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Triticum Vulgare Extract: Pharmacological Activities and Clinical Use

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ABSTRACT

TVE demonstrates significant therapeutic potential in wound care and gynecology due to its various biological properties.

In wound care, TVE exhibits mitogenic and proliferative effects on fibroblasts and keratinocytes, enhancing tissue regeneration and wound healing. It also possesses anti-inflammatory properties by reducing pro-inflammatory markers and inhibiting NF-kB activation. The regenerative activity is further supported by its ability to induce fibronectin expression, increase hyaluronan synthesis, and stimulate actin polymerization. Mechanistically, TVE shows antioxidant capacity and promotes keratinocyte healing by modulating MMP-2, MMP-9, collagen I, and elastin expression. Clinically, TVE formulations have been effective in treating acute skin wounds, diabetic foot ulcers (DFUs), and split-thickness skin graft donor sites (STSG), often showing superior results compared to hyaluronic acid treatments.

In gynecology, TVE formulations have been beneficial in vulvovaginal atrophy (VVA), vulvovaginitis, and cervical ectropion, demonstrating significant symptom reduction and high patient satisfaction. The studies reviewed indicate that TVE is a versatile and effective treatment option in these areas.

Overall, the evidence presented suggests that TVE, particularly in the form of Fitostimoline® products, offers a valuable non-hormonal alternative with significant regenerative and anti-inflammatory properties, making it a promising treatment for various conditions in wound care and gynecology.

Introduction

Triticum vulgare, the binomial scientific name for a plant of the Graminaceae family, is commonly known as the wheat plant. It has been extensively utilized in traditional medicine due to its tissue repair-accelerating properties. Specifically, the use of wheat sprout oil is documented in traditional Iranian medicine for dermotonic and skin beautifying purposes, addressing face freckles, moisturizing and refining facial pores.[1]

The aqueous extract of *Triticum vulgare* (TVE), obtained from the whole germinated plant, is currently an active component employed by Farmaceutici Damor in the manufacture of pharmaceutical products marketed in Italy and abroad under the brand name Fitostimoline®, available in cream and medicated gauze formulations. It is commonly used for the treatment of decubitus ulcers, sores, burns, delayed scarring, dystrophic diseases and, more broadly, in conditions involving re-epithelialization or tissue regeneration. Indeed, it has been reported that TVE, the active component of Fitostimoline® products, significantly accelerates tissue repair processes, stimulates chemotaxis and fibroblastic maturation, and markedly increases the fibroblastic index, all of which are crucial aspects of the repair process.[2-5]

In this review, we aim to explore the pharmacodynamics and clinical uses of TVE. In particular, we focus on the TVE clinical applications in wound care and gynecology.

Methodology

Literature research was performed on pubmed to select the most recent pharmacological and clinical studies related to the activities of Damor patented triticum vulgare extract.

TRITICUM VULGARE EXTRACT PRODUCTION PROCESS

The TVE production process, patented by Damor, involves the generation of a pharmacologically active component through a series of ultrafiltration processes and a unique treatment of the wheat plant. This specific component, results in a peak when isolated via chromatography and is responsible for the distinct pharmacological and clinical activities of the extract. The wheat plant is cultivated under controlled conditions in the laboratories of Farmaceutici DAMOR, Naples, Italy. The voucher specimen, designated DF/237/2014, is deposited in the herbarium of the Medical Botany Chair at the University of Salerno, Italy.

Biological properties of TVE

MITOGENIC EFFECT

A mitogenic effect of TVE has been reported in both plants and the mouse fibroblast line BALB/cNIH-3T3 [6-7], indicating potential trophic properties of this extract. Over the years, several studies have isolated and partially characterized various fractions derived from TVE [8]. These studies have demonstrated the ability of these fractions to stimulate and promote cell proliferation in various cell lines, including human umbilical vein endothelial cells, fetal bovine aortic endothelial cells, and baby hamster kidney cell clone [2-1].

