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Investigating the Efficacy of an Herbal Spray, Immuno Plus, in Mitigating Ulceration: Insights from a Rat Model Study

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ABSTRACT

Treatment for recurrent aphthous ulceration (RAS) is challenging. Immuno Plus spray, which contains Aspidosperma (10% v/v), Ocimum sanctum (20% v/v), Curcuma longa (20% v/v), Tinospora cardifolia (20% v/v), Echinacea angustifolia (20% v/v), and Azadirachta indica (10% v/v) was evaluated for its anti-ulcer activity. Ulcer was induced with acetic acid in fifty-four Wistar albino rats that were divided into nine groups. Treatment began on the third day, once the ulcers had clearly developed. One group served as a control and received no treatment, while the other groups were treated with either individual extracts, Immuno Plus, or a marketed formulation. By day 7, the control group still exhibited disrupted epithelium, whereas re-epithelization and healing were observed in the groups treated with Immuno Plus and the marketed formulation. There was minimal reduction in ulcer size in groups treated with the individual extracts at the same dosage, compared to the Immuno Plus group, which contained a mixture of all the extracts. The spray demonstrated synergistic effects, addressing various aspects of ulcer formation and healing.

Key Words: Ulcer; Curcumin; Ocimum sanctum; Azadirachta; Tinospora.

INTRODUCTION

Nutritional deficiencies, anxiety, infections, trauma, allergies, and genetic factors primarily cause aphthous disease.[1] Globally, 4% of the population suffers from oral ulcers, and 25% experience RAS, also known as recurrent aphthous stomatitis or mouth ulcers, and there are no targeted treatments available [2].outh ulcers are characterized by oval or circular shapes with shallow margins, covered by white or yellowish fibro membranous layers and surrounded by an erythematous halo, causing pain. The intensity and duration of pain can be classified into acute and chronic. Acute ulcers remain for less than two weeks, whereas chronic ulcers pertain for two weeks. Recurrent ulcers extend beyond two weeks with irregular healing patterns [3].

An exact treatment plan for RAS is challenging because of the unidentified causes of ulceration. Consequently, RAS have traditionally been treated with various natural herbal remedies, like tinctures, decoctions, and fresh juices. Clinical trials have shown that herbal remedies can positively impact patients by reducing the duration and discomfort of ulcers [4]. In contrast, synthetic drugs like dapsone, colchicine, thalidomide, and clofazimine, used to manage RAS, are associated with adverse effects, including gastrointestinal upset, peripheral neuropathy, hemolysis, male infertility, methemoglobinemia, skin discomfort, and eye problems. Thus, to evade the side effects of synthetic drugs, herbal drugs are the viable alternatives for RAS [5].

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Curcuma longa (turmeric) of the Zingiberaceae family has long been used to treat oral ulcers and immunological disorders like inflammation, cancer, diabetes, and psoriasis. It is a potent antioxidant because of high polyphenol and flavonoid content. Curcumin, its main active component, serves as an immunomodulator, anti-inflammatory, antibacterial, and antiproliferative agent, aiding in managing various oral disorders [6,7,8]

Curcumin, by inhibiting phospholipase, lipase, and cyclooxygenase-2 mitigates proinflammatory cytokines and offers significant analgesic properties in individuals with recurrent RAS. Curcumin can effectively modulate the production of reactive oxygen species (ROS) and nitric oxide (NO), and regulate the secretion of proinflammatory mediators such as interleukins (IL-1β, IL-2, IL-6, and IL-10). Intracellular signaling pathways, including nuclear factor kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), activation protein-1 (AP-1), and the Notch-1 pathway are influenced by these mediators, all of which play roles in inflammation. [7,9,10]

Ocimum sanctum (Tulsi), from the Lamiaceae family, offers antipyretic, analgesic, anti-inflammatory, hypolipidemic, antioxidant, antidiabetic, hepatoprotective, anticancer, and neuroprotective activities due to the presence of bioactive compounds such as rosmarinic acid, ursolic acid, eugenol, and apigenin. [11,12]. Additionally, tulsi is widely used to treat skin diseases and oral infections due to its antimicrobial, antibacterial, and immunomodulatory effects. [13,14]

Tinospora cordifolia, a member of Menispermaceae family is commonly referred to as Tinospora cordifolia (Guduchi or Giloya) from the Menispermaceae family has immunomodulatory, anticancer, anti-inflammatory, antimicrobial, and antioxidant properties due to Its key phytoconstituents, including tinosporide, cordifol, β-sitosterol, cordifolioside A, and guduchi syringing.[15] The phyto actives, cordifolioside A and guduchi syringin have been identified as immunomodulators in clinical tests. This rich phytochemical profile makes Giloya a common ingredient in herbal formulations [4,16, 17].

