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Efficiency of hypericum perforatum, povidone iodine, tincture benzoin and tretinoin on wound healing

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ABSTRACT

Different topical agents have been used to accelerate wound healing. The purpose of this study is to compare the safety and efficacy of topical application of the extract of *Hypericum perforatum* (HPE), povidone iodine (PI), tincture benzoin (TB) and tretinoin (T) on surgical wound healing. Ten adult female, Wistar albino rats were included in the study. HPE, PI, TB and T solutions were applied on the wounds. After seven days, tissue samples were collected and inflammatory cells, re-epithelialization, granulation tissue, angiogenesis, collagen accumulation, hemorrhage and lysis of cells were investigated histopathologically. No dermal toxicity was noted. HPE, TB, PI have all showed good epithelialization and granulation, but HPE showed the most advanced stage of healing within a short period of time. HPE had significantly higher values of re-epithelialization and collagen accumulation, but lower inflammatory cell count and granulation tissue. TB had the second best in re-epithelialization, collagen accumulation and the highest granulation tissue. PI induced better reepithelialization and granulation than the control group with remarkable cell lysis. As a result, HPE can be a safe, effective, and cheap agent that can be used for surgical wounds.

1. Introduction

Postoperative wound healing is as important as the surgery because of aesthetic outcomes. Many treatments have been used for accelerated healing with less scar formation. However, the healing process depends not only on the closure technique but also patients' habits such as smoking, hygiene and additional diseases. Apart from local infections and trauma, medical treatments are given to reduce the amount of scar formation (Lv and Xia, 2018). Best medical treatment with nontoxic chemicals for tissue regeneration and wound healing is still unknown as the healing process is not completely explained. Particularly, topical applications are considered to be safer and more effective on healing mechanisms than systemic treatments (Hoogewerf et al., 2013).

Traditional therapies such as roots, leaves or extracts of plants have been used for wound healing since the ancient times (Dorai, 2012). Among these, extracts of the aerial parts and the oil of *Hypericum perforatum* (St. John's wort) have an important place in Turkish alternative medicine (Süntar et al., 2011). *Hypericum perforatum* (HPE) has been used to treat wounds, burns, haemorrhoids, ulcers (Zorzetto et al., 2015). It has been believed to accelerate healing by increasing the stimulation of fibroblast and collagen production (Farsak et al., 2017).

Povidone iodine (PI) is generally used in modern therapy for sterilization especially for skin preparation, hand washing and wound dressing. It is also believed to decrease bleeding time and edema. In addition, PI influences initial stages of wound healing by modifying prostaglandin synthesis (Teixeira et al., 2019). PI is an antimicrobial agent against local infections which are responsible for a delay in tissue repair (Bigliardi et al., 2017).

Tincture of benzoin (TB) has been used for topical treatment of rashes, wounds and ulcers in many countries (Cincu et al., 2007). In addition, it is generally used for dressing as it is believed to be an effective antimicrobial agent and very adhesive for tapes after surgical operations (Govila, 2005). It is also suggested to increase healing by improving epithelialization (Karadsheh et al., 2015).

Tretinoin (T), a derivative of retinoic acid (RA) is used for acne vulgaris, psoriasis and skin aging (Cao et al., 2008). In addition to its use

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in systemic diseases, tretinoin increases granulation and production of growth factors including vascular endothelial growth factor, thus increasing angiogenesis and dermal vascularization (Xu and Kopp, 2012). Therefore, tretinoin stimulates epidermal and dermal wound healing (Mukherjee et al., 2006).

The healing process includes inflammatory, proliferative and remodelling phases (Jaja and Allen-Taylor, 2020). In clinical practice, TB a nd PI have been widely used in wound dressing. HPE is a herbal remedy that is traditionally used for wound healing. T is shown to be efficient at healing when taken orally. In this study, the safety and efficacy profiles of 4 different commonly used agents in our clinical practice (*Hypericum perforatum*, providing iodine, tincture of benzoin and tretinoin) that affect different stages of the healing process were evaluated and compared.

2. Materials and methods

2.1. Animals

Ten female Wistar albino rats, weighing between 286 and 357 g were kept individually in cages at a constant room temperature (23 ± 2 °C) with 65–75% of humidity. The rats had free access to food and water and were maintained under a 12-h light/dark cycle. The study was approved by the Gazi University Faculty of Medicine Experimental Animal Local Ethics Committee (90–10842) and followed the international guidelines on animal experimentation and biodiversity. 5 different wounds were created in each rat to form groups. These wounds were marked for application of HPE, TB, PI and T. One area left untreated to form the control group. One rat died at the third day of follow-up, due to her cardiac problems.

2.2. Chemicals

One hundred grams of dried aerial parts of *Hypericum perforatum* were obtained from a local herbalist shop (Akhtar) in Ankara, Turkey. After verification of the plant by a specialist; the aerial parts were coarsely crushed in the laboratory and extracted for 3 hours with a soxhlet apparatus using hydroalcoholic solvent system (Ethanol:Water; 80:20, w/w) as written in monographs and International pharmacopeias (European Medicines Agency, 2009). The yield of hydroalcoholic extract of HPE was 27.4%. Hypericin and hyperforin were accepted as the main active substances of HPE while the flavonoids, xanthones and essential oils were the other major groups responsible for the effects of the extract (Wolfle et al., 2014).

