Review Article
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Comparative Efficacy of *Curcuma longa*, *Azadirachta indica* and *Centella asiatica* in Canine Wound Healing: a Review

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Abstract

Herbal preparation has been an extremely exploited concept in veterinary medicine due to its healing potency in wounds. This review comprehensively scopes the healing effectiveness of the three most popular medicinal herbs: *Curcuma longa*, *Azadirachta indica* and *Centella asiatica*. All these herbs have been proven to possess anti-inflammatory, antimicrobial and antioxidant properties, making them nearly ideal for wound healing in dogs. The active phytoconstituent of *Curcuma longa* is curcumin which encourages synthesis of collagen and supports fast granulation tissue formation for wound closure. Effects of *Azadirachta indica* supports fast tissue regeneration with lesser inflammation, whereas *Centella asiatica* and Asiatic acid stimulate collagen synthesis and enhance wound contraction. The concurrent use of these herbs, although individually beneficial, necessitates careful assessment to avoid over-activation of anti-inflammatory or antioxidant pathways, which could impede the natural healing process. Interaction with conventional medications in veterinary applications also could be important, especially given the metabolic activity in the liver. It is thus based on this hypothetical synergism with these herbs that causes discussion in the context of canine wound healing acceleration that there is a need for further clinical studies on standardized dosing and safety protocols. Instead of allopathic treatments, natural alternative herbal remedies have emerged; a proper understanding and cautious application of these herbs in veterinary practice are essential.

Keywords: Canine wound healing, *Curcuma longa*, *Azadirachta indica*, *Centella asiatica*, Herbal formulations

Introduction:

Wound healing is a common challenge in veterinary medicine, involving complex cellular and extracellular processes (Lux, 2022). Despite many research papers reporting domestic animals' wound-healing process, it is important to study the intricate mechanisms of wound healing and develop prescribed ways. Medical herbs have been the first means to treat wounds and domestic animals for centuries and their therapeutic use has been largely documented in ancient Indian Vedic texts. The wound-healing process is very intricate and involves several phases that are possibly run concurrently with each one building upon the other. Factors such as cytokines and chemokines are secreted by the cells and play important roles in the healing process.

Herbal drugs have been used to treat wounds in animals for centuries, with their use well-documented in ancient Indian Vedic texts. The wound healing process is complex and involves multiple phases that can occur simultaneously, with each phase building upon the previous. Growth factors such as cytokines and chemokines play key roles in mediating the healing process.

Stage 1: Haemostasis: Haemostasis involves immediate blood clotting via platelets and fibrin to stop bleeding. In the case of intense bleeding which is not going away, emergency veterinary care is essential (Whittenburg, 2024).

Figure 1: Fresh wound on the leg of a dog

Stage 2: Inflammatory Phase: Inflammation represents the body's reaction to tissue injury. White blood cells surge into the wound; these carry enzymes that create swelling, warmth, redness and pain (Figure 1). This is crucial in stopping bleeding and accelerating the repair process. If the lacerations are too deep or big, they must be taken to a Veterinarian for proper cleaning, stitching and medication to assist in healing (Whittenburg, 2024).

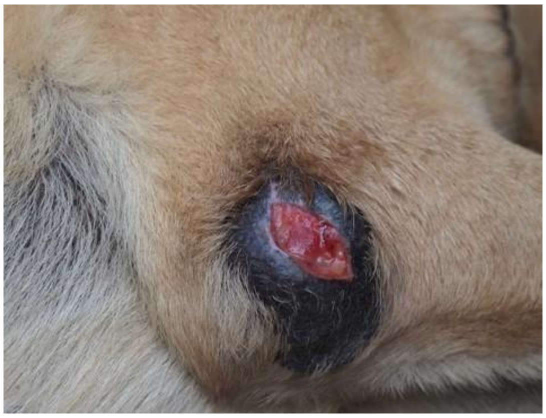

Figure 2: Wound under treatment in the repair phase

Stage 3: Proliferation Phase (repair phase): The phase commonly thought of as healing is characterized by the contraction of the wound and the formation of granulation tissue via collagen, the wound ultimately closes completely (Figure 2). In this phase, the owner should monitor the cleanliness of the wound and follow recommendations provided by the veterinarian to include no bandages unless otherwise indicated. If the wound heals normally, treatment is not required, but there are cases of infection or suture failure that may require attention. These would involve signs of complications such as redness, heat, pain, or discharge of pus, which would present a need for veterinary care (Whittenburg, 2024).