Echinacea angustifolia (purple coneflower) of the Asteraceae family [18] is a strong immunomodulator, anti-inflammatory, antioxidant, and antimicrobial because of the Key compounds like echinacoside, cynarin, chlorogenic, and cichoric acids , with isobutylamides and cichoric acid playing crucial roles [19,20]. Azadirachta indica (Neem) exhibits antidiabetic, anti-inflammatory, antiviral, and antibacterial due to phytochemicals like alkaloids, flavonoids, triterpenoids, and tannins [21,22]. It provides antioxidant and anticancer effects due to compounds such as azadirachtin, nimbin, and nimbolide , while flavonoids inhibit enzymes and pathways involved in inflammation[23]. Furthermore, Carolin et al reported antiulcer property of neem flower [24].

The genus Aspidosperma of the Apocynaceae family is used for treating cardiovascular diseases, diabetes, malaria, fever, rheumatism, and respiratory issues like asthma and coughing. Its antiprotozaol activity is due to key bioactives like monoterpene indole alkaloids aspidoscarpine, apparicine, and ramiflorines while flavonoids, saponins, and organic acids are responsible for hypotensive, bradycardic, and other physiological effects. [25,26].

The current investigation focuses on the evaluation of the antiulcer activity of an herbal spray, Immuno Plus, which contains extracts from six different herbs. Additionally, the activity of each individual herb was examined to determine whether a synergistic effect is present in Immuno Plus spray.

MATERIALS AND METHODS

An Immuno Plus spray which is an herbal medicine comprising ingredients such as Aspidosperma (10 %v/v), Ocimum sanctum (20 %v/v), Curcuma longa (20 %v/v), Tinospora cardifolia (20 %v/v), Echinacea angustifolia (20 %v/v), Azadirachta indica (10 %v/v) and alcohol (20%V/V) , along with their respective HA extracts, was supplied by Mayon's Pharmaceutical Pvt. Ltd. in Nagpur,

Maharashtra, India. These components were individually administered to animals for the study.

Antiulcer Activity

Fifty-four Wistar albino rats (either sex), 250-300g were selected for the study approved by the IAEC (protocol no. 535/PO/ ReRcBt/S/02/ CPCSEA/IPER/ IAEC/2023-24/34). Animals were caged according to the groups and maintained under 12:12 hour light-dark cycle with food and water ad libitum. Animals were grouped into nine, each containing 6 rats. Group I was considered as control, i.e ulcer was induced but treatment was not provided, Groups II to VII received 0.5 mL, Aspidosperma, Ocimum sanctum, Curcuma longa, Tinospora cardifolia, Echinaceae angustifolia and Azadirachta indica extracts, respectively, topically two times a day as a spray at the affected area. Group VIII animals were treated with Mayons's Immuno Plus spray and Group IX was considered standard wherein Marketed formulation (Spray) was applied [27,28].

Before inducing ulcers, rats were anaesthetized by an intraperitoneal injection of ketamine (60 mg/kg) and xylazine (10 mg/kg). Ulcers were induced in all animals by placing a 6 mm diameter filter paper disc soaked in-15 µL of 50% acetic acid over the upper labial gingiva for 60 seconds. On the third day of induction when the ulcer develops with clear boundaries, treatment was started. To the animals in group II to IX, extracts, Mayons's Immuno Plus spray and standard formulations respectively, were sprayed at the ulcer site two times a day daily for 15 days and at each time five actuations were done (5 actuations deliver 0.5 mL). Diameters of the ulcers were measured at three distinct points using a caliper, ensuring precise determination of the ulcer's geometry. Animals were sedated by an intraperitoneal injection of-ketamine (25 mg/kg).[29] This dose was sufficient to reduce the mobility allowing the measurement of ulcer length. .The area was then calculated using the obtained diameter. These measurements were taken on day 3 (when the ulcer with clear boundaries had developed), day 7, and day 15. The mean surface area of the ulcer is reported in ~~the~~ Table 1 and Figure 1 shows the images depicting the development of ulcers and their healing process in rats. 28,30]

Statistical Analysis

The ulcer surface area of group II and group III on day 7 and day 15 were compared with the control and amongst themselves by ANOVA. A non-parametric multi-comparison post-hoc test was done by Kruskal-Wallis test if $p<0.05$.

