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ORIGINAL PAPER

Skin wound healing properties of *Hypericum perforatum*, *Liquidambar orientalis*, and propolis mixtures

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Abstract

Traditional formulation therapies based on natural origin compounds offer new alternatives for treatment of skin wounds. *Hypericum perforatum* (HP), *Liquidambar orientalis* (LO), and propolis have been proved to promote skin wound healing. Extracts of these compounds are traditionally used as folk remedies. They all have different effects on each phases of wound healing. Wound healing effects of the mixtures of these compounds were investigated. HP, LO, and propolis were prepared as combinations of mixtures at an equal rate. Fifty Spraque-Dawley rats were included in this study. They were divided into the following 5 groups: group 1 (control), group 2 (HP-propolis, 1:1), group 3 (HP-LO, 1:1), group 4 (LO-propolis, 1:1), and group 5 (HP-LO-propolis, 1:1:1). Two incisional wounds were made and primarily closed on the interscapular region of every rat. Formulations were applied daily on the wounds. Biopsies were taken on days 3, 7, and 21 postoperatively from every rat. Histopathological and tensile strength parameters were analyzed. Angiogenesis and epithelialization rates were significantly higher in treatment groups compared with control ($p < 0.05$). Inflammation was significantly lower ($p < 0.05$) in treatment groups compared with control. There was no significance in tensile strength between groups. There was no difference between treatment groups. *Hypericum perforatum*, *Liquidambar orientalis*, and propolis have all improved wound healing in incisional wounds. Although they produced different effects on various parameters, mixtures of these compounds ensure a more stable response to wounds. As a result, we can mention about a positive synergy between the compounds. Level of Evidence: Level III, Experimental study.

Keywords Combination therapy · *Hypericum perforatum* · *Liquidambar orientalis* · Propolis · Traditional therapy · Wound healing

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Introduction

Skin wound healing consists of systematically overlapping processes which forms the basis of surgery. The ultimate goals of a healing wound are minimum scarring with advanced epithelialization. Enhancing wound healing processes improves final results of surgical treatments such as reducing scar formation and improving properties of the new skin. A broad array of modern and traditional therapies has been developed in stimulating skin regeneration. Traditional healing agents provide cost-effective, clinically efficient, and simply accessible alternatives among wound care modalities. Herbal and animal derivative compounds are commonly used and are effective in various phases (inflammation, proliferation, and maturation) of the wound healing process [1]. Another advantage of natural compounds is that they could be combined as mixtures and formulations which may have synergistic effects [1]. This may allow the development of innovative therapeutic treatments which improves skin wound healing.

Hypericum perforatum (HP), also known as Kantaron, is long been used throughout the world for various purposes. In traditional medicine, HP is used for gastritis, ulcers, various skin diseases, dermal injuries, burns, bedsore treatments, and moderate-type depressions [2–5]. Hyperforin, hyperisin, hyperozid, isoquersitrin, rutin, and epikatesin are some of the effective components of HP [6]. Hyperforin is shown to be the most effective wound healing component among the flavonoids of HP [7]. The wound healing effect of HP is attributed to shortened inflammation period (anti-inflammatory effect), increased resistance to infection, enhanced fibroblast migration, and collagen deposition [6].

The oily extract is the basic form of the traditional usage of HP. *Hyperici oleum* is mainly composed of the flowering aerial parts of HP macerated in olive oil. Studies have also revealed that olive oil has positive effects on wound healing but the synergistic effect of *Hyperici oleum* is superior [8, 9]. This eye-opening finding leads us to investigate wound healing mixtures and formulations which may have superior effects on what is already revealed. As valuable sources of therapeutic substances, natural compounds are expected to play a primary role in the healthcare. Thus, synergistic effects of healing agents have been investigated for this purpose [1, 10].

Propolis is a generic name of a mixture of resinous substances produced by honeybees. It is combined of over 300 chemical components containing flavonoids, phenolic acids, and caffeic acids which are identified to be varied by geographical locations. With this generous number of compounds, propolis tenders some biological effects that accelerates the healing process and is widely used in folk remedies. Studies have focused on wound healing properties of propolis within anti-microbial, anti-inflammatory, and regenerative activities [11–13]. Anti-angiogenic effects have also been emphasized [14]. Propolis has been proved to be effective in both experimental [15] and in clinical wounds [16].

