al.[16], the anti-inflammatory property of marigold can be explained by the inhibition of the expression of the gene encoding cyclooxygenase type 2 (COX-2) and the significant reduction in the levels of pro-inflammatory cytokines: interleukin β (IL-β); interleukin 6 (IL-6); tumor necrosis factor-α (TNF-α); interferon-γ (IFN-γ) and C-reactive protein. In this study, edema, induced by subplantar administration of carrageenan and dextran in BALB/C mice, was monitored and measured before, shortly after and 1 to 6 hours after the administration of *Calendula officinalis* extracts at concentrations of 250 and 500 mg/kg , with the aid of a paw plethysmometer. In addition, for the determination of TNF-α, the groups were treated for 5 consecutive days with extracts of *Calendula officinalis* at concentrations of 100 and 250 mg/kg. The determination of TNF-α was made from its production by macrophages, stimulated by the previous intraperitoneal administration of calcium caesinate (5%) and 250 µg of lipopolysaccharides (LPS) on the fifth day of the experiment. Then, macrophages were extracted from the peritoneal cavity of the animals, 6 hours after LPS administration, plated for 24 hours. After the incubation period, the plated content was centrifuged and 100 µL was added to the L929 cells for 48 hours. Cells were fixed and stained with crystal violet dye for morphological determination. Pro-inflammatory cytokines were measured after intravenous LPS administration in mice, which were previously treated for 6 consecutive days with different concentrations of marigold extract (50, 100 and 250 mg/kg) and with LPS, on the sixth day. of the experiment.COX-2 activity was determined by the guanidinium-thiocyanate method (250 µg) in mice treated for 5 consecutive days with marigold extracts at concentrations of 250 and 500 mg/kg and LPS, on the sixth day of the experiment. In this study, after a period of 3 hours of administration of 250 and 500 mg/kg of dry marigold extract (1.1 g/100 mL) in the groups of mice, there was an inhibition of 50.6 and 65.9%, respectively, the thickness of paws swollen with the use of carrageenan, and 41.9 and 42.4%, respectively, of the edema induced by the administration of dextran. After 3 days of administration of the same extract, also at doses of 250 and 500 mg/kg, there was still a reduction of 32.9 and 62.3% ($p<0.001$), respectively, in the chronic edema of the animals' paws, induced by the administration of formalin.[16]

In the studies by Efstratiou et. al.[17] the antibacterial activity of *Calendula officinalis* was evaluated through the disc diffusion method, with inoculation of discs impregnated with the methanolic extract (EM) and with the ethanolic extract (EE) of marigold petals (300 mg/mL). The antifungal activity was evaluated by the same method, using discs impregnated with the same extract, but at a concentration of 10 mg/mL. The species tested were: *Bacillus subtilis; Pseudomonas aeruginosa; Bacillus cereus; Escherichia coli; ampicillin resistant E. coli; Staphylococcus aureus; Klebsiella aerogenes; Enterococcus faecalis; Bacillus pumilis; Klebsiella*

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pneumoniae; Candida albicans; C. albicans; Candida krusei; Candida glabrata; Candida parapsilosis; Aspergillus flavus; Aspergillus fumigatus; Aspergillus niger and Exophiala dermatitidis. Although its mechanism of action has not been elucidated, both antibacterial and antifungal activity it has been significant inhibition halos in relation to positive controls (ciprofloxacin for bacteria and fluconazole for fungi), from 10 to 22 mm (EM) and from 9 to 28 mm (EE) among the bacteria, from 8 to 12 mm (EM) and from 8 to 14 mm (EE) among the tested pathogenic fungi. The extract obtained from the methanol extraction showed superior antimicrobial activity in most of the bacteria and fungi of clinical importance tested, with the exception of Staphylococcus aureus strain MSSA 25923 and Enterococcus faecalis strain NCTC 775, in which the extract obtained from Ethanol extraction promoted the formation of longer inhibition halos, of 18 (E. faecalis) and 28 mm (S. aureus) versus 14 (E. faecalis) and 18 mm (S. aureus) in the methanolic extract.[17]

The antimicrobial potential, according to Szakiel et. al.[18] from *Calendula officinalis* may be related to the presence of oleanolic acid and flavonoid glycosides in its composition. Such components can alter the peptidoglycan metabolism of bacteria, promote osmotic stress, damage and destroy the plasma membrane of cells, causing the loss of intracellular components important for the survival of microorganisms.[18]