More recently, the effects of TVE and several fractions obtained from TVE have been evaluated on the proliferation of mouse fibroblast NIH-3T3 cells, aiming to identify fractions capable of maintaining the healing activity of TVE. These fractions were formulated as creams, and their effects on tissue regeneration and wound healing were tested in two different rat skin lesion models: scarification and skin excision. The results obtained in the animal models were consistent with those observed in murine fibroblasts. The in vitro results revealed a pro-proliferative effect of the ST-98 and K>1000 fractions, comparable to that of the entire extract and to that of the commercial product Fitostimoline® cream [9].

ANTI - INFLAMMATORY EFFECT

It has been suggested that TVE may possess anti-inflammatory properties [10]. It has been demonstrated that TVE reduces carrageenan-induced hind-paw edema in rats in a dose-dependent manner and that this effect is not dependent on adrenal steroid secretion, as the activity is also observed in adrenalectomized rats. Sanguigno et al. [9] investigated the anti-inflammatory potential of a TVE extract using in vitro models of LPS-induced neuroinflammation. The researchers employed both murine BV2 microglial cells and primary rat microglia cultures, assessing the extract's ability to modulate key inflammatory mediators. Notably, TVE treatment led to a significant reduction in the release of pro-inflammatory markers, including NO, IL-6, PGE2, and TNFα. Furthermore, the extract effectively inhibited the nuclear translocation of NF-kB p65, a crucial step in the inflammatory cascade. The study also demonstrated that TVE attenuated microglia activation, as shown by decreased Iba1 expression. Importantly, these effects were observed in both cell culture models, highlighting the extract's consistent anti-inflammatory activity [11]. Overall, the findings suggest that the TVE extract possesses promising anti-inflammatory properties by targeting multiple pathways involved in neuroinflammation.

To further support the observed anti-inflammatory effects of TVE, the authors studied its impact on nitric oxide (NO) production, a key inflammatory mediator, using the Griess reaction in primary microglia cultures. Consistent with findings in the BV2 cell line, TVE effectively abolished LPS-induced NO release, returning levels to those of unstimulated controls [12,13]. Furthermore, the study demonstrated that TVE reduces the release of other pro-inflammatory markers, including IL-6, TNFα, and PGE2, in LPS-activated BV2 cells. Mechanistically, TVE also restored the cytoplasmic localization of NF-kB p65, thereby inhibiting its nuclear translocation and subsequent inflammatory signaling [14]. These results align with the established roles of these mediators in inflammatory processes and tissue repair, where a reduction in pro-inflammatory signals is crucial for resolution. Collectively, these data strongly suggest that TVE possesses significant anti-inflammatory properties, effectively modulating key pathways involved in neuroinflammation [15, 16].

A further study from the same research group investigated whether TVE can modulate the

phosphorylation of AKT (pAKT), an early marker of the inflammatory process in vitro, and affect MMP9 protein expression in an in vitro model in LPS-induced inflammatory conditions using BV-2 cells [17]. The researchers observed that LPS stimulation led to a significant increase in the phosphorylated form of AKT (pAKT), indicating activation of this key signaling molecule, which is known to play a crucial role in inflammatory responses. Importantly, the co-treatment of cells with LPS and TVE resulted in a reduction in the pAKT/AKT ratio, suggesting that TVE effectively attenuated LPS-induced AKT phosphorylation. This observation is particularly noteworthy as the study further compared the effect of TVE with two chemical pAKT inhibitors. The finding that TVE also decreased the phosphorylated status of AKT, mirroring the effects of established inhibitors, provides strong evidence for its ability to target this pathway. Furthermore, the study explored the dose-dependent effect of TVE on pAKT status. Intriguingly, TVE demonstrated a significant reduction in pAKT levels at concentrations of 5% and 10%, but not at 20%. This observation suggests a potential bell-shaped dose-response curve, highlighting the importance of optimizing TVE concentration for therapeutic efficacy. The lack of effect at 20% warrants further investigation to understand potential mechanisms, such as saturation or off-target effects. By demonstrating a reduction in the pAKT/AKT ratio, this study provides compelling evidence that TVE acts as an anti-inflammatory modulator by targeting the AKT signaling pathway. Given the pivotal role of AKT in various inflammatory processes, these findings suggest that TVE may have therapeutic potential in conditions characterized by aberrant AKT activation. Future studies should focus on elucidating the precise mechanisms by which TVE modulates AKT phosphorylation and exploring its efficacy in in vivo models of inflammation.

