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Anti-Inflammatory and Regenerative Properties of Herbal Extracts: Wound Management in Equine Models

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ABSTRACT

Introduction: Wound management presents significant challenges, requiring effective treatments. Herbal extracts have been traditionally used to support healing due to their anti-inflammatory, antimicrobial, and cell-regenerative properties.

Methods: This study aimed to evaluate the therapeutic efficacy of Pau D'Arco (*Tabebuia*), Yarrow (*Achillea millefolium*), Gotu Kola (*Centella asiatica*), Figwort (*Scrophularia nodosa*), and Broadleaf (*Plantago major*) extracts, both individually and combined, on wound healing *in vitro* and *in vivo* in equine models. *In vitro* tests using human macrophages and keratinocyte cell lines to assess cellular responses such as cytokine secretion and phagocytic activity under simulated inflammatory conditions. Additionally, pilot case studies on equines with open wounds provided practical insights into the extracts' healing capabilities.

Results: MTT assay was used to assess cytotoxicity. The extracts did not significantly affect the viability of HaCaT or THP-1 cells. The herbal extracts reduced IL-8 levels and increased phagocytic activity in macrophages, indicating an ability to modulate inflammatory responses. *In vivo*, the extracts were well tolerated and associated with supported healing in equines. These effects were suggested to be attributed to the synergistic actions of the herbal components.

Conclusion: These findings suggest that the herbal extracts may be useful for supporting wound healing. Their natural anti-inflammatory and healing properties could provide an additional option alongside traditional wound management approaches.

Keywords: Anti-inflammatory agents, Herbal extracts, Natural compounds, Synergistic effects, Tissue regeneration, Wound healing

Introduction

Wound healing stands as a critical challenge in both human and veterinary medicine, underscoring the pressing demand for novel agents with potent wound-healing capabilities (1). As the largest organ of the body, the skin provides a barrier against infections, minimizes water loss, and it is also among the most frequently injured organs. In response to damage, the skin undergoes repair mechanisms aimed at restoring its integrity and functions. Skin wounds are classified as acute or chronic, based on their development and outcomes (2). Chronic wounds, in particular, present substantial challenges to healthcare, contributing to patient suffering and increased mortality rates (3,4).

During wound healing, the immune system activates processes to restore tissue structure, progressing through four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Hemostasis rapidly interrupts bleeding (5), followed by an immune-driven inflammatory response where platelets start the coagulation cascade and attract neutrophils and macrophages by releasing growth factors (2,6).

Macrophages play an important role in wound healing, initially adopting a pro-inflammatory (M1) phenotype characterized by antigen presentation, phagocytosis of debris, and the secretion of cytokines and growth factors. As healing advances, they transition to an anti-inflammatory (M2) phenotype, highlighting their role in the later remodeling phase. Disruptions in macrophage function can lead to improper healing, resulting in chronic wounds or excessive scarring.

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Understanding macrophages' precise contributions and phenotypic variations in wound repair is essential for developing targeted therapies for wound healing disorders (7).

Subsequently, in the proliferative phase, tissue is rebuilt through granulation, new blood vessel formation, and skin surface repair (3,4). Finally, in the remodeling phase, scar tissue forms and immune cells are cleared from the epidermis through apoptosis or reintegration into the dermis, completing the healing process (3,8).

Wound management in veterinary practice requires an understanding of the healing process and the range of products available to support it. The field is growing quickly, with new products often based on research from human medicine, where conditions such as pressure sores and diabetic ulcers are widely studied (9).

Historically, various botanicals have been used to support the healing process due to their anti-inflammatory, antimicrobial, and cell-regenerative properties. Notably, plants such as Pau d'Arco (*Tabebuia*), yarrow (*Achillea millefolium*), gotu kola (*Centella asiatica*), figwort (*Scrophularia nodosa*), and broadleaf (*Plantago major*) have been documented for their efficacy in traditional healing practices across different cultures. These plants contain active compounds that have been demonstrated to affect cellular activities critical to wound repair, such as inflammation modulation and new tissue formation (10-12).

Pau d'arco, also known as red lapacho or taheebo bark, is derived from the inner bark of the *Tabebuia impetiginosa* and *Tabebuia avellanedae* (TA) trees. These trees belong to the Bignoniaceae family and are native to Central and South America. The inner bark of these trees has been used for medicinal purposes for thousands of years, with indications that may pre-date the Incas. It has been known to be used against diseases like cancer, syphilis, malaria, fevers, trypanosomiasis, fungal infections, bacterial infections, and stomach disorders. Pau d'arco is highly valued for its immune-strengthening properties (11,13,14).

