Assessment the effects of *Mastic Gum Resin*, *Lawsonia Inermis* and *Quercus Brantii* on Cutaneous Wound Healing in *BALB/c* Mice

Kwestan Najm Ali[1], Hardi Fattah Marif[1], Hana Sherzad Raoof[1], Snur M. A. Hassan[2], Dereen Omer Ramzi[3]

[1]Assist. Lecturer, Department of Clinic and Internal Medicine, College of Veterinary Medicine, Sulaimani University, Kurdistan-Iraq, [2]Assist. Prof.,Department of Anatomy and Pathology, College of Veterinary Medicine, Sulaimani University, Kurdistan-Iraq, [3]Assist. Prof. Department of Basic Science, College of Veterinary Medicine, Sulaimani University, Kurdistan-Iraq.

Abstract

The request for more efficient and lower-cost therapeutic methods for wound healing remains a challenge for modern medicine. The goals of this investigation were to recognize and look at the impacts of *Mastic Gum Resin, Lawsonia Inermis,* and *Quercus Brantii* in wound healing by using histopathological study and blood parameters in *BALB/c* Mice. Mice were comprised into four groups: Control negative group (n=10), mice were not treated with plant suspension only applied with normal saline; Treatment group I, mice were applied by *Mastic Gum Resin* (MGR) (n=10), Treatment group II, mice were applied with the *Quercus Brantii* (n=10), and the last group, Treatment III which were applied with *Lawsonia Inermis* (LI) (n=10). One ml for each suspension of *Mastic Gum Resin (MGR)*, *Quercus Brantii (QB),* and *Lawsonia Inermis (LI)* was applied to the wound directly without suturing for 4 days/week for about 3 weeks. Wound healing effects were evaluated by utilizing the hematological profile for each group with the histopathological study. The cutaneous wound in *Mastic Gum Resin* and *Quercus Brantii* treated groups were more effective in progressing wound healing than *Lawsonia Inermis* treated group regarding histological changes at day 8 and day 18, respectively and blood parameters at day 21.

Keywords: *Albino mice, Lawsonia Inermis, Mastic Gum Resin, Quercus Brantii.*

Introduction

Wound healing is an unpredictable procedure that requires a progression of biochemical and cell responses, beginning with homeostasis, re-epithelialization, granulation tissue arrangement, and renovating of the extracellular matrix [1,2]. Searches for better and reliable wound healing agents from medicinal plants have become more relevant fields of active research. From time immemorial, wounds were treated topically with various medicinal herbs or their extracts, according to conventional medicine [3].The oleoresin of *Pistacia atlantica* or " mastic tar " is normally utilized in Pakistan and Iran to treat conditions, for example, gastrointestinal issues [4]. This natural plant has caught the consideration of investigators because of studies on various areas of this plant, for example, the leaves, bits, frames, and gum showing different organic advantages, for example, anti-oxidant, antimicrobial, and anti-inflammatory effect. It has been demonstrated that *Pistachio* species are a rich source of phenolic mixes and they have additionally been discovered a source of durable antioxidant [5]. *Mastic oleoresin* (*MO*) is fundamentally directed topically (as wound dressing), orally, or by smoking [6]. Much examination has indicated the constructive outcomes of MO on wound curative [7]. Other than that, MO has been applied straightforwardly to skin incisions due to its adhesive consistency [8].The oaks (genus Quercus) are among the most major groups of flowering plants that dominate large areas of the northern hemisphere. There are even more than 200 species of oak in the western

Corresponding author:
Snur M. A. Hassan
E-mail address: snur.amin@univsul.edu.iq

hemisphere, and a potentially greater number in Asia and fairly few in Europe [9]. The principal significance of the oak tree is the existence of tannins in its various parts. Due to the different characteristics of the tannins present in them, *Quercus* species can be used in wound treatment according to references and local knowledge [10]. The gall extracts of this plant were historically used on inflamed skin and skin burn in Kurdistan but there are little details about the underlying mechanism [11]. Phenolic compounds, tannic acid, fatty acid, and gallic acid are the major components of The *Lawsonia inermis* (*henna*) [12]. This plant considered to have certain restorative properties, for example, antibacterial, anti-oxidant, and anti-inflammatory effects, oral and effective use of *Lawsonia Inermis* (*LI*) leaves and its isolated part exhibited wound curative conduct in excision and incision wound models [13].The aims of this examination were to distinguish and analyze the impacts of *Mastic Gum Resin*, *Lawsonia Inermis*, and *Quercus Brantii* in wound healing in *BALB/c* mice by utilizing blood parameters and histopathological study.