In the tests by Cecília et. al.[19] incorporation of a hydroethanolic extract of calendula (5%) in a hydroxyethylcellulose gel and in a non-ionic cream base was used to evaluate the antioxidant activity of this formulation. The samples were diluted in methanol to obtain solutions at concentrations of 20 mg/mL; 10 mg/ml; 5 mg/ml; 2.5 mg/mL and 1.25 mg/mL, which were mixed with a methanolic solution of 1,1-diphenyl-2-picrylhydrazyl (DPPH) to determine the antioxidant activity of these dilutions by spectrophotometry at 517 nm. Such formulations showed good antioxidant activity, since at concentrations of 10 to 20 mg/mL they were able to reduce more than 50% of DPPH, especially the cream, which showed an Inhibitory Concentration (IC50) of 35.97 mg/mL and 37.42 mg/mL for creams left outside and inside a refrigerator for 90 days, respectively, while the gel presented an IC50 of 30.77 mg/mL and 26.66 mg/mL, when kept under the same thermal conditions as the cream. Differences in antioxidant potential between creams and gels left inside and outside the refrigerator are explained by the degradation of antioxidant molecules, such as phenolic compounds and flavonoids, at high temperatures or even at room temperature, delayed deterioration by storing such formulations in a refrigerator.[19]

In another work, human fibroblasts, obtained from the foreskin of young and healthy donors, were cultured and exposed to the aqueous extract - EA (500 µg/mL) and to the ethanol extract - EE (100 µg/ml) of marigold.[18] There was an increase in the soluble collagen content produced by the cultured fibroblasts and a concentration-dependent inhibition of 45.34% ± 1.96 (EA) and 44.48% ± 3.75 (EE) of the enzymatic activity of the collagenase of Clostridium histolyticum in vitro, which simulates the action of human matrix metalloproteinase in vertebrates, responsible for the degradation of type I collagen fibers. This effect seems to be related to the presence of triterpenes, flavonoids and saponins, phytochemicals that make up marigolds.[20]

Cordia verbenacea

Cordia verbenacea (Boraginaceae) is a plant native to Brazil that has conquered the popular medicine scene through its wide applicability as an alcoholic extract, infusion and decoction for its anti-ulcer, anti-inflammatory, antimicrobial, anti-rheumatic, analgesic and tonic properties.[21] The crude extract of the aerial part is used by the indigenous people against inflammatory processes by topical use. In the phytochemical analysis, monoterpenes, sesquiterpenes, triterpenes, flavonoids and fatty acids were identified in its composition.[22]

The most important components found in *Cordia verbenacea* essential oil are monoterpenes and sesquiterpenes, whose constituents are *α*-pinene, alloaromadendrene and *trans*-caryophyllene. Other constituents include *α*-humulene, *β*-gurjunene, spathulenol, and epoxycaryophyllene.[23] The *α*-humulene blocks the COX-2, an enzyme that is directly related to the production of prostaglandin, acting on inflammatory processes in the body.[21] Tissue and plasma levels of α-humulene, as well as its tissue distribution and cutaneous absorption have been described after topical, oral and intravenous administration in rats. The absorption of this sesquiterpene through the ear is similar to the oral route, occurring quickly and efficiently, as demonstrated by the quantification by gas chromatography coupled with mass spectrometry.[72]

Perini et al.[24] performed a histopathological, immunohistochemical and biochemical study on wound healing using a topical phytomedicine used for the treatment of trauma, tendinopathy and myofascial pain, which is developed from *Cordia verbenacea*, containing 0.5% of its essential oil and 2.5% of α-humulene. In this way, the phytomedicine was evaluated and compared with collagenase and fibrinolysin, using the wound model by skin excision on Wistar rats.[24] In this work, healing was evaluated through skin samples and the result revealed that those who were treated with the phytomedicine showed a more effective response compared to the control group, and it was possible to observe a complete remodeling of the epidermis. In addition, the groups submitted to collagenase ointments and phytomedicine expressed a higher collagen distribution than the others. Under this analysis, the rapid healing of wounds with the use of ointments can be explained by the increase in dermal remodeling and angiogenesis.[24]

Echinacea purpurea

Echinacea purpurea (Asteraceae) is indicated for topical use as an aid in the treatment of small superficial skin lesions. The whole plant has a therapeutic effect.[11] Alkamides, some caffeic acid derivatives, in addition to polysaccharides are the major secondary metabolic compounds found in this species.[25]