Achillea millefolium, commonly known as yarrow, is an herbaceous plant originally from Greece and a member of the Asteraceae family. It is one of the oldest botanicals known to be used in traditional medicine across various cultures and traditionally used to treat a range of conditions, including spasmodic gastrointestinal and hepatobiliary disorders, gynecological issues, inflammation, and wounds. Additionally, yarrow is known for its effectiveness in treating respiratory ailments such as pneumonia, the common cold, and coughs (10,15,16).

Centella asiatica, known as gotu kola, referred to as *Centella asiatica* (L.) Urb., is an herb used in traditional Chinese and Southeast Asian medicine to address various ailments. Extensive research, including animal and cellular studies, has been conducted on gotu kola and its bioactive compounds. The plant is known for containing several pentacyclic triterpenoids, such as asiaticoside, brahmoside, and madecassic acid, in addition to other components like centellose, centelloside, and madecassoside (12). The extract of *C. asiatica* and its triterpenoid components have been found to have therapeutic benefits and provide relief for conditions such as acne, baldness, vitiligo, atopic dermatitis, and wounds, promoting tissue regeneration (17–20).

Scrophularia nodosa, commonly known as figwort, is a native medicinal plant found in moist and cultivated waste areas. It contains various compounds, including saponins, cardioactive glycosides, flavonoids, resin, sugars, and organic acids. Traditionally, figwort is used for its anti-inflammatory effects and to treat skin disorders. Additionally, it possesses diuretic and cardiac stimulant properties (21).

Plantago major, a perennial herb from the Plantaginaceae family and genus Plantago, is commonly referred to as common broadleaf. It's known to be used especially in Europe, America, and Asia. In addition, Plantago major grows wildly and has been used since ancient times in most parts of Iran. This herb contains several active compounds such as flavonoids, polysaccharides, terpenoids, lipids, iridoid glycosides, and caffeic acid derivates, and is used in traditional medicine for its anti-inflammatory properties and for the treatment of ulcers, diabetes, diarrhea, inflammation, and viral infections (22,23).

For this purpose, this study aims to evaluate the therapeutic potential of extracts from these plants in promoting wound healing. The efficacy of five herbal extracts was investigated - Pau d'Arco (*Tabebuia*), yarrow (*Achillea millefolium*), gotu kola (*Centella asiatica*), figwort (*Scrophularia nodosa*), and broadleaf (*Plantago major*) - both individually and in combination, in models of wound irritation *in vitro* and their potential effects *in vivo* on wound closure on equine wound sites.

Methods

Sample sourcing and preparation

The five herb samples (0.1 g each) were mixed with 1 mL of a 60:40 acetonitrile: methanol (ACN:MeOH) solution and vortexed for 1 minute. Batch samples (0.1 g each) were mixed with 0.2 mL of the same ACN:MeOH solvent mixture and vortexed for 1 minute. Subsequently, all samples were sonicated for 10 minutes and incubated overnight at 37°C to facilitate the extraction of bioactive compounds. After incubation, the samples were dried by evaporation. Subsequently, the samples were weighed and then reconstituted in dimethyl sulfoxide (DMSO) to ensure the solubility of each compound. Since DMSO is toxic at high concentrations, it needed to be diluted 100-fold, resulting in a final concentration of 30 µg/mL on the cells from the initial 3000 µg/mL extract. The combination mixture was formulated through a patented technique that incorporates petroleum jelly, enabling the efficient release of bioactive compounds into the petroleum for *in vivo* applications.

Tissue cell conditions

HaCaT cells, a keratinocyte cell line at passage 90, and THP-1 monocyte cells at passage 14 were originally obtained from the American Type Culture Collection (ATCC). HaCaT cells were cultured in DMEM supplemented with 10% fetal calf serum, 1% penicillin G (100 U/mL), and streptomycin (100 µg/mL) solution, maintained at 37°C in a 5% CO_2 environment. THP-1 cells were cultured in RPMI, supplemented

similarly, and maintained under the same conditions. To induce differentiation into macrophages, THP-1 monocyte cells were treated with phorbol 12-myristate 13-acetate (PMA) at a concentration of 25 nM for 48 hours.