Tincture benzoin (TB) which is a resin dissolved in ethanol, was prepared in a community pharmacy and standardized according to National Formulary (Guven, 2011). Fresh TB was used for the experiments.

Povidone iodine (PI) is an iodine complex with polyvinylpyrrolidone which is used regularly in hospitals for antibacterial purposes. Povidone iodine solution (Dermosept-Baticonol 10% Antiseptic Solution) was obtained from Aktas Saglik Kozmetik A.S, Istanbul, Turkey.

Retinoic acid or tretinoin(T), a derivative of vitamin A, was dissolved in propylene glycol and mixed with 96% ethanol and butylhydroxytoluene. Concentrated alcohol had been used to avoid deterioration of T from environmental factors. Topical tretinoin solution of 0.05% was applied directly to the wounds. As skin irritation is a common complication of topical use of tretinoins, dressings were removed after 10 min.

2.3. Linear incision wound model

Rats were anesthetized with 30 mg/kg ketamine (Ketalar, Pfizer, New York, USA). Dorsal hairs were shaved with a razor and sites were cleaned with chlorhexidine. Five horizontal paravertebral incisions with 1 cm size were made with a sterile blade at 1.5 cm from the dorsal midline on each side (Fig. 1). Incisions were 2 cm apart from each other.



Fig. 1. Linear incision wound model.

Incisions included dermis and subepidermal tissue and went deep until the muscle tissue was exposed. The incisions were sutured primarily with 3.0 polyglactin. All operations were carried out by the same surgeon in the marked areas.

0.3 mL of *Hypericum perforatum* extract, solutions of T, PI and TB were applied topically with the help of a dropper on cotton buds on incisions twice a day for seven days followed by dressings with cotton sponges. There was no intervention after dressing in the control group. To avoid the individual differences, we marked 5 different localizations and incised those areas in each rat. Localization of topical agents were changed for each group to obtain homogenous distribution for vascularization (Fig. 2). Topical applications were performed with cotton buds only on the incision sites and sites were closed with sponges to avoid interactions between different agents. All topical applications, saturation and postoperative care were carried out by the same physician to avoid any technical and handy differences.

The rats were treated humanely and ideal wound care that consists of clean and warm environment with adequate moisture were provided.

On the postoperative 7th day, all animals were sacrificed with overdose of anesthetics. Square shaped and full thickness samples were obtained by leaving a 10 mm skinless region around the sample. The samples were collected by the same surgeon and fixed with 10% formalin solutions for histopathological examination. Scar thickness was measured by a a caliper and tension strength was calculated with tensiometer and recorded in megapascals (MPa) in each group.

2.4. Histopathological analysis

After fixation with formalin, the samples were processed and put into paraffin. Samples were sectioned into 5 μm pieces and stained with hematoxylin and eosin (HE). All specimens were analyzed by a single blinded examiner. The tissues were examined by light microscope under 40× magnification. The steps of wound healing including the parameters of inflammatory cell count (leukocytes, monocytes, macrophages, lymphocytes), re-epithelialization, granulation tissue, angiogenesis, collagen accumulation were investigated (Lazarus et al., 1994). Any side effects and toxicity such as hemorrhage, edema, fibroblasts or cell lysis were noted.

Sultana et al. (2009), standardized quantitative evaluation of healing by scoring parameters including granulation tissue, inflammatory infiltration, types, patterns and accumulation of collagen. These parameters were modified according to previous studies and added epithelialization and angiogenesis (Gupta and Kumar, 2015; Salehi et al., 2017). The amount of granulation was also examined according to Rao et al. (2015).