Histopathology

Three animals from each group I (control), group VIII (Treated with Immuno Plus Spray) and group IX (Treated with commercial formulation) were sacrificed by an overdose of ether, at day 3 (when the ulcer was produced), day 7 and day 15 respectively. The area of ulcer was excised and fixed in 10% neutral buffered formalin. The specimens were processed several times with the increasing concentration of ethanol before paraffin embedding. Serial sections, 4 µm thick were cut, stained with Hematoxylin and Eosin and visualized under Trinocular Microscope (Magnus MLXi Plus, Mumbai, India) (Figure 2) [27,28].

RESULTS

Antiulcer activity

On the third day, ulcer area in the labial mucosa was clinically visible. At that time ulcer area was measured and then treatment was started in group II to IX. On day seven area was measured and compared statistically. Reduction in the ulcer area of the group VIII treated with Immuno Plus was very significant with $p<0.01$ and p was 0.0056 for Post-hoc test by Kruskal-Wallis Non-parametric method which is considered to be very significant. Reduction in area was also observed in group IX which was treated with the standard marketed formulation but the reduction was not statistically significant when compared to the control on the same day. Also the difference between the ulcer area of group VIII and IX was statistically insignificant.

Table1. Ulcer Surface Area

Time Point	Ulcer Surface Area (Cm^2)[a]								
	Group I (Control)	**Group II**	**Group III**	**Group IV**	**Group V**	**Group VI**	**Group VII**	**Group VIII (Treated with ImmunoPlus)**	**Group IX (Treated with commercial Spray)**
Day 3	1.88 ±0.19	1.93 ±0.23	1.88 ±0.2	1.95 ±0.35	1.89 ±0.25	1.88 ±0.18	1.95 ±0.123	1.88±0.25	1.94±0.23
Day 7	1.73 ±0.26	1.71 ±0.05	1.58 ±0.56	1.68 ±0.23	1.43 ±0.65	1.45 ±0.35	1.45 ±0.65	1.1±0.15**	1.47±0.32
Day 15	1.36 ±0.16	1.15 ±0.15	0.96 ±0.93	1.23 ±0.45	0.92 ±0.65	1.05 ±0.98	0.92 ±0.23	0.47±0.17**	0.63±0.19*

[a] Mean of 6 observations ± S. D ** Compared to Control, difference was very significant with $p<0.01$ * Compared to Control, difference was significant with $p<0.05$

Also, Ulcer area of group VIII and group IX measured on day 15 were compared with control. Immuno Plus treated group revealed a very significant decline in the area of ulceration with the $p<0.01$ and p was 0.0015 for Post-hoc test by Kruskal-Wallis Non-parametric method which is considered to be very significant. Visually there was complete healing of the ulcers (Figure 1). On day 15 group IX treated also showed significant decline in the ulcer area in contrast to control with $p<0.05$. However, there was insignificant difference when Immuno Plus treated and the group treated with Standard marketed preparation. There was little reduction in the ulcer area when group II to VII were treated with the extracts individually at the same dose level as compared to the Immuno Plus having mixture of all the extracts. This indicates synergistic activity of extracts when they were combined.

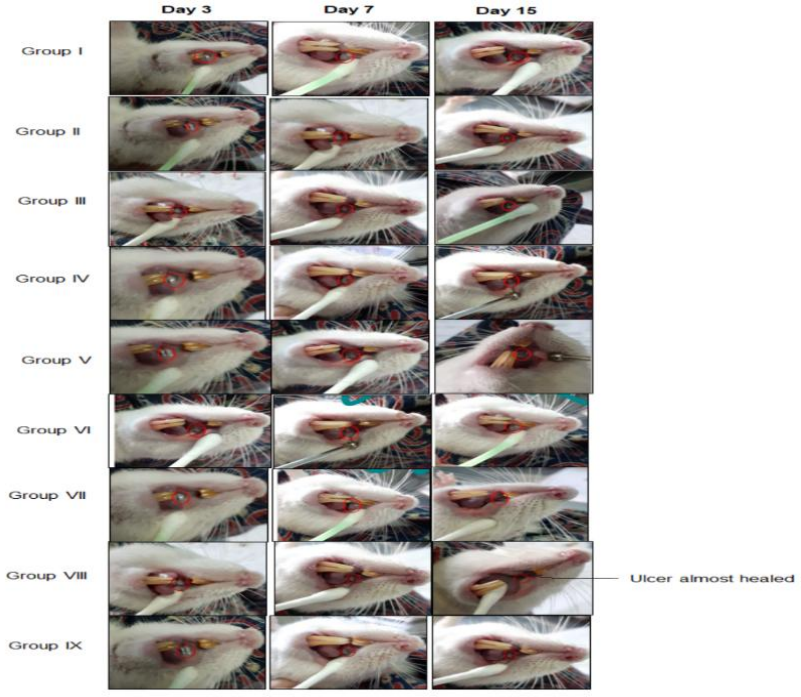

Figure 1. Development of ulcers and their healing process in different groups of rats.