Cell irritation and treatment

Injury assays were performed using LPS at 100 ng/mL. For the injury assays, THP-1 PMA-differentiated macrophage cells were seeded at a density of 4×10^5 cells per well in 96-well plates. After 24 hours, they were subjected to LPS in RPMI supplemented with 1% penicillin/streptomycin. Similarly, HaCaT cells were seeded at a density of 4×10^5 cells per well in 96-well plates. After 24 hours, these cells were exposed to LPS (100 ng/mL) in RPMI supplemented with 1% penicillin/streptomycin. Following 3 hours of exposure, the cells were washed three times with PBS and subsequently treated with 30 µg/mL of extracts in their respective cell culture media for an additional 24 hours before analysis (24).

Cytotoxicity assessment

Cytotoxicity was assessed by MTT assay following a 24 hour treatment with various drug concentrations. The culture medium was removed, and cells were exposed to 10% MTT in RPMI for 4 hours at 37°C in a humidified incubator with 5% CO_2. After the incubation, both the MTT solution and culture medium were aspirated, and the formazan product was dissolved by adding 100 µL of DMSO per well. The dissolved product was quantitatively assessed at 540 nm. The results were expressed as percentage viability relative to the vehicle control (25).

ELISA analysis of secreted soluble mediators (IL-8 and IL-10)

A Ready-SET-Go human ELISA kit (Thermo Fisher) was used to measure the levels of interleukin-8 (IL-8) and interleukin-10 (IL-10) in the medium after injury and treatment. All ELISA assays were performed according to the manufacturer's instructions, and the results were expressed in pg/mL. Dexamethasone (30 µg/mL) (Thermo Fisher) was used as a control in the inflammation assay following LPS induction due to its well-established role as a potent anti-inflammatory agent. As a corticosteroid, it has been widely used to treat various inflammatory conditions and immune-mediated diseases. Its inclusion as a positive control allowed for a comparison of the inflammatory effects of the test compounds against a reliable standard drug (26-28).

Phagocytic assessment of THP-1 (monocytes) cells

Macrophage phagocytic activity was evaluated using the Vybrant Phagocytosis Assay Kit (Thermo Fisher) following the manufacturer's instructions. After the cells were cultured as described previously, they were exposed to LPS (100 ng/mL) for 4 hours. Subsequently, the culture medium was replaced, and the cells were treated with various batch products or herbs for 12 hours. Following this treatment, the culture medium was removed, and fluorescein-labelled Escherichia coli bioparticles were introduced. After a 120-minute incubation, the supernatant was extracted, and 100 µL of trypan blue was added to each well for 1 minute to halt extracellular fluorescence. Excess trypan blue dye was removed by aspiration, and the plate was analyzed using a microplate reader with excitation at 480 nm and emission at 520 nm. The results were expressed as the percentage of phagocytosis relative to the untreated cells.

In vivo application

Pilot studies on the treatment of equine injuries were conducted by veterinary practitioners on horses that presented to the clinic with open wounds and were adapted to each individual case as required, since the cases involved different wound severities and conditions. The case studies are described in detail in the results section. The wound healing progression was visually monitored, and photographs were taken to document the process.

Statistical analysis

Data are presented as mean ± SEM (n = 4). Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparisons test. Differences were considered significant at $p < 0.05$.

Results

Cytotoxicity assessment

The MTT assay was used to determine whether the extracts, either alone or in combination, influenced cell viability and subsequently affected cellular responses. Individually, the extracts had no significant impact on cell viability on either cell type as seen in Figure 1, panel A (HaCaT) and THP-1 (Fig. 1, panel B). They were tested alone and combined in petroleum, where the bars represent the mean ± standard error of the mean of the different tested compounds.

ELISA analysis of secreted soluble mediators (IL-8 and IL-10)

To evaluate the effects of the extracts on keratinocytes, HaCaT cells were treated with each extract alone and in combination, followed by quantification via ELISA of cytokine secretion quantification. Under uninjured conditions (Fig. 2, panel A), the herbal combination increased IL-8 expression compared to PBS, figwort, and broadleaf alone. Following LPS-induced injury (Fig. 2, panel B), IL-8 levels were significantly reduced, suggesting an anti-inflammatory response from both the individual and combined herbal extracts. The levels of IL-10, an anti-inflammatory mediator, were significantly higher when the cells were treated with yarrow and figwort (Fig. 2, panel C).