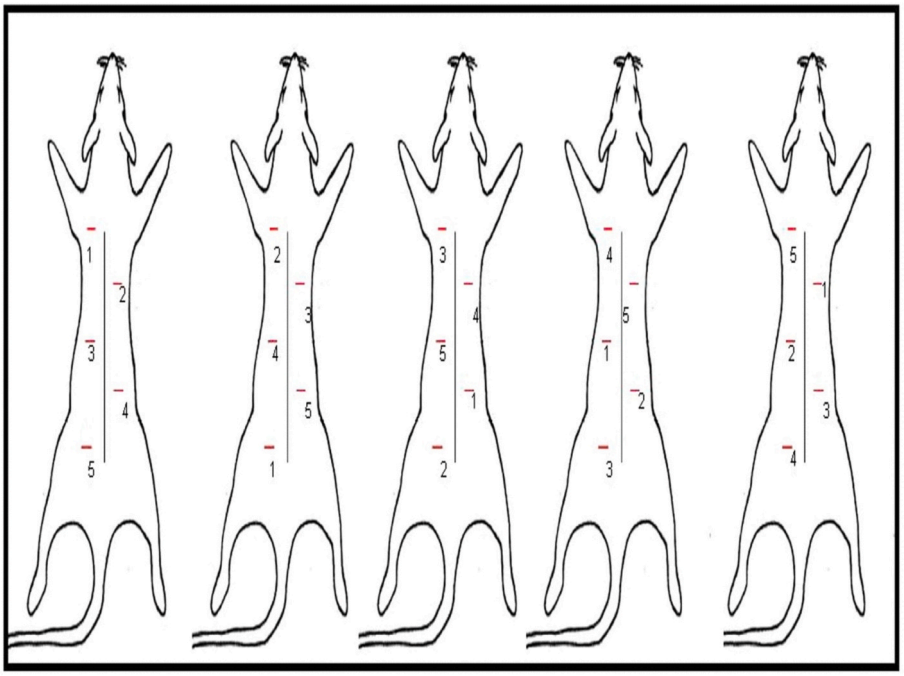


Fig. 2. The topical applications were applied at different sides on each group. In this way, results were not affected from the vascularization of different sides of rat's dorsum. 1:Hypericum Perforatum Extract 2:Tincture Benzoin 3:Povidone Iodine 4:Tretinoin 5:Control Group.

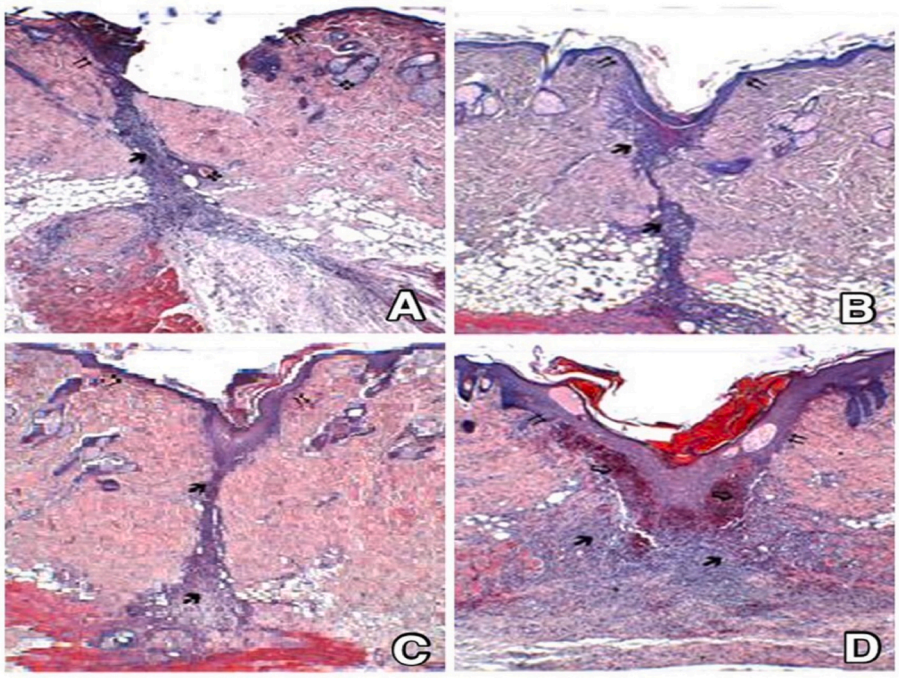


Fig. 3. All specimens were investigated on x40 magnification with Hematoxylin- Eosin under light microscope. Sections from A: Control group, B: Tincture Benzoin group, C: *Hypericum perforatum* group and D: Povidone Iodine group show epithelialization (twin black arrow) and granulation tissue (thick black arrow). On the control group, partially completed epithelium, granulation tissue and degenerated hair follicles (⬡) were seen. Tincture benzoin showed good epithelialization and dense granulation tissue. *Hypericum perforatum* showed completed re-epithelialization and decreased amount of granulation tissue. Povidone iodine showed dense granulation tissue and hemorrhage (thick white arrow).

2.5. Statistical analysis

Power analysis of the study showed that the number of animals (10) was sufficient for statistically significant p values. Unfortunately, one animal was lost due to cardiac problems. Therefore, all data was limited to 9 rats in all groups. Effect size was calculated as 1.63 and actual power was 0.91 using GPower3.1.

Statistical analysis was done with Statistical Package for the Social Sciences for Windows, version 20 (SPSS, IBM Corp, Armonk, NY, USA) The results were reported as mean ± standard deviation (SD). The differences between experimental groups were determined by Kruskal Wallis test. The statistical differences of dual comparisons were done with Mann-Whitney-U test. P values less than 0.05 were considered as statistically significant. Statistical differences between study groups were evaluated by Bonferroni correction. Consistency of variables was done with Shapiro-Wilks's test. For comparison of data from same subjects, Student's t-test was used.