Chicca et. al.[67] using extracts from *Echinacea purpurea*

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root, as well as purified N-alkylamides applied to HL60 cells, demonstrated in vitro that ethanolic extracts have a similar action to the endocannabinoid system and it was also possible to observe the release of calcium as a result of the activation of the receptor of calcium by N-alkylamide. This study also included testing the expression of stimulated cytokines in human peripheral lymphocytes (PBMCs) in which a synergism of root and herb tinctures was observed. It was observed that the *Echinacea purpurea* alkylamides (alkylamide 1 - A1 and alkylamide 2 - A2) binds to the CB2 cannabinoid receptor more effectively than endogenous cannabinoids and at low nanomolar concentrations significantly inhibited the expressions of TNF-α, IL-1β and LPS-induced IL-12 and p70 (5–500 nM) in human whole blood.[26]

Oláh et. al.[75], using *Echinacea purpurea* extract in human immortalized HaCaT keratinocytes evaluating through ELISA and statistical analysis, demonstrated in vitro anti-inflammatory *Echinacea purpurea* activity extract in said cells, where significant reductions in mRNA expression induced by poly (I:C), an inflammatory factor, as well as in the release of pro-inflammatory cytokines (IL-6 and IL-8). The study also conducted a clinical trial with 104 Caucasian male and female volunteers aged between 19.9 and 74, 2 years, using *Echinacea purpurea* root extract, prepared with supercritical CO2 extraction, patented and formulated in an emulsion A/O (water in oil), and showed clinically relevant anti-inflammatory effects, with relief of skin symptoms and improvement of the epidermal lipid barrier of patients with atopic eczema.

Equisetum arvense L.

The species *Equisetum arvense L.* (Equisetaceae) has anti-inflammatory, antibacterial and antioxidant potential, being therefore indicated for the treatment of small superficial skin lesions, through the topical use of its extracts, infusions or decoctions, prepared from its leaves, aerial parts or the entire broken plant.[11]

The effects of *Equisetum arvense L.* extract on immune cells was verified using PBMCs, isolated from the blood of healthy adults. The PBMC were treated with extract of *Equisetum arvense L.* at concentrations of 0.05 µg/mL; 0.1 µg/ml; 0.2 µg/ml; 0.4 µg/mL and 0.8 µg/mL were able to inhibit in 95% ± 3.2; 89% ± 6.6; 86% ± 5.1; 78% ± 9.8 and 54% ± 29.8, respectively, the proliferation of $CFSE^{+}$ mitogen-activated lymphocytes in relation to the positive control of cyclosporine A (CsA). This study also revealed that the same extract, at the concentrations previously described, generated a reduction of 95% ± 6.2; 91% ± 6; 86% ± 7.5; 78% ± 8.9; 71% ± 9.7, respectively, in the expression of CD69, T cell-activating cytokines. *Equisetum arvense* extract at concentrations of 0.4 µg/mL and 0.8 µg/mL also produced an inhibition of 70% ± 14 and 55% ± 35, respectively, for IL-2 production, 63% ± 26 and 70% ± 18, respectively, for IFN-γ and 82% ± 22 (0.8 µg/mL) for TNF-α.[27]

The antimicrobial potential of the lyophilized extract of *Equisetum arvense L.* against *Staphylococcus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus* and *Candida albicans* was determined by the disk diffusion method.[28] The extract showed significant antibacterial activity, observed through the diameter of the inhibition halos formed in the clinical isolate of *Streptococcus pyogenes* (9 mm) and *Streptococcus pneumoniae* (11 mm), however, it did not show antifungal activity against *Candida albicans* (6 mm) and antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* (6 mm). In addition, the five dilutions (100 mg/mL, 50 mg/mL, 25 mg/mL, 12.5 mg/mL and 6.25 mg/mL), prepared from horsetail extract (200 mg/mL) enabled the evaluation of the antimicrobial potential of the extract against *Staphylococcus aureus* and the clinical isolate of *Staphylococcus aureus*, in which the last dilution with bacterial growth was 25 mg/mL and 12.5 mg/mL for *Streptococcus pneumoniae*, *Streptococcus pyogenes* , Group A *Streptococcus pyogenes* and Group G beta-hemolytics *Streptococcus*. Tubes containing Columbia agar and sheep blood showed positive results at concentrations of 25 mg/mL for *Stapylococcus* and 12.5 mg/mL for *Streptococcus*, concentrations that represent their Minimum Inhibitory Concentration (MIC). On the other hand, tubes containing the same lyophilized extract at a concentration of 50 mg/mL for *Stapylococcus* and 25 mg/mL for *Streptococcus* had a negative result, representing their Minimum Bactericidal Concentration (MBC).[28]