Similarly, to assess the impact on macrophages, THP-1 cells were treated with the extracts, and cytokine secretion levels were evaluated using ELISA. To simulate injury or inflammation like a wound environment, macrophages were stimulated with LPS. All herbs, whether used alone or combined, significantly reduced the levels of IL-8 (Fig. 2, panel D), demonstrating an anti-inflammatory response comparable to the control, dexamethasone.

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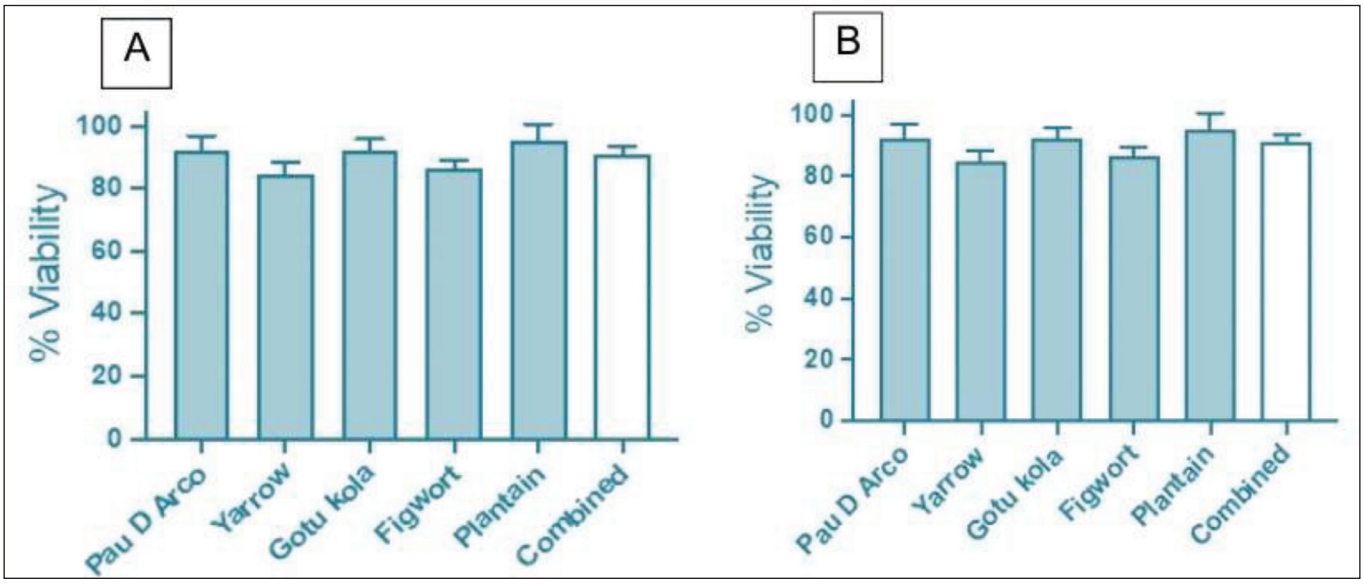


FIGURE 1 - Effect of individual and combined herbal extracts on the viability of HaCaT keratinocytes (A) and PMA-differentiated THP-1 macrophages (B) after 24 hours of treatment. THP-1 monocyte cells were differentiated using 25 nM phorbol 12-myristate 13-acetate (PMA) for 48 hours prior to treatment. No significant effect on cell viability was observed. Results are expressed as percentage viability relative to the untreated control set at 100%, shown as mean ± standard error of the mean (SEM).