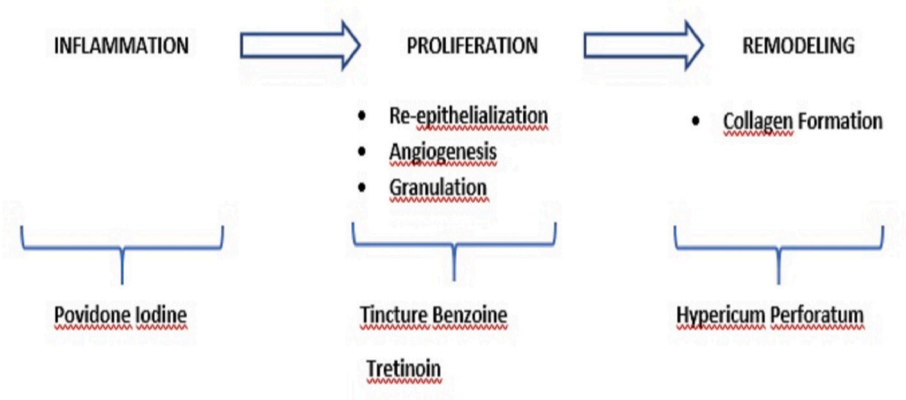


Fig. 4. Stages of Physiological Healing Process and the stages of the wound healing affected by topical agents at the time of histopathological examination (at the 7th day).

3. Results

Macroscopic evaluation showed similar healing processes in each group. There was no toxic reactions or adverse effects. Histologic scoring system was based on inflammatory cell count, re-epithelialization, granulation tissue, angiogenesis, collagen accumulation, cell lysis and hemorrhage. Inflammatory cells were calculated and scored between 0 and 3 according to cell count. Re-epithelialization was scored in terms of completion and maturation. Granulation, collagen accumulation, cell lysis and hemorrhage were scored as absent to mature between 0 and 3. Angiogenesis was scored considering the number of vessels (Table 1). Data calculated with histologic scoring system between different treatment agents were shown in Table 2.

Inflammatory cells were the highest in PI applied group. PI, TB and T all had higher inflammatory cells than the control group ($p = 0.001$, Kruskal Wallis test). HPE had the lowest inflammatory cells among PI, TB and T ($p = 0.02$, $p = 0.05$, $p = 0.05$; respectively, with Kruskal Wallis test). HPE showed even lower inflammation than the control group ($p = 0.003$; Mann-Whitney *U* test) (Graph 1).

There was intense re-epithelialization in the edges of the wound in HPE applied group ($p = 0.001$; Kruskal Wallis test). PI, TB and T also showed higher re-epithelialization than the control group ($p = 0.002$, $p = 0.00$; $p = 0.003$, respectively; Mann-Whitney *U* test). A partial and immature re-epithelialization were observed in the control group as there was an increase in number of cells at the borders of the wound with tissue re-organization (Graph 2).

Collagen deposition was the highest in the HPE applied group ($p = 0.00$, Kruskal Wallis test). The collagen fiber sequences were remarkably smooth. TB also showed good collagen synthesis with dense type I collagen fibers in dermis ($p = 0.002$; Kruskal Wallis test). T also showed higher collagen depositions than the control group ($p = 0.02$; Mann-Whitney *U* test). However, amount of collagen showed no significant difference between PI and the control group ($p = 0.357$; Mann-Whitney *U* test) (Graph 3).

PI and TB showed the same amount of granulation tissue which were higher than T applied group and the control group ($p = 0.003$ and $p = 0.006$, respectively; Kruskal Wallis test). HPE showed the lowest granulation ($p = 0.002$; Kruskal Wallis test) (Graph 4).

After surgical trauma, all groups including the control group showed angiogenesis. No necrosis was seen. PI, TB and T groups showed significantly higher amount of angiogenesis than the control and HPE groups ($p = 0.002$; Kruskal Wallis test). Angiogenesis was the lowest in the HPE ($p = 0.001$; Kruskal Wallis test) (Graph 5).

Only in PI applied group, cell lysis and hemorrhage, and perivascular edema were present with various lymphocytes and capillary vessels ($p = 0.00$; Kruskal Wallis test). Histopathologic examination results were shown in Fig. 3.

No dehiscence was found in all wounds. Tensile strengths were found significantly similar in groups which were significantly higher than the control group ($p = 0.001$, Kruskal Wallis test). Although found insignificant HPE, TB and T showed more tensile strengths (7.8 ± 0.82 MPa, 6.24 ± 0.54 MPa and 6.14 ± 0.72 MPa, respectively). Tensile strength in PI group showed 5.8 ± 0.8 MPa.