WOUND HEALING ACTIVITY

The regenerative activity of TVE during the wound healing process has been demonstrated in a study on human fibroblasts [18, 19]. This study provides compelling evidence for TVE's regenerative capabilities during wound healing, demonstrating significant positive effects on key processes in both dermal fibroblasts and epidermal keratinocytes. Notably, TVE significantly induced fibronectin gene expression and protein production in fibroblasts, comparable to TGFβ, and increased fibronectin protein localization in the extracellular matrix in a dose-dependent manner [20, 21]. Furthermore, TVE enhanced HAS2 gene expression by approximately 70%, indicating increased hyaluronan synthesis. Strikingly, TVE treatment led to a 250% increase in polymerized actin in fibroblasts, suggesting a strong stimulatory effect on cell migration. In epidermal keratinocytes, TVE significantly increased both GBA gene expression and activity, resulting in substantial increases in neutral lipid accumulation, specifically 40% and 60% at 3% and 15% TVE concentration respectively, indicating improved epidermal barrier formation. These results collectively highlight TVE's ability to promote critical aspects of wound healing, including ECM remodeling, cell motility, and epidermal barrier restoration [22, 23].

Mechanism underlying the pharmacologic effects of TVE

ANTIOXIDANT CAPACITY

Oxidative stress typically arises from either excessive reactive oxygen species (ROS) generation, impaired endogenous antioxidants, or a combination of these factors. High concentrations of ROS can damage major biological macromolecules, leading to protein oxidation, lipid peroxidation, DNA base modifications, and strand breaks [2]. Enzymatic and non-enzymatic antioxidant molecules are produced to protect organisms from oxidative stress. Non-enzymatic antioxidants from natural sources are of significant interest due to their potential for isolating phytochemicals with health benefits [7], and their use in the prevention and/or treatment of oxidative stress-related diseases [8]. TVE has been evaluated for its antioxidant capacity using the Folin-Ciocalteu (F-C) method, ORAC, and DPPH assays [27]. The F-C method, a simple technique, assesses antioxidant capacity based on the single electron transfer from various substrates, such as phenols or other antioxidant compounds [12], to the complexed Mo (VI) present in the F-C reagent. This study revealed that TVE has an antioxidant compound content of 61.2 ± 3 mg GAE/L, a value lower than that of fruit juices, but comparable to that of goat and/or cow milk, and elderflower beverages [29,31]. To confirm the presence of antioxidant molecules, TVE was also analyzed, showing a content lower than Maqui fruit [32], but higher than roasted Yak-kong [33] or Koji mold (Aspergillus sp.) [34]. The correlation between the antioxidant compound content measured by F-C and the ORAC values of TVE was determined using regression analysis. The determined correlation coefficient (R^2) was 0.998, suggesting that the redox activity of the extract could be attributed to phenol-like/antioxidant compounds. To further investigate the antioxidant capacity, the DPPH assay was also performed on TVE. The DPPH radical, widely used to evaluate free radical scavenging activity due to the simplicity of the reaction, showed that the DPPH radical scavenging activity of TVE was comparable to that determined for various vegetable and fruit extracts [7, 13, 19]. The antioxidant capacity of TVE was also assessed through an oxidative hemolysis inhibition assay, which evaluates the inhibition of free radical-induced membrane damage in sheep erythrocytes by antioxidants. The results obtained reflect biologically relevant radical scavenging activity and microlocalization of antioxidants. Erythrocyte hemolysis was monitored spectrophotometrically (A524 nm) every 20 minutes from the addition of AAPH, which induces free radical generation. In the absence of the extract, the percentage of erythrocyte hemolysis was approximately 6% at 40 minutes after the onset of oxidative stress, rising to 100% after 100 minutes (Figure 2). Conversely, in the presence of the extract, the degree of hemolysis

remained constant (~6%) up to 140 minutes, indicating its radical scavenging activity. Interestingly, this result suggests that TVE performs better than ascorbic acid.