Figure 3: Long-sutured wound in the final stage of repair

Stage 4: Maturation Phase: Maturation, or remodelling, is the final phase in which the last layers of collagen are deposited, laying down a scar, thereby fully closing the wound. The scar will decrease in size and flatten over time. There is usually no need for further treatment, though the site can still be tender and may reopen at this stage (Figure 3). At this point, the healing process can begin again and veterinary treatment may be required to ensure correct healing (Whittenburg, 2024).

Table 1: Different growth factors thathelp in wound healing

Growth factor	Phase of healing	Target cells	Biological effects
CTGF	Inflammatory, Repair	Endothelial cells, epithelial cells, fibroblasts	Fibroblast proliferation, ECM protein induction, angiogenesis.
EGF, FGF	Inflammatory, Repair	Keratinocytes, macrophages, platelets, Endothelial cells,	Keratinocyte proliferation, ECM deposition, Angiogenesis, migration.
IGF, HGF	Inflammatory, Repair	Mesenchymal cellsFibroblasts, liver, macrophages, platelets, skeletal muscles	Angiogenesis, Fibroblast growth, keratinocyte migration, MMP production.
PDGF	Inflammatory, Repair, Maturation	Endothelial cells, fibroblasts, macrophages, keratinocytes	Leukocyte migration, angiogenesis, ECM deposition, collagen turnover.
TGF-α	Inflammatory, Repair	Keratinocytes, fibroblasts	Keratinocyte migration, ECM deposition.
TIMP, MMP	Inflammatory, Repair, Maturation	Endothelial cells, fibroblasts, macrophages	Inhibits MMPs and controls collagen turnover and ECM stability.
IL-6	Inflammatory, Repair	Keratinocytes, Fibroblasts, macrophages, neutrophils	Fibroblast growth, ECM synthesis, keratinocyte proliferation. ECM synthesis.

Herbal Formulations

Herbal formulations increasingly gain more recognition in modern medicine to enhance wound healing through the bioactive constituents present in them. They constitute a combination of herbs that may possess anti-inflammatory, antimicrobial and antioxidant activities useful in managing and accelerating the healing of wounds. The inclusion of herbal remedies is bound to further support conventional treatments in the quest for a holistic approach to wound care through natural plant-assisted healing.

In the case of veterinary medicine, herbal formulation for dogs acts as a very potential alternative to conventional synthetic medication, with minimal side effects. The application of herbal products in the treatment of wounds of dogs serves not only to return to nature but also focuses on the combination of traditional knowledge and modern therapeutic practices.

The most common herbs of high activity include *Curcuma longa*, *Azadirachta indica* and *Centella asiatica*, which are discussed individually in subsequent sections. The important benefits from these herbs could be achieved when it is first fully recognized which herbs are being used and what their modes of action and clinical uses are.

Curcuma longa

Curcumin is derived from turmeric and holds much promise in not only human medicine but also in veterinary medicine, as it contains strong bioactive properties. The chemical structure of this molecule consists of two aromatic rings joined by a seven-carbon linker that contains an α, β-unsaturated β-diketone moiety, which confers several physiological effects and bioactivities.

Therapeutically, it has been explored in animal models for anti-inflammatory, antioxidant and antimicrobial properties. It has proven to decrease inflammation in diseased states such as arthritis and dermatitis, while simultaneously assisting with oxidative stress in chronic diseases of diabetes and cardiovascular disease in pets. Additional uses of curcumin in animals are to foster wound healing and reduce fibrosis, adding new vigor to conventional veterinary treatments.

Curcumin exhibits antifungal and antibacterial properties, making it an aid in fighting infections, especially in livestock and pets where antibiotic resistance is already a growing concern. It also plays a vital role in maintaining liver health and preventing cataracts and hence, it is very useful in aged animals as a dietary supplement.

A Mechanistic Insight (Kumari et al., 2022)

1. Anti-inflammatory Actions: Curcumin effectively modulates this phase by inhibiting key inflammatory cytokines like TNF-αand IL-1, which are crucial for the inflammatory response mediated by monocytes and macrophages.