4. Discussion

The wound healing process consists of a complex cascade of phases including inflammation, proliferation, and remodelling. The first stage of the healing process is the inflammatory stage where blood vessels contract, thrombocytes and platelets aggregate to reestablish homeostasis. Leukocytes migrate to the wound area within the first two days. Mastocytes, gamma-delta and Langerhans cells secrete chemokines and cytokines. After 48 h, macrophages release growth factors especially prostaglandin growth factor (PDGF) and vascular endothelial growth factor (VEGF) which are necessary for the proliferative stage. The proliferative stage is responsible for angiogenesis, fibroplasia and re-epithelialization. This stage generally begins within the first 2 days and can last up to 2 weeks. Fibroplasia begins with granulation. Granulation tissue is formed approximately 4 days after onset of the lesion. Fibroblasts produce collagen near the border of the wound. The last stage of healing is re-modelling which can last for a year or even more (Rao et al., 2015). In this stage, keratinocytes cover the surface of the lesion and collagen fibers become thicker; blood vessels, fibroblasts and inflammatory cells disappear from the area (Gonzalez et al., 2016). Paterniti et al. (2010), showed that anti-inflammatory activity was required in order to shorten the healing period, as well as for minimal

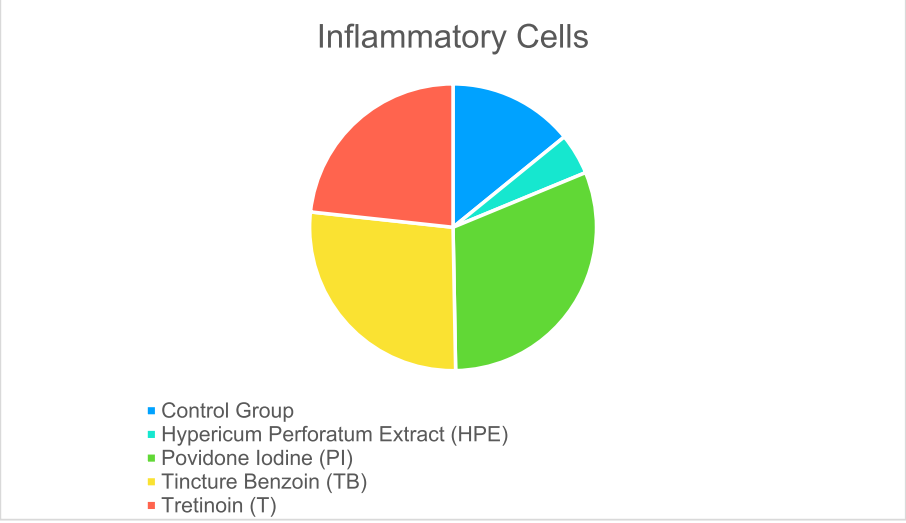
Table 1
Wound healing process evaluation by Histological Score Scale first described by Sultana et al.

Score	İnflammatory cell count	Re-epithelialization	Granulation tissue	Angiogenesis	Collagen accumulation	Cell lysis, hemorrhage
0	Absent	Absent	Absent or immature	Absent	Absent	Absent
1	Mild	Partially completed	Mild	<5 vessels	Mild	Mild
2	Moderate	Completed but immature or thin	Moderate maturation	6-10 vessels	Moderate	Moderate
3	Generous	Completed and mature	Mature	>10 vessels	Generous	Generous

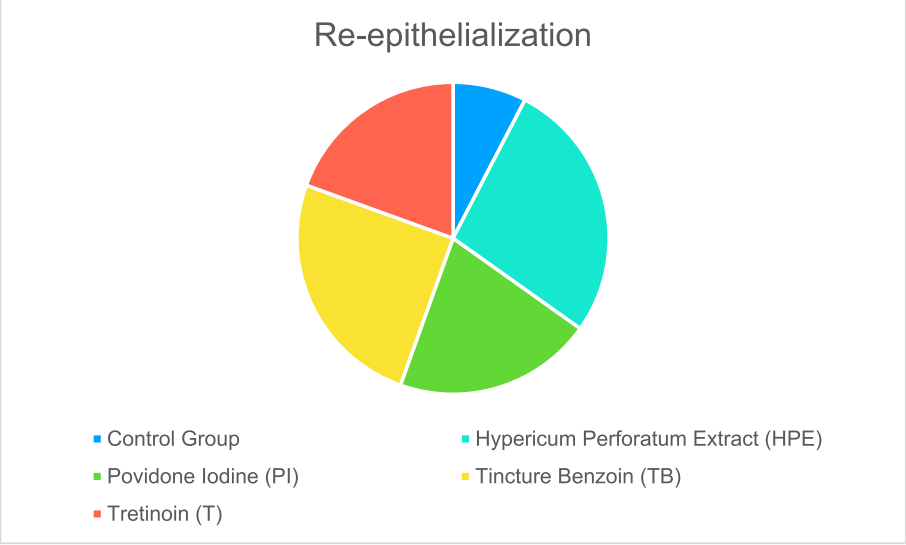
Table 2
Comparison of elements of wound healing between *Hypericum Perforatum*, povidone iodine, tincture benzoin, tretinoin and the control group[a].

	Control Group	Hypericum Perforatum Extract (HPE)	Povidone Iodine (PI)	Tincture Benzoin (TB)	Tretinoin (T)
Inflammatory Cells	1.22 ± 0.66	0.44 ± 0.52	2.67 ± 0.50	2.33 ± 0.50	2.01 ± 0.60
Re-epithelialization	0.78 ± 0.44	2.78 ± 0.44	2.11 ± 0.60	2.56 ± 0.52	1.99 ± 0.60
Granulation	1.56 ± 0.52	0.78 ± 0.44	2.67 ± 0.50	2.67 ± 0.50	1.89 ± 0.33
Angiogenesis	1.56 ± 0.52	1.16 ± 0.52	2.56 ± 0.52	2.78 ± 0.44	2.44 ± 0.52
Collagen	1.33 ± 0.50	3.0 ± 0	1.56 ± 0.52	2.33 ± 0.50	2.30 ± 0.52
Lysis/Hemorrhage	0	0	2.44 ± 0.72	0.44 ± 0.50	0

[a] The results were given as the mean ± standard deviation.