Liquidambar is a genus of trees which has 4 different species. The most common species is *Liquidambar orientalis* (LO), also called sweetgum or sığla which is also named as Turkish sweetgum. The medicinal products mostly come from storax, the product obtained by damaging the outer surface of the tree. Sweetgum storax has medicinal usage far back to ancient times. It has been used for treating dysentery, coughs, wounds, and infections [17]. Sweetgum storax has been reported to contain numerous compositions (terpinen-4-ol, α-terpinol, sabinene, γ–terpinene etc.) having anti-oxidant and anti-microbial effects [18–20]. Stimulation of wound healing and anti-bacterial effects has also been reported [21, 22].

Recent trends are moving toward combination therapies in order to develop specialized treatments and new products [1]. HP (kantaron), propolis and *Liquidambar orientalis* (sığla) have all been proved to be effective in wound healing. This study aimed to investigate various combinations of kantaron, propolis, and sığla and their synergistic or repressive effects on wound healing.

Materials and methods

Animals

A total of 50 male Spraque-Dawley rats weighing 180–200 g were included in this study. Throughout the experiment, the rats were placed in individual cages and fed by standard pellet diet and water ad libitum. The international ethical guidelines for the care of laboratory animals were approved by Ankara Education and Research Hospital Commission of Animal Ethics. This study was carried out in Ankara Education and Research Hospital Experimental Investigation Center.

Wound model

The back hairs of all animals were shaved before surgery. Each group of animals was anesthetized by Ketalar®:Rompun® (80–120:10–16 mg/kg intraperitoneally [i.p.]). Incisional wound models were prepared to all groups in order to evaluate wound healing activities. Two linear 5-cm long paravertebral full-thickness incisions were made at a distance of 1.5 cm to the vertebral column. The wounds were closed with 3 interrupted 3/0 silk sutures.

Extract Preparations

Hypericum perforatum was collected in June from Muğla region of Turkey. The olive oil macerate was prepared in a traditional manner. Fresh leaves and flowering parts of the plant were inserted into a transparent jar without pressure. After putting in 50 g of *Hypericum perforatum*, the jar was filled with 500 ml of olive oil as a vehicle and closed. The olive oil contains no more than 1% free acidity (extra virgin olive oil). After 4 weeks of maceration, the oleum was red, partially viscous, and ready to use for treatment (Voucher specimen No. H-102).

Liquidambar orientalis, so called sığla, was prepared as a balsam. It was obtained from the wood and inner bark of the Sığla tree which is called Günlük tree in Turkey. The balsam is not a natural part of the tree but is produced as a result of the stimulus from wounds in the bark. The outer bark is bruised, and then the inner bark becomes saturated with this pathological exudation. This secretion is boiled and pressed afterwards.

Propolis, as it is called Turkish propolis, is collected in June from Sivas region of Turkey. It is endemic to inner Anatolia. In order to prepare the extracts, beeswax was melted and 10 ml of HP, 10 g of LO, and 10 g of propolis w equally shared to each group.

Study groups

There were 5 groups with 10 rats in each group. The rats were randomly divided to each group. The groups were categorized as group 1 (control), group 2 (HP + propolis, 1:1), group 3 (HP + LO, 1:1), group 4 (LO + propolis, 1:1), and group 5 (HP + LO + propolis, 1:1:1). The extracts in each group were distributed equally. The extracts were daily applied to the treatment groups as thin layers on the wounds starting from day 0 (surgery day) until day 21. The control group received saline moisturizing daily. No dressings were applied to any of the groups in order to imitate the traditional usage.

Biopsies

The biopsies of 1 × 1 cm were taken under anesthesia while excluding the sutured areas on days 3, 7, and 21. Histopathological analyses (epithelialization, angiogenesis, fibroblastic activity, inflammation, and collagen density) were carried out using biopsies taken on days 3, 7, and 21. Tensile strength was estimated from 2 biopsies taken on day 21. Therefore, 3 biopsies from the left and 2 biopsies from the right wound were taken from each rat. Tensile strength biopsy dimensions were 3 × 1 cm horizontally.