2. Reduction of Oxidative Stress (ROS): In this regard, curcumin acts through high-power antioxidant activity by scavenging free radicals and thereby reducing ROS formation. Curcumin moderates the activities of various enzymes such as lipoxygenases and enhances the intrinsic antioxidant machinery of the body like glutathione, thereby protecting tissues from oxidative damage and hence promoting natural wound healing in animals.

3. Promotion of Proliferative Phase: Curcumin enhances collagen synthesis during the proliferative phase and the proliferation of fibroblasts during wound healing. Animal wound studies have demonstrated increased deposition of collagen and enhanced formation of granulation tissue, events necessary for the strength and integrity of tissues in curcumin-treated wounds. This accelerates the healing and improves the quality of the healed tissue.

4. Enhancing Activities of Fibroblasts: Fibroblasts are one of the major cells responsible for wound healing; they take part in the development of granulation tissue and deposit collagen. Curcumin enhances the migration of fibroblasts at the wound site and helps in their proliferation. This activity is important since it relates to the structural rebuilding of the area of injury.

5. Granulation Tissue Formation: It also facilitates the quality of the granulation tissue hugely vascularized and collagen-dense tissue that forms at the site of injury. Indeed, curcumin allows for a sturdy scaffold necessary for new tissue growth through the induction of angiogenesis and maturation of collagen, two important preludes to rapid and effective wound closure.

6. Collagen Deposition and Remodeling: Finally, curcumin helps in the critical phase of collagen deposition and remodeling. Besides hastening the synthesis, curcumin also facilitates better organization of collagen, thereby accelerating the rate of wound closure and providing strength with improved appearance to the healed area, thus minimizing the chances of scar formation in animals.

Curcumin, a class IV compound in the BCS classification, has low bioavailability and permeability, limiting its therapeutic response. Enhancers such as lipids, surfactants, or biopolymers can improve water insolubility in animal treatments (Du et al., 2016) explored the use of phospholipid complexes to address this. A curcumin-encapsulated nanoliposomes CPC was prepared using solvent evaporation and incorporated into an in-situ hydrogel-forming poloxamer (ISG).

Formulations like CPC have been proposed, which enhance the bioavailability of the ingredient and hence its effectiveness in animals, showing promising applications in therapeutic and preventive health. Inventions like these in curcumin delivery are of utmost importance to maximize the benefits of veterinary use (Kumari et al., 2022).

Various ways can be used to extract the curcumin from *Curcuma longa*, which are listed below:

Table 2: Different Extraction Methods of Curcumin

Sample Type	Extraction Method	Solvent or Condition	Extraction Time (min)	Temperature (°C)	Extraction Yield (%)	Reference
Powder	Surfactant-free microemulsion (SFME)	Triacetin: Ethanol: Water (36:24:40)	-	-	0.921	(Degot et al., 2021)
Powder	Refluxing	Dichloromethane	60	-	81.81-86.36	(Eltoum and Elfaki, 2020)
Powder	Ionic liquid bath	1-butyl-3-methylimidazolium bistrifluoro methyl sulfonylimide	10-60	25-55	0.776-2.94	(Gökdemir et al., 2020)
Powder	Dissolving	Ethanol (95%)	10,080	Room temp	-	(Win and Thandar, 2020)
Powder	Soxhlet extraction	Ethanol	480	70	-	(Nurjanah and Saepudin, 2019)
Powder	Soxhlet extraction	Petroleum ether	60	-	1.55-5.163	(Ahmad et al., 2017)
Powder	Enzyme-assisted ionic liquid extraction	N,N-dipropyl ammonium and N,N-dipropylcarbamate	120	Room temp	1.48-3.95	(Sahne et al., 2017)
Powder	Subcritical water extraction	Water	60	140	76	(Mohammad et al., 2016)
Powder	Subcritical solvent extraction	Water	120	60	10.49-13.96	(Kwon and Chung, 2015)

Normal considerations for dogs are recommended to achieve safety and efficacy. In one study published in the Journal of Veterinary Pharmacology and Therapeutics, an appropriate safe amount for canines is from 15 to 20 mg per pound of body weight daily for example, a 20-pound dog needs approximately 300 to 400 mg of curcumin a day. It would be good to gradually go for higher dosages after starting with a small dosage, looking out for any prospective side effects in your pet (Candy, 2024). As each dog would react differently to curcumin, it's better to consult a veterinarian before adding the supplement to their diet to make sure the proper dosage is given without complications arising in the first place.