Graph 1. Distribution of inflammatory cells by topical agents at the end of 1st week.

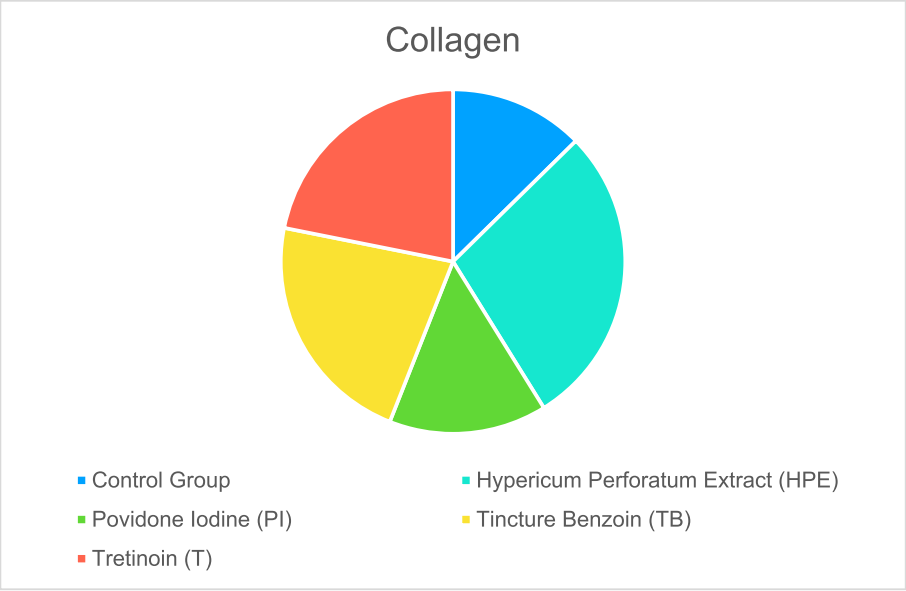


Graph 2. Re-epitalialization density according to topical agents at the end of 1st week.

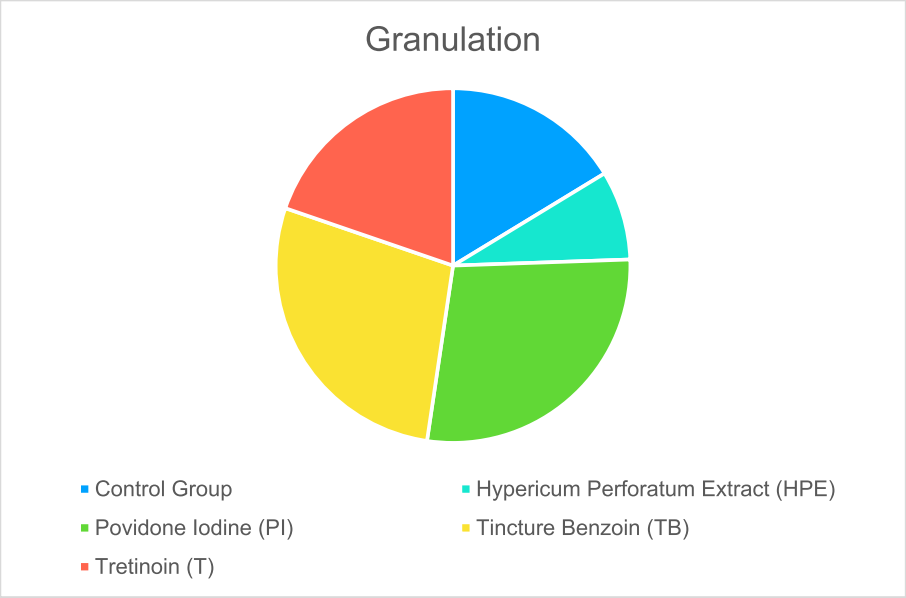
pain and scar. In this study, the modulating effects of topical administration of *Hypericum perforatum* extract, solutions of povidone iodine and tincture of benzoin and tretinoin at the first week of wound healing were investigated.

Topical agents are useful to accelerate and improve the healing process. HPE showed significantly low amount of inflammatory cells but high amounts of re-epithelialization and collagen formation. PI showed significantly high amounts of inflammatory cells, vascular structures, re-epithelialization and granulation. TB had also good epithelialization, and high amounts of collagen formation, granulation and vascular structures. T had high amounts of vascular structures, collagen formation and re-epithelialization. According to our results, HPE showed the most advanced stage of recovery (Fig. 4). Tensile strengths of the wounds showed correlation with the collagen deposition and found similar in each group.