On day 3, when ulcer was formed, histological findings revealed disruption of stratified squamous epithelium with infiltration of inflammatory cells mainly polymorphs and macrophages and small areas of blood clot in all 3 groups. On 7th day, ulcers continued to persist in control group with an increase in inflammatory cells including polymorphs and macrophages. In contrast to the control group, Immunoplus and marketed preparation treated groups showed significant progress in the ulcer healing with a proliferation of basal layer of squamous epithelium at both edges of ulcers. Neovascularisation (new capillary formation) accompanied with phagocytosis of cell debris by macrophages was observed. Inflammation persisted without significant healing progress in the control on day 15. However, in the Immunoplus and marketed preparation-treated groups, complete re-epithelialization of the squamous epithelium facilitated by the proliferation of basal cells from both edges of ulcerative area was observed. The squamous epithelium was fully restored with proper stratification, and complete healing was observed. (Figure 2)

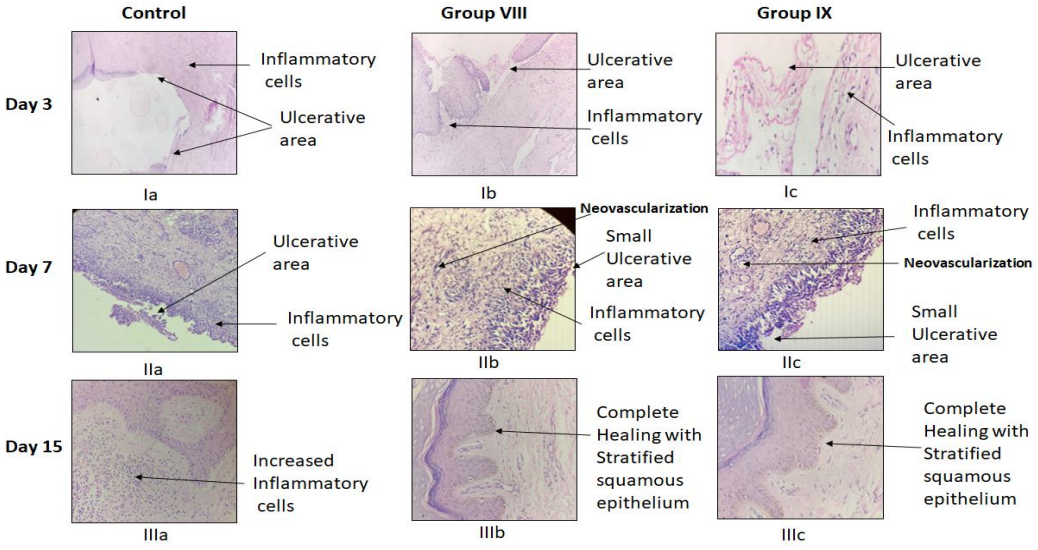

Figure 2. Microscopic examination of oral ulcer: I a, b and c on the third day in Group I (control), Group VIII and Group IX; II a, b and c on the seventh day in Group I (control), Group VIII and Group IX and III a, b and c on the fifteenth day in Group I (control), Group VIII and Group IX.

DISCUSSION

The complementary mode of action of each of these herbal extracts is likely the reason for the synergistic effect of Aspidosperma, Ocimum sanctum, Curcuma longa, Tinospora cordifolia, Echinacea angustifolia, and Azadirachta in Immunoplus spray. Turmeric and Aspidosperma are both credited with strong anti-inflammatory action. Curcumin lessens inflammation by inhibiting pro-inflammatory mediators like cytokines and prostaglandins, which are more often than not elevated in ulcerated tissues [31,32]. This effect is made stronger by Ocimum sanctum and Tinospora cordifolia, which regulate the immune system to reduce the inflammatory response, declining pain and swelling associated with oral ulcers [33,34].

Azadirachta indica and Ocimum sanctum have widely recognized broad-spectrum antimicrobial properties. They combat bacteria, fungi, and viruses, including many pathogens responsible for oral infections that exacerbate

ulcers [35]. Phytoconstituents present in Azadirachta exhibit antimicrobial activity by breaking down their cellular structure.[36] Azadirichtin a complex tetranortriterpenoid limonoid is the key constitutent responsible for antimicrobial activity.[37] Aspidosperma and Echinacea angustifolia enhance this further by acting on oral pathogens involved in inflammation and delayed healing of ulcers. [38,39]

Ocimum sanctum, Tinospora cordifolia, and Echinacea are recognized for their immunomodulatory action, helping the body raise an appropriate response to infection without triggering excessive inflammation. [33,34] Such immune support is crucial for faster healing of oral ulcers, which often result from or are worsened by immune dysfunction. Echinacea is specifically known for stimulating immune cell activity and enhancing the body's defense mechanisms to fight infections and promote healing [39].