In summary, curcumin is a very promising adjuvant in veterinary wound care. Its natural origin is combined with strong anti-inflammatory and antioxidant activities, with substantial tissue regeneration properties precious candidate for incorporation into topical wound treatment mixtures and dietary supplements for animals suffering from wounds or in surgical conditions.

Azadirachta indica

The leaves of neem have traditionally been used for decades because of their high bioactive compounds responsible for effective therapeutic benefits. Other major active principles are nimbidin, nimbin and sodium nimbidinate. These are majorly responsible for the therapeutic potentiality of neem, especially in wound healing processes. To be more specific, neem exhibits strong anti-inflammatory, antimicrobial and antioxidant activities due to these active principles; hence, neem can be considered one of the potent natural remedies to accelerate the process of wound healing (Chundran et al., 2015).

Neem promotes the production of collagen, a vital protein for skin regeneration and wound closure. Its rich nutritional profile enhances blood flow to the wound site, speeding up tissue repair. The essential nutrients in neem aid in rebuilding damaged tissue and support recovery, while its anti-inflammatory and antimicrobial properties help prevent infections, allowing for quicker and more effective healing.

Neem has been reportedly very promising in veterinary medicine for the treatment of certain wounds in dogs. Some experimental studies are continuously made to assess, for the first time, the neem leaves healing potential in canine wound care regarding the reduction of healing time and minimizing infection risks by enhancing tissue regeneration.

Neem extracts: The physical and chemical properties of neem seed, leaves and bark were analyzed, revealing differences. Neem leaves had the highest oil yield (37.73%), followed by seeds (34.85%) and bark (27.70%). Neem leaves also showed greater moisture content (57.6%) compared to seeds (41.0%) and bark (34.2%). Densities were 1108 kg/m³ for leaves, 1089 kg/m³ for seeds and 1029 kg/m³ for bark. Acidic values were 12.34 for seeds, 10.56 for leaves and 13.46 for bark, while the iodine value for seeds was 7.61 (Kamble et al., 2022).

Table 3: Percent yield of neem extracts (Hashim et al., 2021)

Solvent	Soxhlet extraction	Immersion Extraction
Methanol	16.0%	18.0%
Ethanol	15.0%	15.0%
Ethyl acetate	15.0%	15.0%
Hexane	15.0%	13.0%
Distilled water	N/A	Varied by temperature (1.3% at 25°C to 16.5% at 90°C)

To sum up, neem leaf is enriched with powerful active ingredients like nimbidin and nimbin with great therapeutic efficacy especially in wound healing due to their anti-inflammatory, anti-microbial and oxygen scavenging effects. Laboratory experiments have also shown that extracts of neem leaves are comparable to povidone-iodine in treating wounds but perform better owing to a faster rate of tissue regeneration and lesser inflammation. Due to its herbal origin and few adverse effects, it is used as a potential substitute in the treatment of wounds in dogs.

Centella asiatica

Centella asiatica (L) Urban, known as Gotu kola, belongs to the family Apiaceae. This small perennial herb is widely distributed in Southeast Asia and forms part of traditional medicine that was practiced over 2000 years ago. This herb is mentioned in ancient texts such as the "Sushruta Samhita". The plant has been a mainstay of traditional Chinese and Indian medicine for the treatment of various skin conditions like leprosy, varicose ulcers and eczema.

Centella asiatica is reported to possess a rich phytochemical composition. Among others, it contains flavonoids, plant sterols, eugenol and pentacyclic triterpenoids. The most identified active component responsible for the drug's wound healing property is a pentacyclic triterpenoid saponin called asiatic acid with the molecular formula $C_{30}H_{48}O_5$. This asiatic acid, being an aglycone of the saponin, has a complicated structure due to the presence of five rings in its molecular structure. The above structure empowers asiatic acid to interact with various biological targets, enhancing collagen synthesis and modulating inflammation, which are important in wound healing.