Hypericum perforatum, also known as St. John's wort, is used orally for ulcers, mild depression, neurological disorders, diabetes mellitus, common cold, gastrointestinal disorders and topically for burns and



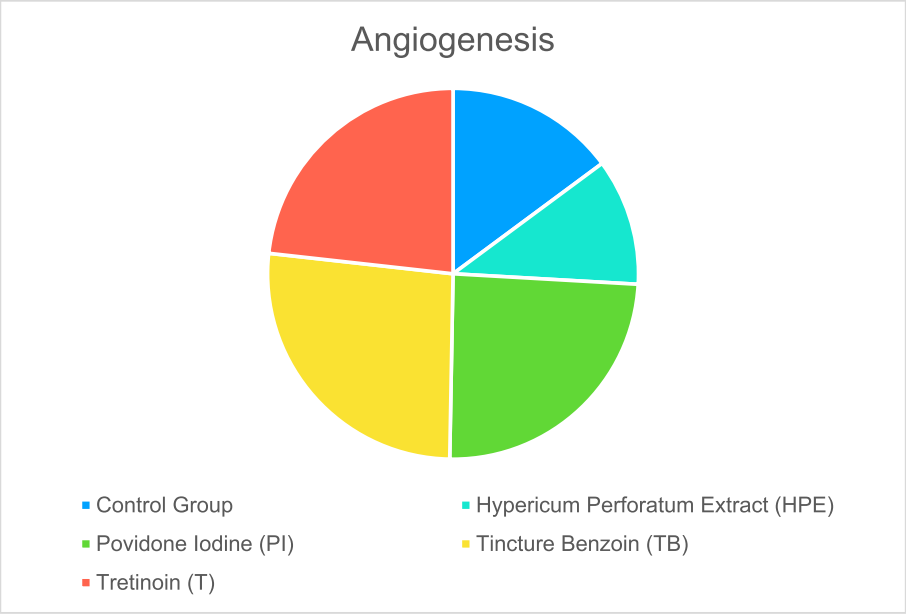
Graph 3. Collagen deposition in each group at the end of 1st week.



Graph 4. Granulation tissues according to topical agents at the end of 1st week.

wound healing (Saddiqe et al., 2010; Suntar et al., 2010; Izol et al., 2019). The plant is consistent of numerous compounds that provide various biological activities. Naphthodianthrones, phloroglucinols, flavonoids, bioflavonoids, phenylpropanoids are believed to be responsible for less inflammation period, and enhanced fibroblast migration and collagen deposition (Butterweck, 2003). Hypericin, pseudohypericin and hyperforin are the main anti-inflammatory components (Suntar et al., 2010; Mainetti and Carnevali, 2013). Hyperforin is found to inhibit the growth of *Gram-positive* bacteria (Uchida et al., 2008) while hypericin exert antiviral, antimicrobial, antioxidant and antitumor properties (Tavakoli et al., 2020). Flavonoids and xanthones increase the polygonal fibroblasts which stimulate collagen synthesis, and influence epithelial cell proliferation and migration (Ozturk et al., 2007). Pseudohypericin, hypericin and hyperforin are believed to accelerate wound healing (Süntar et al., 2011; Castro et al., 2012; Solati et al., 2021). Additionally, Orcic et al. (2011) evaluated the antioxidant activity of phenolic compounds of HPE which was found to be beneficial on wound healing. Studies on caesarean scars have revealed that oily extracts of the plant increase epithelial reconstruction and reduce pain and pruritus (Samadi et al., 2010). Giuggioli et al. (2020) investigated that topical use of HPE with Neem oil showed cicatrizing and bacteriostatic effects on wounds and HPE has been suggested as a useful treatment for difficult wounds.

Histopathologically, HPE accelerated fibroblast migration and collagen formation and shorten the inflammation period to cause better re-epithelialization in vivo studies. Suntar et al. (2010) also found a significant improvement on the wound surface at the 7th day as epithelialization was almost completed. Altan et al. (2018) evaluated the effects of HPE on diabetic rats and found out that the inflammation period was shortened and number of inflammatory cells was significantly lower, formation of angiogenesis was widespread and concluded that fibroblast and collagen deposition were the cause of better healing.



Graph 5. Amount of angiogenesis in each group at the end of 1st week.

HPE was found to inhibit apoptosis and showed anti-inflammatory properties (Novelli et al., 2016).