Histopathological examinations

Tissues were fixed in %10 formalin and embedded in paraffin blocks. Serial sections of paraffin embedded tissues of 4–5-μm thickness were cut. Hemotoxyline- and eosin-stained preparations were examined under light microscope (Olympus BX46-Tokyo-Japan) and epithelialization, inflammatory cell infiltration, and fibroblastic activity were evaluated.

Vascular structures were clarified by CD34 (Novocastra, monoclonal clon:QBEnd/10, 1:100) which is an immune-histochemical antibody that stains endothelial cells by full automatized Leica Bond-Max immune-histochemical staining device in order to see the angiogenesis. The immune-stained slides were also examined under light microscope.

Collagen density was evaluated on slides which were stained by histochemical collagen tissue stain Masson Trichrome (Bio-Optica, ready to use) under light microscope.

Epithelialization, inflammatory cell infiltration, fibroblastic activity, collagen density, and angiogenesis were semi-quantitatively evaluated using the following scale: −(n/a), +(mild), ++(moderate), and +++(dense).

Calculating tensile strength

On day 21, after sacrificing the rats, 3 × 1-cm specimens were taken from the right sutured wounds and tensile strength analysis were performed due to the method of Özbek et al. [23]. Tensile strength was estimated on a tensiometer device (TT-CM Model, Instron Eng Cooperation, MA, USA). The sutured incision lines were inserted just in the middle of the device. The tension was adjusted to be 10 mm/min, and the tensile strength was calculated in Newtons (N).

Statistics

The parameters of angiogenesis, epithelialization, inflammation, fibroblastic activity, and collagen deposition were analyzed with the Pearson chi-square test. Tensile strength parameter was analyzed with the Kruskal-Wallis test. Statistical comparisons between groups were done by SPSS statistical software program (v22.0). $p \leq 0.05$ was considered as statistically significant.

Results

Angiogenesis

On days 3 and 7, all treatment groups had significantly higher angiogenesis than group 1 ($p < 0.05$). There were no differences between groups on day 21. Treatment groups were not significantly different among each other. Histopathological comparison of groups 1 and 2 in terms of angiogenesis is shown in Fig. 1.

Epithelialization

There were no significant differences on days 3 and 21. Epithelialization on day 7 was higher in all the treatment groups compared with group 1 ($p < 0.05$). There were no significant differences between the treatment groups. Groups 3 and 5 had faster epithelialization macroscopically. Histopathological specimens of groups 1 and 2 are shown in Fig. 2.

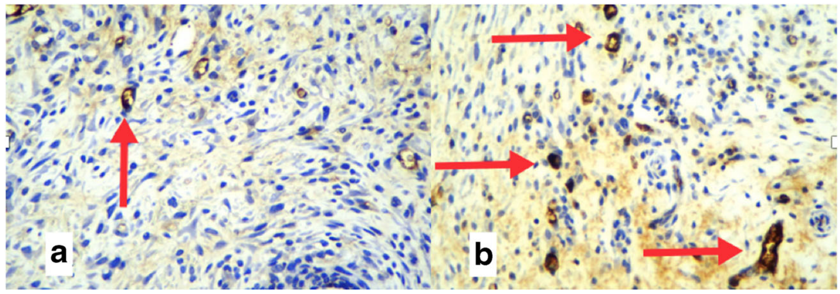

Fig. 1 A comparison of group 1 (**a**) and group 2 (**b**) in terms of angiogenesis. CD34 staining with × 400 magnification. Vascular structures are indicated with red arrows

Inflammation

There were no differences on days 3 and 7. All treatment groups had significantly lower inflammation on day 21 compared with group 1 ($p < 0.05$). There were no differences between treatment groups. Inflammation of groups 1 and 5 are shown in Fig. 3.

Fibroblastic activity, tensile strength analysis, and collagen deposition

Fibroblastic activity, tensile strength analysis, and collagen deposition were not statistically different between treatment groups and the control group.

Discussion

HP, LO, and propolis have all been proved to influence wound healing processes. HP and LO are examples of herbal-derived compounds, while propolis is an example of animal (bee)-derived compound. Herbal-derived compounds have been shown to stimulate all 3 phases (inflammation, proliferation, and remodeling) while animal-derived compounds are effective on only inflammation and proliferation phases. On the other hand, conventional dressings (gauze, silver etc.) are only affective on the first phase of the wound healing process [1].