The antioxidant activity of *Equisetum arvense L.* extract appears to be associated with the total phenolic content and phenolic compounds of each extract, which were identified, separated and quantified by high performance liquid chromatography.[29] The main phenolic compounds found, quantified and expressed in mg/g of dry extract (DE) through this technique were isoquercitrin (152 mg/g DE); apigenin 5-O-glycoside (22.4 mg/g DE) and kaempferol 3-O-glycoside (26.2 mg/g DE) in acetic extract, isoquercitrin (382 mg/g DE) and di-E-caffeoyl-meso-tartaric acid (100 mg/g DE) in butanolic extract, di-E-caffeoyl-meso-tartaric (10 mg/g DE) and two different phenolic acids (phenolic acid 1:6 mg/g DE and phenolic acid 2:3 mg/g DE) in the aqueous extract. Such phenolic compounds had their antioxidant potential determined from the capacity of the antioxidant components of the aqueous, acetic and butanolic extracts of *Equisetum arvense L.* to reduce lipid peroxidation and the DPPH and NO free radicals. The extracts that showed the highest and lowest reducing power in terms of DPPH-reducing capacity (DPPH-RSC), NO-reducing capacity (NO-RSC) and lipid peroxidation (LP), respectively, were the acetic extract (EC_{50}= 2.37 µg/mL - DPPH-RSC, EC_{50}= 90.07 µg/mL - NO-RSC and EC_{50}= 14.50 µg/mL - LP) and the aqueous extract (EC_{50}= 37.20 µg/mL - DPPH-RSC, EC_{50} > 333.33 µg/mL - NO-RSC and EC_{50} = 192.31 µg/mL - LP).[29.]

Lippia sidoides Cham.

Lippia sidoides Cham. (Verbenaceae) flowers, leaf infusions and aerial parts are used as a topical lotion to treat respiratory diseases such as bronchitis, asthma and flu, but also gastrointestinal disorders such as stomach pain, indigestion and nausea, as well as serving as an anti-inflammatory mouthwash for throat and skin wounds.[65]

Analysis of the essential oil of *Lippia sidoides Cham*. reveals thymol as the major compound, with a content of approximately 85%, in addition to 5.33% of p-cymene. Aiming to demonstrate the properties of these substances, they applied topically the essential oil on the ear edema induced with arachidonic acid (45.1% and 47.4%) and with phenol (33.2% and 54.7%) and obtained a significant reduction. On the other hand, when applied for a time longer than 24 hours, it was shown that the use of *Lippia sidoides* essential oil (LSEO) and thymol cause a pro-inflammatory effect. In this study, they did not identify statistical differences in the anti-edematogenic activity between LSEO and thymol, for this reason, it is concluded that the topical anti-inflammatory activity of LSEO is due to its constituent thymol, however, when used chronically, it has an inflammatory effect.[73]

Malva sylvestris

Malva sylvestris (Malvaceae) exhibits therapeutic properties, which are generally attributed to leaves and flowers, due to the presence of flavonoids and mucilages.[31] Its topical use is recommended for bruises and the treatment of inflammatory processes in the mouth and throat.[32] Its biological activity is associated with the control of inflammatory processes, as it acts on prostaglandins and a variety of cytokines such as IL-1β, IL-6, IL-8 and granulocyte-macrophage colony-stimulating factor (GM-CSF).[33]

In the studies by Martins et al.[34] the anti-inflammatory effects of the alcoholic extract of *Malva sylvestris* were evaluated by measuring the pro-inflammatory mediators prostaglandin E_2 (PGE_2) and prostaglandin D_2 (PGD_2) in U937 cells stimulated by desferoxamine. Concentrations of 10 µg/mL and 50 µg/mL of the extract significantly reduced the levels of PGE_2 and PGD_2, suggesting anti-inflammatory activity. Martins et al.[35] demonstrated inhibition of prostanoids with extracts from the leaves and flowers of *Malva sylvestris* and inhibition of $PGF_{2\alpha}$ and TXB_2 by the hexane fraction of the leaf extract, while PGE2, PGD2 and TXB2 were reduced in the presence of the crude extract of leaf at a concentration of 50 µg/mL.[35]