PROMPTING KERATINOCYTES HEALING ACTIVITY

The biochemical mechanisms underlying the beneficial effects of TVE have been investigated using a well-established cell model based on scratched HaCaT monolayers. Specifically, the biological effects of TVE were evaluated through robust quantitative analysis using time-lapse video microscopy (TLVM), followed by a study of key biomarkers to elucidate the molecular mechanisms involved in tissue repair at both gene (MMP-2, MMP-9, collagen I, and elastin) and protein (integrins, collagen I, elastin, and Aqp3) levels [36]. TVE was able to support growth at all tested dilutions, as evidenced by a significant increase in cell viability after 24 and 48 hours. In particular, TVE supplemented at concentrations between 3% and 5% v/v in the medium demonstrated optimal efficiency.

Wound closure was evaluated using TLVM, monitoring monolayers during the healing process at various time points (0, 6, 12, 24, and 48 hours) for both the control and TVE-treated samples. All TVE dilutions accelerated wound repair compared to the control. While no significant difference was observed between treatments and the control at early stages, a significant divergence emerged after 10 hours, particularly with samples treated with 5% and 10% v/v TVE, which outperformed the control. Furthermore, a slight, albeit non-significant, difference was noted between the 5% and 10% TVE treatments, primarily within the 10–20 hour range. A confluence of 80% was achieved by the 19th hour for the 5% v/v TVE treatment, whereas it took approximately 11 hours for the 10% treatment. The 3% treatment, while slightly slower, still significantly surpassed the control in achieving complete scratch repair. MMP-2 gene expression was found to be elevated after 6 hours of treatment with all TVE dilutions and decreased after 24 hours compared to the control, where expression was upregulated at 24 hours, likely due to the delayed scratch repair necessitating continued matrix remodeling for keratinocyte migration. Matrix metalloproteinases (MMPs), a large family of ubiquitously expressed zinc-dependent enzymes with proteolytic activities, are involved in both physiological and pathological conditions, including epithelial-to-mesenchymal transition. MMP-9 modulation by TVE was observed, but with a delayed time frame. In control samples, MMP-9 expression was higher at 24 hours than at 6 hours, while this upregulation was less pronounced in TVE-treated samples. During healing, proper assembly of key matrix proteins is crucial for functional tissue formation, whereas dysregulated collagen or matrix component expression can lead to fibrosis. Consequently, collagen I expression, evaluated via RT-PCR, was found to be increased by TVE treatments after 24 hours, consistent with the repair timing observed in the TLVM experiments (scratch test). Elastin expression was observed only at 24 hours, with a notable beneficial effect of TVE, particularly at low doses (3% v/v). Collagen I, elastin, and integrin αV expression were also increased in the presence of 3% and 5% v/v TVE compared to the control. Additionally, the water channel protein Aqp3, a specific biomarker for water transport along an osmotic gradient, was upregulated, indicating a potential positive role of TVE in dermal regeneration.

This in vitro study, using human keratinocytes, clarifies the molecular basis for TVE's efficacy. All tested doses were non-cytotoxic and enhanced cell viability and proliferation. Regarding scratch repair, TVE increased cell migration compared to the control, appropriately modulating metalloproteinase expression timing for consistent and efficient matrix remodeling. Moreover, TVE increased collagen I and elastin expression, and positively modulated integrin and aquaporin [3], all of which contribute to improved dermal tissue remodeling during healing.

Therapeutical applications

ACUTE SKIN WOUNDS

The efficacy and tolerability of TVE (Fitostimoline® Plus gauze and cream; a specific TVE formulation for the treatment of acute superficial skin lesions) was compared with a product containing hyaluronic acid (Connettivina® Bio Plus gauze and cream) in a single-center, parallel-group, randomized trial involving adults over 18 years of age with acute skin lesions resulting from burns, trauma, or surgical wound dehiscence [37]. Sixty patients meeting the inclusion criteria were enrolled and randomly assigned to receive either Connettivina® Bio Plus (Fidia Farmaceutici S.p.A., Abano Terme, Italy) (Group A) or Fitostimoline® Plus (Farmaceutici Damor S.p.A., Napoli, Italy) (Group B) in the form of cream and gauze for a six-week observation period. A computer-generated block randomization was prepared by an investigator not clinically involved in the study. Patients were treated as follows: every 24 hours, the wound bed was uniformly covered with cream, followed by the application of soaked gauzes, which were then covered with sterile gauze; bandaging was performed as needed.