Vehicles of the three compounds are different. Olive oil is the vehicle of HP, while balsam is used in both propolis and LO. The vehicles have also proved to be limitedly affective in wound healing [8]. Thus, in order to minimize flaw, the control group received daily saline moisturizing and kept open like as other groups.

Although HP has various stimulations on dermal wounds, it is mostly known as an anti-inflammatory or an immune-modulatory traditional compound [8]. LO, which is another plant-derived compound, also influences wound regeneration with numerous stimulative factors. However, the anti-oxidant and inflammatory stimulation effects are the dominant factors of LO in skin wound healing [20, 24]. Propolis, the bee product, is mainly known with its anti-bacterial and anti-angiogenic effects [14, 25]. All three traditional compounds have intricate impacts on skin wound healing besides their major effects. Recent studies have turned the lights on combination therapies in order to develop specialized treatments [1]. Therefore, in this study, different combinations of these three therapeutic substances have been investigated for their synergistic or repressing activities on skin wound healing.

Re-epithelialization is one of the ultimate goals of wound healing. The treatment groups were found to be significantly effective in terms of re-epithelialization on day 7. This is supported by previous studies [8]. As all wounds were healed until day 21, it is not a surprising finding. Despite the fact that group 3 and group 5 had faster epithelialization macroscopically, the treatment groups had no significant difference between each other.

Stimulation of angiogenesis is effectively seen in compounds including flavonoids and it is a determining factor in wound healing [1]. The angiogenic effect of propolis varies in the literature. Some have shown no influence [12] while others have proved inhibition of angiogenesis [14]. Vascular structures were evaluated by immune-histochemical antibody staining which provides better vision of angiogenesis. According to the literature, group 3 was expected to have the highest angiogenic rates due to inhibitor factors of propolis in other groups. However, all the mixtures in the present study stimulated angiogenesis on days 3 and 7, without having any repressing effect. This could be explained by the immunomodulatory effect of HP which is emphasized on angiogenic stimulation and inhibition equilibrium in groups 2, 3, and 5 [8]. The primary angiogenic effect in group

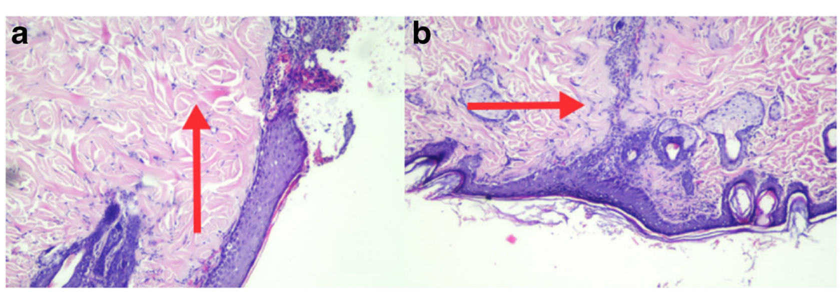

Fig. 2 An example of epithelialization of group 1 (**a**) and group 2 (**b**). Hemotoxyline-eosine stainment with × 100 magnification. Red arrows indicate the sutured areas

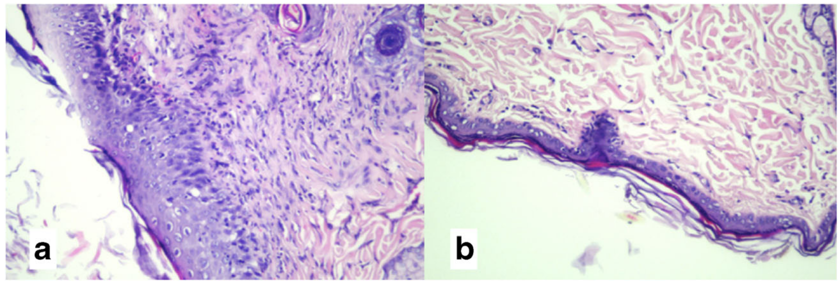

Fig. 3 The difference of inflammatory response between group 1 (**a**) and group 5 (**b**) on day 21 is shown. Hemotoxyline-eosine staining with × 200 magnification. Note the dense inflammation on group 1 while no inflammatory cells on group 5

4 is interpreted as the angiogenic effect of LO [24]. Therefore, including LO and HP in mixtures could be a sensible choice in terms of angiogenesis.