Another study on the anti-inflammatory activity of *Malva sylvestris* used a murine model of inflammation induced by 12-O-tetradecanoylphorbol-acetate to evaluate the topical action of the hydroalcoholic extract (HE) of *Malva sylvestris*. The results showed a reduction in edema and leukocyte migration, probably due to the action of the compound malvidin 3-glycoside.[36] Pirbalouti et al.[37] observed better healing of wounds generated by burns in diabetic rats, after topical application of extract of *Malva sylvestris* flowers. Bariknin et al.[38] performed a randomized clinical trial with 50 patients with hand eczema divided into groups A and B. Group A was treated topically with malva ointment (4%) and group B received a placebo (ointment of eucerine) for 6 weeks. Results showed that malva treatment improved all measured scores (erythema, edema, excoriation, liquification, aridity, pruritus, discharge) when compared to the placebo group. In addition, no adverse effects were detected in any of the groups evaluated 3 and 6 weeks after the start of treatment.

Matricaria chamomilla L.

Matricaria chamomilla L. (Asteraceae) has in its chemical composition flavonoids (apigenin and luteolin), coumarins (umbelliferone), alpha-bisabolol (BISA), alpha-chamazulene, farnesene and spiroethers, which confer anti-inflammatory, antimicrobial and antioxidant activity.[11,15] The anti-inflammatory activity of chamomile was analyzed by macrophage culture, where cells were pre-treated with LPS and exposed to different concentrations of apigenin-7-glucoside (APG) (3 µg/mL, 30 µg/mL and 300 µg/ml). As a result, it was observed that APG promoted a significant and dose-dependent reduction in the production of TNF in macrophages stimulated by LPS. Cultures exposed to APG at concentrations of 30 and 300 µg/mL were able to reduce by approximately 50% and 100%, respectively, the production of TNF by macrophages, when compared to cultures exposed only to LPS and to LPS and APG at their lowest concentration (3 µg/mL).[39] Alpha-bisabolol (BISA), present in chamomile essential oil, was evaluated in an *in vitro* study with RAW264.7 macrophages exposed to BISA and subsequently to LPS.[38] As a result, there was a reduction in the synthesis of prostaglandins E and nitric oxide, as well as inhibition of activation of activator protein-1 (AP-1), nuclear factor kappa B (NF-kB) and phosphorylation of activated kinases. by mitogens (MAPs): p38, kinases regulated by extracellular signals (ERK) and inhibitors of LPS-induced NF-kB (Ik-Ba).[40]

The study of a nanoemulsion containing 100 mg/mL of chamomile essential oil, demonstrated activity against *Escherichia coli*; *Pseudomonas aeruginosa*; *Bacillus subtilis*; *Staphylococcus aureus*; *Streptococcus pyogenes*; *Schizosaccharomyces pombe*; *Candida albicans* and *Candida tropicalis* at MIC90 of 2.19 µg/mL; 1.02 µg/ml; 1.13 µg/ml; 1.06 µg/ml; 2.45 µg/ml; 1.28 µg/ml; 2.65 µg/mL and 1.69 µg/mL, respectively, when compared to nanoemulsion with Tween 80 as a stabilizing agent.[41] Although camomile antimicrobial mechanism is not elucidated yet, it seems to be associated with the generation of free radicals and destabilization of the membrane of microorganisms.[41] Al-Dabbagh and colleagues conducted a study associating the antioxidant activity of chamomile with the presence of polyphenols and flavonoids.[40] The phenolic content found in the dry extract of chamomile was 21.4 ± 0.327 mg GAE/g, while the amount of flavonoids present in the chamomile extract (600 µg/mL) was 157.9 ± 2.22 mg QE/g . The antioxidant activity of chamomile, determined by the DPPH method, showed an EC50 of 26.7 µg/mL and the antioxidant activity found was 94.8% ± 0.03 and 84.2% ± 0.86 in the chamomile extracts at concentrations of 1.5 mg/mL and 0.15 mg/mL, respectively.[42]

Stryphnodendron adstringens

Stryphnodendron adstringens, (Fabaceae), traditional from the Brazilian Cerrado region[68] is used to treat diarrhea, gynecological problems and wound healing.[43] Furthermore, the antimicrobial, anti-inflammatory, anti-ulcerogenic and wound healing properties of the bark extract have already been reported in the literature. These effects are attributed to tannins, its main components, found

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in the bark and leaves of this tree, which has fungicidal activity against *Candida albicans, Candida spp*., *Trichophyton rubrum* and *Cryptococcus neoformans*.[69]

Giffoni de Carvalho et al.[44] verified the properties of the hydroethanolic extract *Stryphnodendron adstringens* (HESA) on M2 macrophages and the inhibitory potential of costimulatory molecules in M1 macrophages of C57BL/6 mouse. The results indicated modulatory and suppressive properties, as well as nitric oxide, iNOS, IL-6, TLR2, CD206, CCR7, CD86, MHC class II were reduced. An increase in CD206 and IL-10 was also observed. In addition, the presence of proanthocyanidins, flavan-3-ols and chromones in HESA was verified.