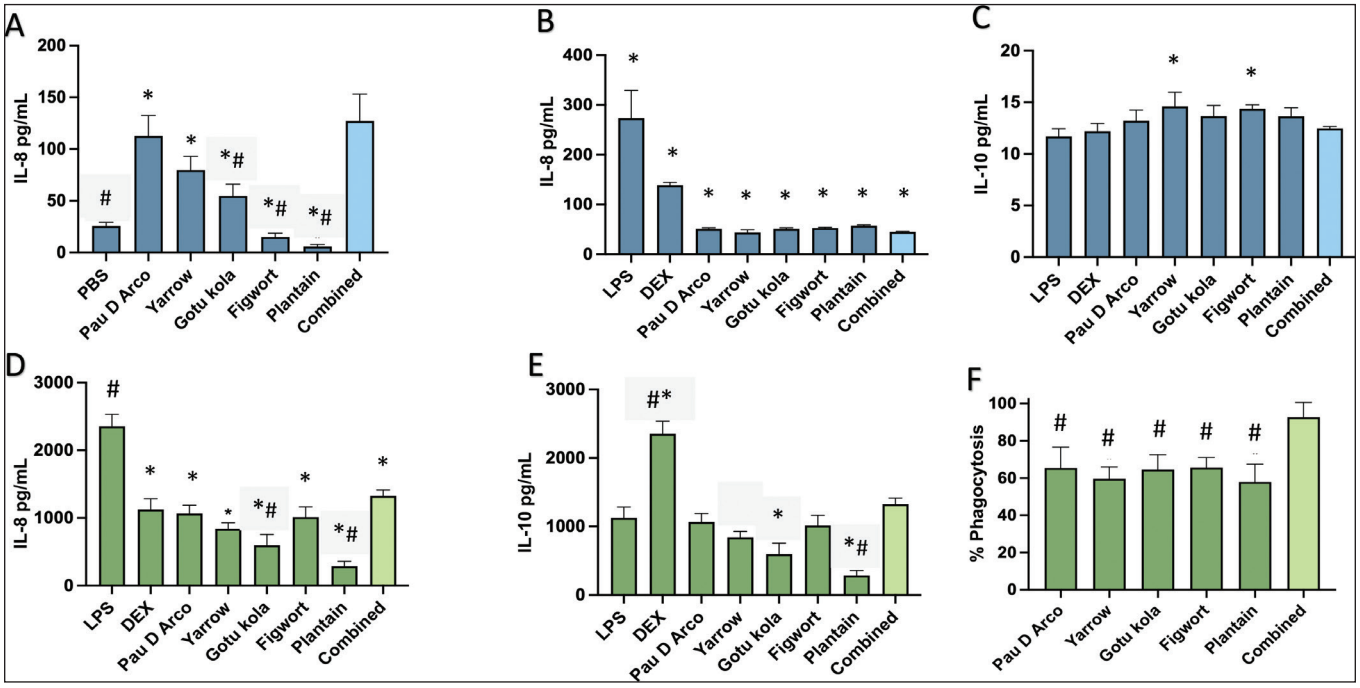


FIGURE 2 - Effect of herbal extracts alone and in combination, on cytokine secretion and phagocytic activity in HaCaT keratinocytes and PMA (25 nM, 48 h) differentiated THP-1 macrophages. (A) IL-8 levels in uninjured HaCaT cells; (B) IL-8 levels in HaCaT cells injured with 100 ng/mL LPS; (C) IL-10 levels in LPS-injured HaCaT cells; (D) IL-8 levels in THP-1 macrophages injured with 100 ng/mL LPS; (E) IL-10 levels in LPS-injured THP-1 macrophages; (F) Phagocytic activity in LPS-injured THP-1 macrophages. Phagocytic activity is expressed as a percentage relative to PBS-treated controls. Cells were treated with 30 µg/mL extracts for 24 hours. Dexamethasone (DEX, 30 µg/mL) was used as an anti-inflammatory control. Pau D'Arco, Yarrow, Gotu Kola, Figwort, and Broadleaf and their combination in petroleum were tested. Results are expressed as mean ± standard error of the mean (SEM). # = $p < 0.05$ versus Combined;* = $p < 0.05$ versus PBS/ LPS.

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Phagocytic assessment of THP-1 (monocytes) cells

To explore how different extracts, both alone and in combination, affect the phagocytic activity of macrophages, THP-1 cells were treated with each extract, and their phagocytic activity was assessed using the Vybrant Phagocytosis Assay Kit (Fig. 2, panel F). To simulate injury or inflammation like that at a wound site, the macrophages were stimulated with LPS. The results showed that the combined herbal extracts significantly enhanced phagocytic activity compared to the individual extracts.

In vivo case studies

Case study 1: equine fetlock wound

A horse was presented with a deep, penetrating wound on its fetlock, the joint located between the cannon and long pastern bones, which serves as the horse's ankle. This area is important for lower limb movement and is highly sensitive. Due to its extensive motion and less vascular skin, wounds in this region can be slow to heal and often require extensive care. The treatment involved daily cleaning and application of a combination of five herbs infused in petroleum jelly for twenty days (Fig. 3).