Materials and Methods

Collection and preparation of plant material

Fresh *Mastic Gum Resin*, *Lawsonia Inermis*, and *Quercus Brantii* were collected from a local market in Sulaimnai city of Kurdistan provinces, Iraq. Two gm of Mastic gum Resin was applied directly without mixing with any materials to the wound area, while the *Lawsonia Inermis*, and *Quercus Brantii* (grinded by a mixer till become a powder) were prepared by adding 2 gm of each of them with 4ml of normal saline and mixed by stirrer till become the creamy or suspension like. Each mouse was received 200mg/kg.bw from each types of plant.

Animals

Forty *BALB/c* mice (six weeks age, male and female with bodyweight 20-40 grams) were housed in the veterinary teaching hospital animal lab, Sulaimani province. Animals were having free access for food and drinking water and they were maintained during the research time on a 12 hours light and dark cycle. The exploration was done with the authorization of the Ethics Committee (1237) at the College of Veterinary Medicine, University of Sulaimani, under the counsel and rules of the College of Veterinary Medicine for the Maintenance and Use of Laboratory Animals.

Experimental design

All surgical procedure was performed under Isoflurane general anesthesia, and all attempts were made to reduce suffering. The surgical procedure was performed in *BALB/C* mice in an operating room with very good facilities. After 1 week of acclimation, the back of the animal was shaved and a full-thickness skin was incised (1cm x 1cm) from the dorsum as seen in figure 1.

Mice were allotted into four groups: Control negative group (n=10), mice were not treated with plant suspension only applied with normal saline; Treatment group I, mice was applied by *Lawsonia Inermis* (LI) (n=10), Treatment group II, mice were applied with the *Mastic Gum Resin* (MGR) (n=10), and the last group, Treatment III which were applied with *Quercus Brantii* (n=10). Each suspension 200mg/ml was applied to the wound area by sticks directly without suturing for 4 days/week for about 3 weeks. No dressing was used.

Figure 1: The back incised wound.

Histological procedure

The skin biopsies were taken from each wound side on day 8 and 21. Tissue biopsies were fixed in 10% neutral formalin buffer for 48 hours and afterward prepared by paraffin-embedding procedure. Tissue sections 4μm thick were made utilizing a microtome (Leica, Germany). One slide from each example at every period was recolored with hematoxylin and eosin for distinguishing any histological features of the injured tissue. The tissue areas were analyzed by light microscopy and photographed utilizing a camera (Amscope^{TM}, Japan).

Haematological Study:

On day 21, animals were sacrificed under general anesthesia and peripheral blood was collected from the tail vein with Ethylene Di-amine Tetra Acetic acid (EDTA). The vacuumed blood collection tubes were shaken immediately to mix well and were analyzed directly. The total white blood cells (WBC) and differential white blood cells [lymphocytes (LYM), granulocytes (GRA)] and Minimum Inhibitory Dilution," a measure of rare cells and several precursor white cells (MID)], total red blood cells (RBC), hemoglobin (HGB), packed cell volume (PCV), and platelets in each sample were measured by automatic hematology analyzer (Medonic M-series M32, Sweden).

Results

All mice survived and even no complications reported, including infection, correlated to the method was detected.

1. Histopathological Study:

a. Microscopical assessments of cutaneous wound healing on days eight:

On day 8th after wounding, the histological assessment of healed wound area shown inflammatory phase, on the surface, necrosis of skin tissue was placed as a consequence of mechanical damage, a continuous layer of marked granulation (Inflammatory cell, collagen deposition, and angiogenesis) tissue across the entire wound gap and depth, in which the thickness of the granulation tissues was higher in surface layer than in dermal layer, moreover, collagen fibers arranged in a disorganized manner and randomly distributed as fibrils with intense angiogenesis which were a main features of the granulation tissue, the intense inflammatory reaction (inflammatory cells including, neutrophils, macrophages, lymphocytes, plasma cells, and fibroblasts) was dominant in Control negative group (Figure 2 a and b), in comparison to treated group I that showed the late phase of granulation tissue and healing more progressed as in (Figure 2 c and d). While in Treatment groups of II and III, the healing became more pronounced and displayed an early stage of the re-epithelization phase, with forming immature-hyperplastic and disorganized epidermis surrounding the wound area with an increase in the thickness of the dermal layer by the presence of mature collagen fibers (Figure 3).

b. Microscopical assessments of cutaneous wound healing on days eighteen:

On day 21, after wounding, wound healing more progressed (proliferative phase) was apparent in Control negative group, epidermis formed as immature-hyperplastic and disorganized that overlying the area of the wound, the mild inflammatory reaction is seen in dermis and hypodermis with an increase in the thickness of dermal layer due to presence of well-organized collagen fibers as bundles with proliferative fibroblast (Figure 4 a and b). In Treatment group I, the wound thickness increased and covered by small scab and the wound showed the late stage of proliferation as in figure 4 c and d, tissue regenerated very well, while in Treatment groups II and III, the wound area covered by a normal epidermis and in the dermis, collagen fibers were thicker and denser. In the center of the wound the scar tissue was formed but in diverse levels in each group, for instance, in Treatment group II, new epidermis was formed with a mild thickness of keratinization, but marked density of scar tissue (granulation tissues beneath all wounds had matured to form scar tissues) were observed in the center of the wound, in dermal layer well organized thick bundles of collagen fibers was observed (Figure 5 a and b) if compared to the Treatment group III, that had well-uniformed epidermis with organized skin histological tissue layers encircle the wound area completely, with mild-moderate keratinization thickness, also, the moderate density of scar tissue and thick and well-arranged bundles of collagen fibers found in the dermis (Figure 5 c and d).