Inflammation is the first and maybe the most important phase of the wound healing process. LO has been shown to maintain rapid inflammatory response to burn wounds [24]. By accelerating the inflammatory process, LO accumulates neutrophils, macrophages, and fibroblasts to the healing wound which results with early epithelialization [24]. Therefore, LO is not an anti-inflammatory compound. Propolis, as an animal-derived compound, is shown to be effective on the inflammatory phase [1]. With significant anti-inflammatory properties attributed to caffeic acid, propolis inhibits the release of prostaglandins and leukotrienes resulting with successful reduction in edema and enhanced wound healing [11, 26]. HP is also known as an anti-inflammatory plant-derived compound. The anti-inflammatory effect is attributed to components such as flavonoids (quercetin etc.) and hyperforin which reduce the duration of inflammatory phase [27]. It is demonstrated that these components inhibit the production of pro-inflammatory mediators but not enhancing inflammation suppressing mediators [27]. HP and propolis are both attributed to have anti-inflammatory effects while LO increases inflammatory response. In group 2, HP and propolis both reduces the inflammatory response. In groups 3, 4, and 5, LO should have inflammatory stimulating effect theoretically. However, both HP and propolis have repressed the inflammatory effect of LO and delayed the response. Thus, all groups had similar inflammatory response on days 3 and 7, while treatment groups had lower inflammation on day 21. This finding is dedicated to the dominant anti-inflammatory activities of the compounds in the treatment groups.

Wound healing process consists of overlapping phases affecting each other. Fibroblastic activity in the inflammatory phase and collagen deposition in the proliferation and remodeling phases affect the tensile strength of the wound. Besides, collagen density was analyzed with histochemical staining which ensures better evaluation. However, these parameters were not significantly different between the control group and the treatment groups. Tensile strength has an equivalent importance with epithelialization in the resultant healing wound, but the tensile strength was not affected while the latter was enhanced by the treatment groups. Caffeic acid, a component of propolis, has been shown to increase fibroblastic activity and collagen deposition [12, 13]. HP also has the same influence on these parameters [8]. However, LO has no reported effect on both fibroblastic activity and collagen density. Ocsel et al. [21] have also found no impact on these parameters in their wound healing study with LO. However, this did not repress the effect of groups 3, 4, and 5 against group 2 which did not contain LO.

Comparing three independent wound healing compounds causes limitations which should be considered. At first, the variability in the present study may seem to aggravate the standardization of the experimental design. However, the aim of this study was to explore the synergistic or repressing effects of the compounds which were ultimately revealed. The wound healing properties of every compound were investigated thoroughly in the literature. And combination therapies and synergistic effects are commonly examined, especially in phytotherapeutic research [1]. Nevertheless, comparing two compounds instead of three might have maintained a better standardization. Secondly and unfortunately, there is not a consensus about a tensile strength evaluation in rat skin wound healing experiments. Some authors examine this parameter on day 21 [8, 10], while some analyze it on day 10 [9] and others on days 7 and 14 [28]. Therefore, there is a slight conflict in standardization of wound healing parameters in the literature. And this might have caused underestimated results in the present study.

Conclusion

Combination therapies with traditional medicine for healing wounds are growing trends in experimental medicine. Studies aim to develop innovative treatment modalities in order to advance wound healing. LO, HP, and propolis have all individually proved their positive impacts on wound healing. Although they have different effects on various parameters such as angiogenesis and inflammation; combining these compounds ensures a more stable response to wounds. As a result, we can mention about a positive synergy between the compounds. In order to obtain new treatment modalities, various mixtures of traditional therapies should be benefited.

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Compliance with ethical standards

Conflict of interest Mehmet Altıparmak, Mustafa Kule, Yasin Öztürk, Serkan Y. Çelik, Mehmet Öztürk, Mehmet E. Duru, and Uğur Koçer declare that they have no conflict of interest.

Ethical approval This study was ethically approved by Ankara Education and Research Hospital Ethical Committee No: 0030 Decision: 403.

Informed consent N/A

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