Case study 2: equine wound in left hock

A horse presented with a large wire cut on the front of its left hock, a wound that was unsuitable for stitching due to the location and nature of the injury (Fig. 4). The hock joint, essential for the performance and mobility of horses, includes multiple small bones, such as the calcaneus, which contribute to its complex, angular structure. Due to the horse's high usage and critical role in the horse's hind legs, healing this area presents unique challenges. These include the joint's high mobility, limited available skin for repair, and poor blood supply, which complicate suture retention and overall wound closure. Over a five-month period, the horse underwent treatment that included bandaging, sequential surgical debridement, various topical applications, and several laser therapy sessions. Although the wound initially healed well, it developed a persistent granulomatous area that did

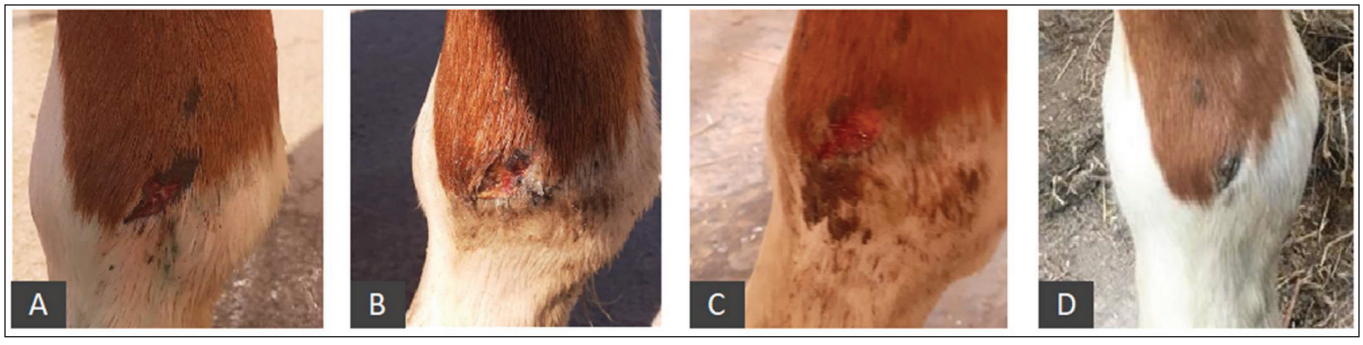


FIGURE 3 - Visual progression of the equine fetlock wound treatment using the combination of the five herbs in petroleum applied topically for 20 days. Panel A: Initial presentation of the wound on day 1. Panel B: Condition of the wound on day 4. Panel C: By day 9, the wound exhibited significant granulation. Panel D: On day 20, the wound showed good healing, with almost complete restoration of skin integrity.

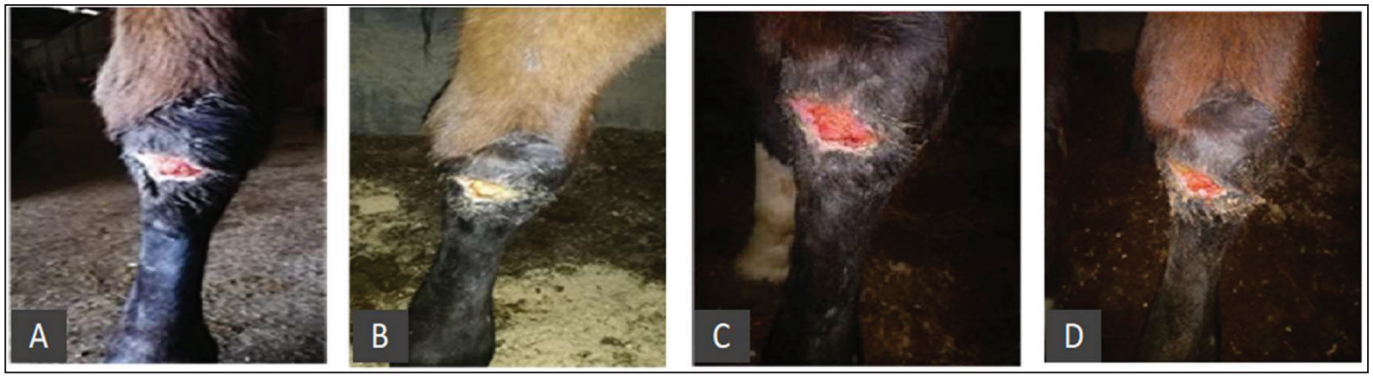


FIGURE 4 - Visual progression of the treatment of equine left hock wound using the combination of the five herbs in petroleum applied topically for 40 days. Panel A: Initial presentation of the wound on day 1 of topical application. Panel B: Condition of the wound on day 6. Panel C: By day 20. Panel D: On day 40, the wound significantly decreased in size.