There were no significant differences between the two groups in terms of age, sex, baseline skin lesion area, or wound etiology. The average number of days elapsed between the initial visit (V1) and complete healing or the final visit was 42.3 ± 6.2 days in Group A and 35.4 ± 8.2 days in Group B. Complete wound healing was achieved in 17 patients in Group A and 28 patients in Group B. The greater effectiveness of Fitostimoline® Plus was statistically significant ($p = 0.001$, risk ratio 0.15, 95% CI 0.04 to 0.62). The wound healing rate tended to be higher in Group B; however, this difference did not reach statistical significance. A reduction in fibrin and wound edge maceration was observed in both treatment groups, but Group B showed more favorable results regarding fibrin reduction on the wound bed ($p = 0.04$, risk ratio 0.2, 95% CI 0.02 to 1.70). The authors concluded that both Connettivina® Bio Plus and

Fitostimoline® Plus are safe and effective for treating acute superficial skin lesions. Fitostimoline® Plus was shown to be more effective than Connettivina® Bio Plus in promoting the healing of acute superficial skin lesions, particularly in wounds with fibrin presence.

DIABETIC FOOT ULCERS (DFUS)

The efficacy and safety of TVE and polyhexanide (Fitostimoline® hydrogel/Fitostimoline® Plus gauze) versus saline gauze dressings in patients with DFUs was assessed in a monocentric, two-arm, open-label, controlled trial in patients with DFUs (Grades I or II, Stage A or C, based on the Texas classification [41] randomized to 12 weeks of dressing with Fitostimoline® hydrogel/Fitostimoline® Plus gauze or saline gauze [42]. The primary outcome was the proportion of patients who, at the end of the study period, were categorized as complete responders—defined as 100% wound re-epithelialization without medications. Secondary outcomes included the time to complete re-epithelialization from the initial visit (V1) at any interval; the proportion of patients categorized as partial responders (≥50% reduction in the product of the two longest perpendicular diameters from baseline); the reduction of wound area in non-complete responders (<50% reduction in the product of the two longest perpendicular diameters from baseline); the evaluation of local signs and symptoms of the wound and perilesional skin; and treatment safety and tolerability. Thirty-seven patients (18 in the Fitostimoline® hydrogel/Fitostimoline® Plus gauze group and 19 in the saline gauze group) completed the study. Anthropometric, clinical, and biochemical parameters, and wound characteristics were similar between groups at baseline. On average, patients were 74% male, equally distributed among groups, with an average age of 64 years and a body mass index of 30.5 kg/m². Blood glucose control and fasting plasma lipids were similar between groups. The etiology was mostly neuropathic. The proportion of complete responders was similar between the two groups (61% vs. 74%, p = 0.495, Fitostimoline® hydrogel/Fitostimoline® Plus gauze vs. saline gauze, respectively), without a clinically significant difference. In non-complete and partial responders (39% vs. 26%, Fitostimoline® hydrogel/Fitostimoline® Plus gauze vs. saline gauze, respectively), there was a significant reduction in the largest and smallest diameters, depth, and area of the wounds in both groups, without significant differences between groups. From the third visit (V3) to the sixth visit (V6), a significant reduction in erythema and wound bleeding scores was observed in the Fitostimoline® hydrogel/Fitostimoline® Plus gauze group compared to the saline gauze group. Similarly, from V3 to V4, a significant reduction in pain, burning, and itching scores was observed in the Fitostimoline® hydrogel/Fitostimoline® Plus gauze group, with a complete absence of these symptoms from V5 to V7 only in the Fitostimoline® hydrogel/Fitostimoline® Plus gauze group. Regarding perilesional skin signs and symptoms, from the second visit (V2) to the fifth visit (V5), a significant reduction in erythema, edema, and dry and flaky skin scores was observed in the Fitostimoline® hydrogel/Fitostimoline® Plus gauze group compared to the saline gauze group, while pain, burning, and itching symptoms decreased similarly in both groups. These findings support the conclusion that Fitostimoline® hydrogel/Fitostimoline® Plus gauze and saline gauze dressings have similar efficacy for DFU local care in terms of complete wound healing in a clinical setting; however, a significant improvement in local signs and symptoms of the wound and perilesional skin was observed only in the Fitostimoline® hydrogel/Fitostimoline® Plus gauze group, suggesting greater patient comfort during treatment.