Ocimum sanctum increases the levels of IFN-γ, IL-4, and percentages of T-helper cells and NK-cells to promote healing [40]

The antioxidant actions of curcumin present in turmeric and other phytoactives in Ocimum sanctum and Azadirachta indica increase the speed of tissue healing and stall damage of ulcerated areas by redressing free radicals. Curcumin is also enhances production of growth factors and promotes wound-healing properties [41]. It increases the expression of transforming growth factor-β (TGF-β), that promotes wound healing, reduce inflammation by inhibiting nuclear factor kappa B signaling, and promotes the switch from the inflammatory phase to the proliferative phase of healing, which is characterized by enhanced neovascularization, rapid re-epithelialization, elevated collagen deposition, and tissue formation. [42] Azadirachta indica and Ocimum sanctum support tissue regeneration by rendering the ulcer site free from microbial infections and further irritation [43,44].

These ingredients in Immunoplus oral spray acted synergistically to address the multiple elements in ulcer formation and healing. The anti-inflammatory effects of Curcumin, Ocimum sanctum, and Aspidosperma reduced pain and swelling, the antimicrobial actions of Azadirachta, Ocimum, and Aspidosperma prevented infection and the growth of microbes and Tinospora, Ocimum, and Echinacea reinforced the body's immune system to provide healing without excessive inflammation. Likewise, antioxidant and wound-healing ability of curcumin supported tissue regeneration and reduced oxidative stress. Therefore when these extracts were combined, a stronger therapeutic effect resulted than when used individually, ensuring a more rapid and effective healing of oral ulcers. This synergistic effect increased treatment efficacy by targeting multiple pathways in oral ulcer pathology.

CONCLUSION

Immunoplus showed clear anti-ulcer activity in the rat model. Aspidosperma, Ocimum sanctum, Curcuma longa, Tinospora cordifolia, Echinacea angustifolia, and Azadirachta components of it exerted their effect synergistically to reduce the inflammation and helped in tissue generation and prevention of microbial infection. This, in turn, enhanced the healing process more effectively than with individual extracts owing to immunomodulatory, anti-inflammatory, and anti-oxidant combined effects. These findings identified Immunoplus spray as a potentially good therapeutic option in treating oral ulcers because it acts on multiple aspects of the pathology of ulcers to ensure better recovery.

Conflict of Interest

Authors declares no conflict of interest.

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التحقيق في فعالية بخاخ عشبي، Immuno Plus، في التخفيف من القرحة :رؤى من دراسة نموذج الفأر

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ملخص

علاج القرحة القلاعية المتكررة (RAS) يمثل تحديًا .تم تقييم بخاخ Immuno Plus، الذي يحتوي على Aspidosperma (10% v/v)، Ocimum sanctum (20% v/v)، Curcuma longa (20% v/v)، Tinospora cardifolia (20% v/v)، Echinacea angustifolia (20% v/v)، و Azadirachta indica (10% v/v)لنشاطه المضاد للقرحة .تم تحفيز القرحة بحمض الأسيتيك في أربعة وخمسين فأرًا من نوع ويستار الألبينو تم تقسيمهم إلى تسع مجموعات .بدأ العلاج في اليوم الثالث، بمجرد أن تطورت القرحة بوضوح .مجموعة واحدة عملت كمجموعة تحكم ولم تتلق أي علاج، بينما تم علاج المجموعات الأخرى إما بمستخلصات فردية، أو Immuno Plus، أو تركيبة مسوقة . بحلول اليوم السابع، لا يزال لدى مجموعة التحكم ظهارة متقطعة، في حين لوحظت إعادة تكوين الظهارة والشفاء في المجموعات المعالجة بـ Immuno Plus والتركيبة المسوقة .كان هناك تقليل طفيف في حجم القرحة في المجموعات المعالجة بالمستخلصات الفردية بنفس الجرعة، مقارنةً بمجموعة Immuno Plus، التي تحتوي على مزيج من جميع المستخلصات .أظهر الرذاذ تأثيرات تآزرية، حيث عالج جوانب مختلفة من تكوين القرحة وشفائها.

الكلمات الدالة: قرحة؛ كركمين؛ أوكيموم سانتوم؛ أزاديراختا؛ تينوسبورا.

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