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not resolve. Consequently, the blend of five herbs infused in petroleum jelly was topically applied. Prior to application, the area around the wound was clipped, cleaned, and moistened with gauze for 40 days.

Case study 3: equine wire lesion

A horse presented with a cut on the front of the hock on its hind leg, caused by wire (Fig. 5). The treatment involved liberally applying ointment (5 herbs in jelly) twice daily—once in the morning and again in the evening after cleaning and drying the wound with clean gauze. This regimen was followed for 18 days.

Case study 4: equine forearm cut

A horse presented with a two-week-old cut Figure. 6 on the forearm (front leg, above the knee). The wound was purulent and appeared infected, and the surrounding leg was notably swollen. A treatment regimen was initiated using a blend of five herbs infused in petroleum jelly. The treatment protocol included preparing the wound area twice daily: the surrounding fur was clipped, the wound was cleaned, and the skin was moistened with gauze. Following preparation, the herbal ointment was applied liberally each morning and evening for 22 days. The herbal treatment produced a positive outcome. The wound's size reduced significantly, the tissue healed properly, and the infection was resolved, demonstrating the efficacy of the herbal infusion in treating complex equine wounds.

Discussion

Severe tissue damage and wound infection are major contributors to delayed healing and poor wound closure. This study evaluated the therapeutic potential of Pau d'Arco, yarrow, gotu kola, figwort, and broadleaf in wound healing, using both *in vitro* and *in vivo* equine models. The results demonstrated that these herbal extracts modulate inflammatory responses, enhance macrophage activity, and accelerate tissue repair, supporting their potential as complementary treatments for wound management.

In vitro, macrophage and keratinocyte assays confirmed that the herbal extracts were non-cytotoxic while significantly influencing cytokine production. IL-8 levels decreased following LPS-induced inflammation in both cell models, indicating anti-inflammatory effects, while yarrow and figwort increased IL-10 expression, further supporting their immunomodulatory role. Phagocytic activity assays revealed enhanced macrophage function, particularly when extracts were combined, suggesting a synergistic effect in immune modulation.

In vivo, equine wound models exhibited positive healing outcomes, including reduced infection rates, accelerated granulation, and enhanced tissue regeneration. However, these findings should be interpreted with caution, as there

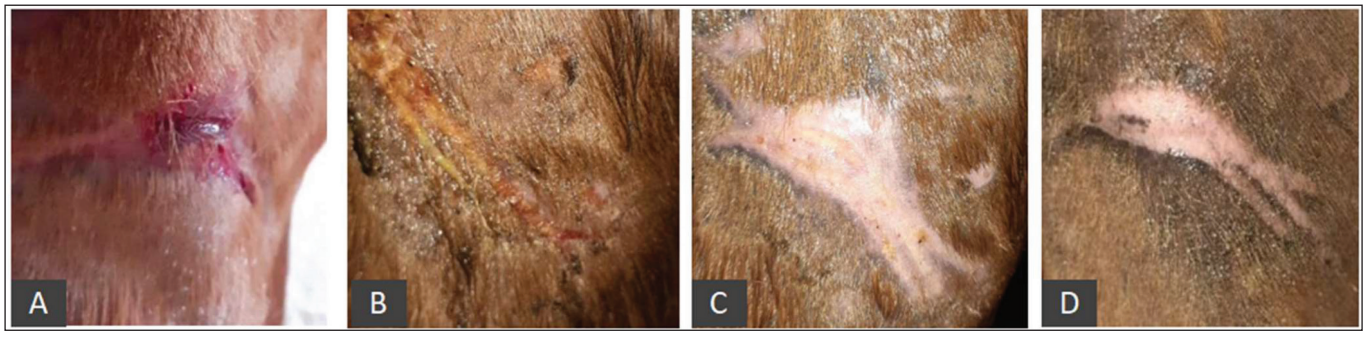


FIGURE 5 - Visual progression of the treatment of a wound caused by a wire using the combination of the five herbs in petroleum applied topically for 18 days. Panel A: Initial presentation of the wound on day 1 of topical application. Panel B: Condition of the wound on day 3. Panel C: By day 6. Panel D: On day 18, demonstrating the healed wound.