In the present study, HPE treated wounds showed lower inflammatory cells, granulation and angiogenesis than the untreated wounds. Although we believe this result can be explained by the advanced stage of the healing process, on the contrary, Nayak et al. (2017) demonstrated that HPE had significant healing potential with a significant increase in angiogenesis. A similar result was found by Altıparmak et al. (2019) as they also found increased angiogenesis on the postoperative 3rd and 7th day with increased epithelialization and lower inflammation rates. However, they found no significant increase in angiogenesis on the postoperative 21st day. We believe the healing process is directly related with time and results may vary depending on the time when the biopsy is taken. In accordance with our study, Kiyan et al. (2014) also found the hypericum oils have antiangiogenic properties. Gunpinar et al. (2018) also found lower VEGF levels on palatal wounds which were treated with HPE oil. Lower VEGF levels are believed to be related with anti-inflammatory or antiangiogenic activites in the early stage of healing (Schempp et al., 2005; Dell'Aica et al., 2007; Lorusso et al., 2009). In addition, we found that re-epithelialization and collagen deposition were found to be significantly higher in HPE than other groups. Enhancement with more regular sequence of type I collagen formation was found in the HPE applied area. This histopathological finding supported the idea of acceleration of re-epithelialization and reduction of the wound. A previous study revealed that the plant had a collagenase inhibitory effect which supported our increased collagen accumulation finding (Dikmen et al., 2011). Therefore, HPE is believed to increase re-epithelialization (Süntar et al., 2011; Tanideh et al., 2014; Altıparmak et al., 2019). In our study, HPE healed the wound quicker than any other topical agent without any toxicity. It was observed that wounds treated with HPE passed to the last stage of healing only in 7 days. Hajhashemi et al. (2018) also showed that HPE showed significant antiinflammatory, analgesic effect after a week of usage. Gunpinar et al. (2018) also showed early maturation of the wound on the postoperative 1st week.

Povidone iodine is generally used for dressing after surgeries because of its antimicrobial effects. PI enhanced angiogenesis modified cellular mechanisms and enhanced healing by activating monocytes, lymphocytes and macrophages with proinflammatory cytokines (Arakeri and Brennan, 2011). It is also believed that it accelerated epithelialization and granulation (Vogt et al., 2006). Nakao et al. (2006) reported that topical application of a mixture of sugar and PI accelerated healing of cutaneous wounds by promoting re-epithelialization and granulation tissue formation. On the other hand, PI was found to decrease fibroblasts, keratinocytes and osteoblasts and induce necrosis and apoptosis (Teixeira et al., 2019). Arai et al. (2013) also showed the toxic effects of PI and they recommended to clean the wound with saline after dressing to minimize its cytotoxic effects. Similarly, we also found enhancement of inflammatory cell count and granulation tissue. Iodine products are known to denature cell membrane proteins and this cytotoxic effect causes cell lysis (Sun et al., 2012). We also found hemolysis, perivascular edema and cell lysis in the PI applied areas contrary to other agents.

Tincture of benzoin, a benzoin solution in alcohol, is used for its adhesive, therapeutic and odoriferous effects. It is generally used preoperatively for surgical preparation because of its adhesiveness (Cincu et al., 2007). It is believed to be an efficient antibiotic against several aerobic, anaerobic, and spore-forming bacteria, candida albicans and mycobacterium fortitum (Washer and Barcia, 1996). Therefore, it can be used in the treatment of upper respiratory disorders, laryngitis, and bronchitis. It is widely used against skin rashes, wounds and ulcers. However, the effects on wounds are still unknown (Cincu et al., 2007). In our study, TB accelerated re-epithelialization and collagen deposition. We think that the enhancement of epithelialization might be related with its adhesive effect which helps to keep wound edges together. Since data on the subject is limited, our finding of collagen accumulation requires further investigations. We also found an apparent increase of granulation and angiogenesis in this group.

Retinoic acid is used against many dermatologic disorders such as acne vulgaris, rosacea, hypertrophic scars, hyperkeratotic and dyskeratinization disorders. Retinoic acid can function as anti-inflammatory, comedolytic and sebolytic. Tretinoin which is a derivative of retinoic acid has effects on angiogenesis, collagen formation, fibroplasia and cellular differentiation and granulation (Paquette et al., 2001). Histologically, topical treatment with tretinoin induces epidermal and dermal hypertrophy and increases dermal vasculature and inflammatory cell invasion (Akdogan et al., 2009; Peseto et al., 2016). Topical treatment with tretinoin is also known to improve the healing of wounds (Muehlberger et al., 2005). In our study, tretinoin showed the highest granulation and angiogenesis rate with good collagen synthesis on the first week. However, tretinoin had the lowest re-epithelialization among

other agents.

The low number of animals is the biggest limitation of the present study. Initially, we used 10 rats but one rat was lost due to cardiac problems.

5. Conclusion

According to our results, *Hypericum perforatum* extract is found to be quite effective in wound healing, by increasing the re-epithelialization and collagen accumulation more than other agents in a short period of time. Because of anti-inflammatory and antigranulation activities, less scar formation was seen. Considering all parameters, HPE is found to be the optimal topical agent for wound healing compared to TB and PI which also showed good results. Although tretinoin had good angiogenesis and collagen formation, because of the slow re-epithelialization, its topical use was not found to be as effective as the other agents.

CRediT authorship contribution statement

Esin Yalcınkaya: Project administration, Investigation. **Mustafa Mert Basaran:** interpreting data, prepared the figures, Writing – original draft. **Mehmet Emin Tunckasık:** Data curation, Investigation. **Gulce Naz Yazici:** Formal analysis. **Çigdem Elmas:** Visualization, prepared the figures. **Sinan Kocaturk:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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