Asiatic acid has poor bioavailability because of its low water solubility, which is about 5.98 × 10-2 mg/L at 25°C; it is primarily absorbed from the jejunum. It binds with albumin and distributes through the tissues, including plasma, brain, heart, liver, kidney, colon and bladder. To increase its therapeutic value, chemical modifications have been tried to be carried out in an attempt to improve its aqueous solubility and bioactivity.

Given the enormous therapeutic potential of *C. asiatica* and its derivative asiatic acid, the application of these substances in veterinary medicine, in particular about cutaneous lesions in dogs, represents a particularly valuable resource. Indeed, in this respect, asiatic acid has the peculiar property of enhancing collagen synthesis and modulating inflammation, thereby acting to speed the course of the healing process in dogs.

A Mechanistic insight

The experimental and preclinical studies increasingly support the traditional use of *C. asiatica* extracts for wound healing. Although wound healing phases are interconnected, the effects of CAE and its major triterpenoid, Asiatic acid, on cellular and molecular mechanisms typical for each phase of the wound healing process are discussed, pointing out the involved underlying mechanisms related to the wound healing activity of both *C. asiatica* and Asiatic acid.

The Inflammatory Phase:

CAE and Asiatic acid have well-documented anti-inflammatory effects, though fewer studies focus on the inflammatory phase of wound healing. It also inhibits the expression of iNOS, COX-2, NF-κB and LOX at the injury site (Bylka et al., 2014; Arribas-López et al., 2022) confirmed that Asiatic acid (100 mg/kg orally) lowers IL-17A and IL-23 levels in an imiquimod-induced psoriasis model, blocking the differentiation of CD4+ T cells into pro-inflammatory Th17 cells that produce IL-17, IL-17F, IL-6 and TNF-α (Sorg et al., 2017).

The proliferative phase:

CAE positively impacts the proliferative phase of wound healing by enhancing fibronectin and collagen synthesis, supporting connective tissue and strengthening veins. It promotes collagen formation and angiogenesis, boosting tensile strength and accelerating the healing process (Songvut et al., 2021). In vitro, studies also prove that CAE and Asiatic acid enhance the synthesis of type I collagen and fibronectin in human dermal fibroblasts (Shukla et al., 1999). In vivo studies confirm these observations, as fibroblast proliferation, collagen synthesis and even angiogenesis are increased (Shukla et al., 1999). Oral CAE administration reduces wound size and accelerates healing by boosting collagen synthesis and cellular proliferation. Additionally, applying CAE locally three times daily for 24 days accelerated epithelization and wound contraction in rats (Shetty et al., 2006), it is reported that CAE enhanced the strength of the wound and the weight of the granulation tissue besides overcoming the inhibitory action of dexamethasone (Shetty et al., 2006).

The Remodelling Phase:

Centella asiatica and Asiatic acid positively impact the remodelling phase of wound healing through various cellular and molecular mechanisms. Studies with human dermal fibroblasts show that *C. asiatica* enhances type I collagen synthesis and cross-linking (Lee et al., 2006). Pharmaceutical formulations containing CAE and/or asiatic acid effectively improve this phase by stimulating extracellular matrix accumulation, maintaining granulation tissue and enhancing collagen synthesis, maturation, cross-linking and tensile strength (Maquart et al., 1999). Wu et al. (2012) found that *C. asiatica* constituents likely promote healing via the TGF-β/Smad pathway, indicated by increased p-Smad 3, elevated TGF-β 1 and TβRII mRNA levels and decreased Smad 7 expression in fibroblasts. Elevated procollagen types I and III at both mRNA and protein levels were also noted. These findings support previous research that *C. asiatica* triterpenes stimulate TGF-β 1, enhance fibroblast proliferation and improve ECM secretion, contributing to accelerated wound closure during the remodeling phase. Yao et al. (2017) demonstrated that gelatine nanofibers containing CAE increased fibroblast proliferation and collagen synthesis, resulting in a higher recovery rate of rat skin wounds compared to other dressings.

Chronic Wound Healing:

Although less studied, the roles of CAE and asiatic acid are promising in chronic wound healing. It enhances the healing process in diabetic rats and contains significant anti-inflammatory activity that can be used in managing chronic wounds (Liu et al., 2022). For example, in diabetes, dry skin has been treated with CAE and enhanced the healing of diabetic foot ulcers.