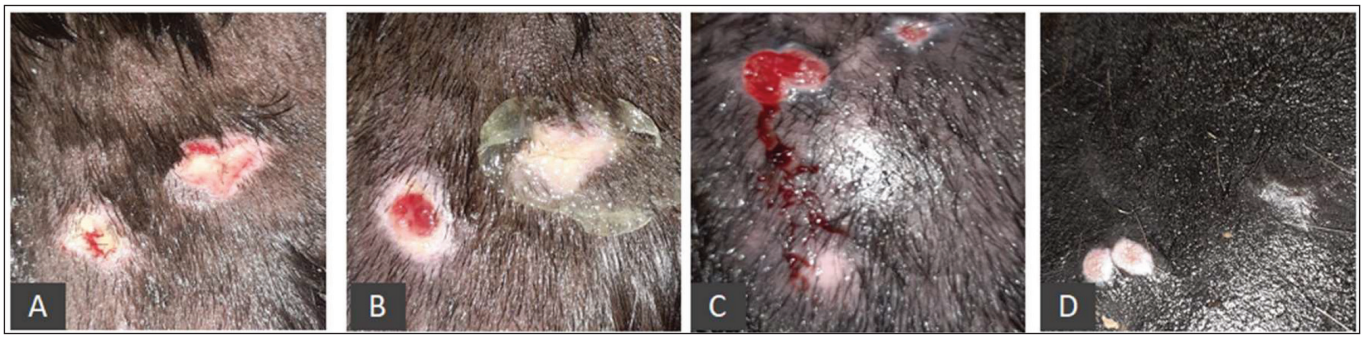


FIGURE 6 - Visual progression of the treatment of equine forearm cut using the combination of the five herbs in petroleum applied topically for 22 days. Panel A: Initial presentation of the wound on day 1 of topical application. Panel B: Condition of the wound on day 4. Panel C: By day 11. Panel D: On day 22, demonstrating the healed wound, no infection that has decreased in size.

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was no comparison to an untreated control group. While the observed improvements, combined with the *in vitro* findings, point toward a therapeutic benefit, spontaneous recovery cannot be ruled out. These results mainly demonstrate the tolerability of topical application of extracts in equine models, rather than confirming their efficacy. Further studies need to be made to assess the therapeutic potential of these formulations in a controlled manner.

The wound-healing properties observed align with previous findings on individual components. Pau d'Arco and its active compounds, such as lapachol and β-lapachone, have been reported to suppress PGE2 and COX-2, key mediators of inflammation (14,29). Yarrow, widely recognized for its wound-healing effects, has been shown to regulate inflammatory cytokines and promote fibroblast proliferation (30,31). Gotu kola and its triterpenoids have been linked to enhanced keratinocyte migration and improved skin repair (32), while figwort and broadleaf contribute to anti-inflammatory and antimicrobial responses (33,34).

These findings demonstrate the potential of multi-herbal formulations in wound management by modulating inflammation, promoting immune function, and accelerating tissue repair. Future research should focus on identifying the specific bioactive compounds responsible for these effects, elucidating their molecular mechanisms, and conducting expanded clinical trials to further validate their efficacy in veterinary medicine.

Conclusions

This study highlights the therapeutic potential of Pau d'Arco, yarrow, gotu kola, figwort, and plantain in wound healing by modulating inflammatory responses and promoting tissue regeneration. The extracts effectively reduced pro-inflammatory markers such as IL-8 and, in some cases, enhanced IL-10 expression, demonstrating their immunomodulatory properties *in vitro*. Additionally, preliminary studies in equine wound models suggested favorable healing outcomes; however, these findings are not sufficient to establish causality and necessitate subsequent investigation.

This research supports the integration of herbal formulations as complementary therapies in veterinary wound management. Future research should focus on conducting expanded clinical trials to further validate their efficacy. Additionally, a deeper understanding of their pharmacological properties could facilitate the development of natural, evidence-based treatments for both veterinary and human medicine.

Disclosures

Conflict of interest: The authors declare no conflicts of interest.

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