SPLIT-THICKNESS SKIN GRAFT DONOR SITES (STSG)

Split-thickness skin grafting (STSG) is a reconstructive technique widely used in plastic surgery. An STSG donor site represents a partial-thickness wound at high risk for infections, making the development of new, effective dressings to promote rapid wound healing highly important. A single-blind, randomized trial was conducted to compare two dressings [43]. The study included 61 adult patients, all with Fitzpatrick skin types II and III. Of these, 59% were male, and the mean age was 70.3 ± 16.5 years. Thirty-three donor sites were randomized to Fitostimoline® Plus dressing, and 28 to a product containing hyaluronic acid (Connettivina® Bio Plus dressing). All donor sites were digitally photographed at regular intervals during the wound healing process and again three months later. The primary endpoint was to compare the long-term scar outcome of STSG donor sites three months post-surgery. Scar quality was assessed using two different scar scales: the Vancouver Scar Scale (VSS) and the Manchester Scar Scale (MSS). In both scales, a lower score indicates a better scar outcome. The average VSS total score was 3.6 for Fitostimoline® Plus and 5.5 for Connettivina® Bio Plus (p = 0.017). Similarly, the mean MSS total score was 7.4 for Fitostimoline® Plus dressing and 9.2 for Connettivina® Bio Plus dressing (p = 0.03). Both dressings demonstrated positive results, but Fitostimoline® Plus, in both impregnated gauze and cream forms, showed significantly better scarring of the donor site. Although the time to epithelialization was similar in both treatment groups, these results suggest that Fitostimoline® Plus may provide superior long-term scar outcomes compared to Connettivina® Bio Plus.

GYNECOLOGY

Vulvovaginal atrophy (VVA), a prevalent condition in postmenopausal women [44], is characterized by decreased vaginal estrogenization. While hormonal therapies exist, non-hormonal alternatives are sought due to potential adverse effects 44. Notably, hyaluronic acid has shown greater efficacy than estrogen in alleviating VVA symptoms [45]. Recent evidence highlights the potential of aqueous extracts of Triticum vulgare (TVE) in cream [46] and pessary [47] formulations to reduce VVA signs and symptoms in postmenopausal women, suggesting comparable efficacy to hyaluronic acid in tissue re-epithelialization and inflammation reduction.

Consequently, Damor TVE formulations (Fitostimoline®) are utilized clinically as a hyaluronic acid alternative.

A study by Mainini et al. [48] investigated the impact of patient choice on long-term adherence to Damor TVE treatment (cream or pessaries) in 91 women with VVA. Both formulations significantly reduced the Total Symptoms Score (TSS) over three months, with high patient satisfaction and no significant differences between groups. Although lacking a comparator, the findings suggest that patient involvement enhances treatment compliance, and the observed TSS reduction aligns with the efficacy reported for hyaluronic acid [45], supporting the potential of TVE in VVA management [46, 47].

Vulvovaginitis, an inflammatory condition of the vulva and vagina [49], often infection-related but also linked to hormonal changes [50], is commonly treated with antibiotics or antifungals 52. A prospective study by Riemma et al. [52] evaluated Fitostimoline® Septagel (TVE hydrogel) in 615 women with suspected vulvovaginitis, demonstrating high rates of complete symptom resolution (94.1%) within approximately two weeks, with significant reductions in all evaluated symptoms and a slight decrease in Gardnerella vaginalis and Candida albicans.

Cervical ectropion, a physiological condition [53] with higher prevalence in specific hormonal states [54, 55, 56], is often treated with ablation [57]. Manna et al. [58,59,60] explored topical TVE ovules for cervical ectropion in women awaiting surgery. After two months, the TVE group showed a significant reduction in ectropion area and improved symptoms (postcoital bleeding, leucorrhea, dyspareunia) compared to a control group, suggesting TVE's potential in managing this condition.

Conclusion

TVE has a wide range of therapeutic benefits, also thanks to its mode of action.

All the evidences reviewed in this paper suggest that TVE can be used as an effective treatment for wound care and gynecology.

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