Centella asiatica, rich in phytochemicals such as asiatic acid, plays an important role in wound healing through the enhancement of collagen synthesis, modulation of inflammation and facilitation of tissue regeneration. Asiatic acid, a pentacyclic triterpenoid, was reported to enhance tensile strength and accelerate wound healing by affecting the inflammatory phase, proliferative phase and remodeling phase of wound healing. Poor bioavailability limits its efficacy, but ongoing chemical modifications continue to improve its solubility and therapeutic potential.

A detailed comparison of the medicinal flora *Curcuma longa*, *Azadirachta indica* and *Centella asiatica* regarding various aspects may help to understand better each herb's contribution towards wound healing. The table below summarizes the active principles, modes of action and therapeutic benefits of these herbs in wound healing.

There is very little data to support the occurrence of adverse interactions with the combination of *Curcuma longa*, *Azadirachta indica* and *Centella asiatica*. However, the following are a few potential issues to consider when combining these herbs:

1. Additive Effects on Inflammation
2. Influence upon Blood Coagulation
3. Increased Antioxidant Stress

Table 4: A detailed comparison of all three herbs			
Category	***Curcuma longa***	***Azadirachta indica***	***Centella asiatica***
Active Components	Curcumin (α, β-unsaturated β-diketone moiety)	Nimbidin, Nimbin, Sodium Nimbidinate	Asiatic acid, Asiaticoside, Madecassoside
Primary Properties	Anti-inflammatory, antioxidant, antimicrobial	Anti-inflammatory, antimicrobial, antioxidant	Anti-inflammatory, collagen synthesis, antioxidant
Mechanism of action	- Suppresses NF-κB activity, reducing TNF-α, IL-1, COX-2 - Antioxidant activity - Promotes fibroblast migration, collagen synthesis	- Enhances collagen production - Stimulates blood flow for faster tissue repair - Prevents infection through antimicrobial action	- Increases collagen synthesis - Modulates inflammation by suppressing IL-17, IL-23, TNF-α, COX-2 - Enhances ECM deposition and fibroblast proliferation
Wound Healing Phases Affected	- Inflammation: - Proliferation: - Remodeling:	- Inflammation: - Proliferation: - Remodeling:	- Inflammation: - Proliferation: - Remodeling:
Application in Canine Wound Healing	- Reduces inflammation in dermatitis and arthritis - Assists in oxidative stress-related conditions - Supports wound healing and reduces fibrosis in pets	- Promotes quicker healing of wounds in dogs - Reduces healing time and minimizes infection risk - Enhances tissue regeneration and collagen formation	- Promotes rapid collagen synthesis and wound closure - Enhances tensile strength and reduces inflammation - Effective in treating cutaneous lesions in dogs
Formulation and Bioavailability	- Curcumin is highly lipid-soluble but has low water solubility - Enhanced bioavailability via nanoliposomes or curcumin-phospholipid complexes	- Leaves, seeds and bark used for extraction - Neem oil is commonly used, with high yield from leaves	- Poor water solubility (5.98 × 10^-2 mg/L) - Chemical modifications enhance solubility and bioactivity
Experimental Studies	- Animal models show reduced inflammation and improved tissue repair - Nanoliposomes enhance bioavailability and efficacy in animals	- Studies on rats show reduced wound size, enhanced collagen formation and quicker healing	- Rat models show enhanced collagen deposition and wound contraction - Accelerates healing, especially in diabetic wounds
Special Considerations	- High lipid solubility but poor water solubility limits bioavailability without enhancement - Effective in chronic conditions like arthritis	- Natural, non-toxic alternative with potential for standard veterinary treatments - Proven to reduce healing time and infection risk	- Poor bioavailability but high therapeutic potential after modification - Effective in chronic and diabetic wound healing

Conclusion:

These herbs may synergistically act when put together in wound treatment, with complementary anti-inflammatory, antioxidant and wound-healing properties. However, cautious monitoring of dosage will be required, taking into consideration the possibility of additive effects on inflammation, clotting and overall metabolic processes. Consulting a veterinarian or healthcare provider is recommended when combining herbal treatments, especially in cases involving chronic health conditions or concurrent medication use.

Conflict of Interest:

The author declares no conflict of interest related to this review.

Author's Contribution:

The author is responsible for the conception, design, literature review, writing and editing of this manuscript.

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