Hernandes et al.[45] observed a trophic effect of *Stryphnodendron adstringens* on keratinocytes, resulting in a healing effect from the application of an ointment containing 1% of the ethyl acetate fraction in Wistar rats submitted to lesions. Pinto et al.[46] studied the healing action of *Stryphnodendron adstringens* extract in diabetic Wistar rats. Proliferative stimulation of keratinocytes and cell migration were observed at the beginning of the treatment. Another observation was the replacement of type III collagen fibers by type I fibers. The photoacoustic spectroscopy technique showed that the gel containing 1% of crude extract permeated from the skin into the dermis, and after the seventh day of treatment, stimulation of endothelial growth factor was observed.

Table I - Medicinal plants and secondary metabolites with biological activity.

Species	Extracted region	Active Principle	Activity
Aesculus hippocastanum (Indian nut)	Seeds and leaves	Hydroxycoumarins, triterpenes, saponins, flavonoids and tannins.	Anti-exudative, vasoprotective and anti-inflammatory[8, 9, 70 ,10]
Aloe vera barbadensis (Aloe Vera; Babosa)	Mucilage	Aloesin, aloin and emodin	Anti-inflammatory, cicatrization and angiogenic[48, 49].
Arnica Montana (Arnica)	Flower	Flavonoids, inulin, carotenoids and tannins	Anti-inflammatory, cicatrization, antioxidant, antiseptic and antimicrobial[59, 61]
Caesalpinia ferrea/ Libidibia ferrea (Jucá; Pau-ferro)	Fruits	Tannins and Polysaccharides	Anti-inflammatory, cicatrization, antioxidant, antiseptic, analgesic and antimicrobial[12, 14, 13]
Calendula officinalis (Calendula/Marigold)	Flower	Flavonoids, glycosides, triterpenes, saponins, phenolic acids and oleanolic acid	Anti-inflammatory, antioxidant, cicatrization, antimicrobial and antiseptic [16, 17,18, 19, 20].
Cordia verbenacea / Cordia curassavica (Erva-baleeira/Whaling herb)	Leaves	Artemetin, alpha-humulene and trans-caryophyllene.	Anti-inflammatory, edematogenic and angiogenic[21]
Echinacea purpurea	The whole plant	Alkalides, caffeic acid and polysaccharides.	Anti-inflammatory[67]
Equisetum arvense L.	The whole plant	Phenolic acids; isoquercitrin; apigenin; kaempferol and E-caffeoyl-meso-tartaric acid	Anti-inflammatory, antioxidant, antimicrobial and antiseptic[27, 28, 29]
Lippia sidoides Cham./ Lippia origanoides kunth	Flowers and leaves	Flavonoids, hydrochalcones, naphthoquinones and monoterpenes	Anti-inflammatory, analgesic, hepatoprotective and antioxidant[65, 73, 74]
Malva sylvestris	Flowers and leaves	Flavonoids, mucilages and malvidin 3-glucoside	Anti-inflammatory and cicatrization[34]

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Matricaria chamomilla L./Matricaria recutita L. (Camomila)	Flowers	Apigenin, alpha-bisabolol and polyphenols	Anti-inflammatory, antioxidant, antimicrobial and antiseptic[39, 40, 41, 41].
Stryphnodendron adstringens (Barbatimão)	Peel	proanthocyanidins	Anti-inflammatory and cicatrization[43, 44, 45, 46]

CONCLUSION

Medicinal plants and herbal medicines for topical use with action on the integumentary system, described in *Memento Fitoterapico* and in the *Formulário de Fitoterápicos da Farmacopéia Brasileira* are in line with their popular use and the mechanisms of action described in the literature, where most of them have anti-inflammatory activity, antimicrobial, antiseptic, antioxidant and healing. However, each plant species has its specificities, acting in a unique way, highlighting the need for further studies and research in order to validate, promote and deepen the knowledge about the described plant species and their respective mechanisms of action, allowing a greater understanding of its therapeutic effects, improvement and development of new drugs.

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