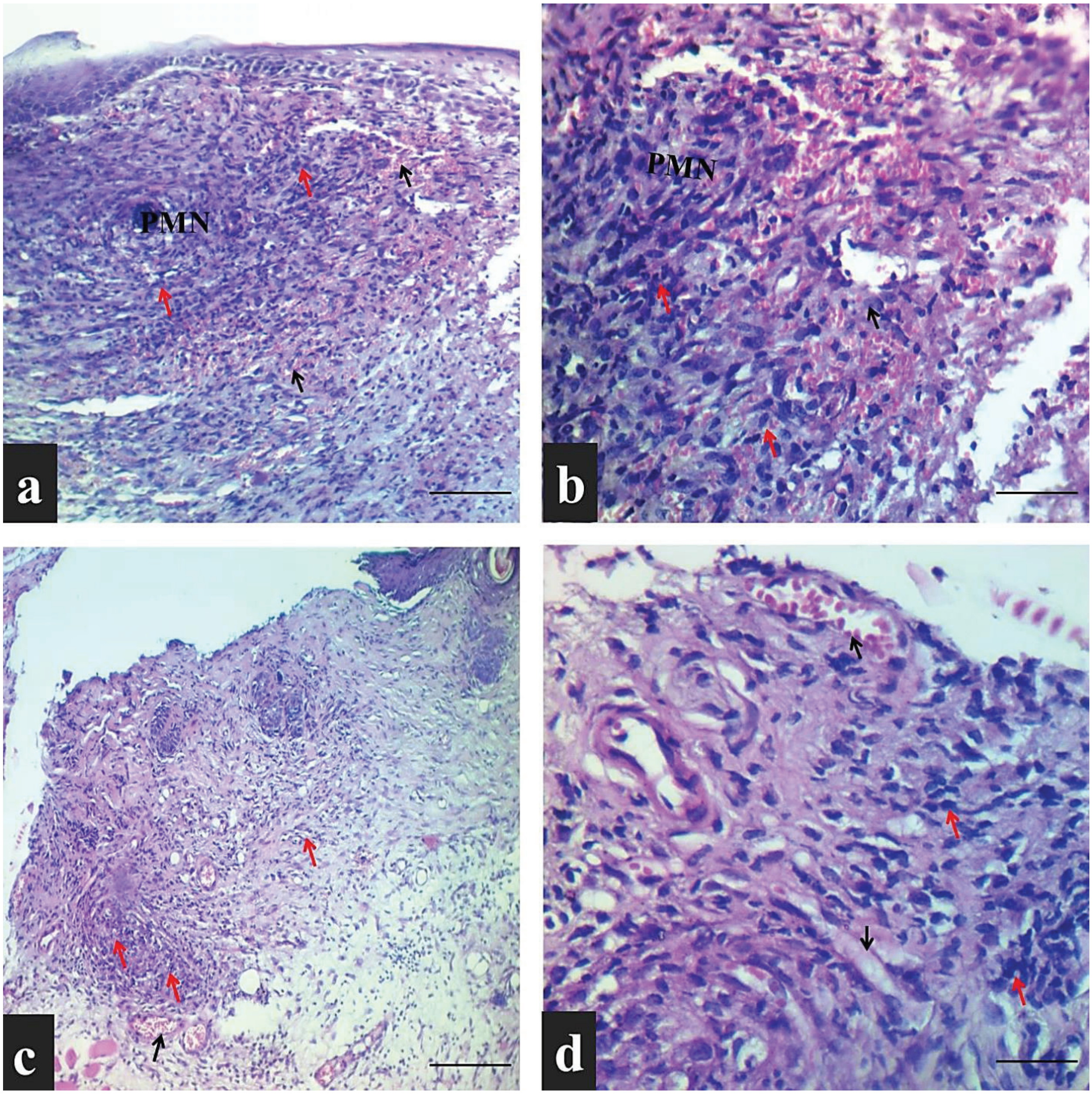

Figure 2: Histological sections of skin wound in Control negative group and Treatment group I showing granulation stage of healing wounds on day 8 following wounding. a and b: Presence of necrotic debris in the tissue surface with marked granulation tissue in the epidermis and dermal layers, epidermis, and dermis rich with newly formed granulation tissue, newly blood vessels (black arrows), and infiltration of inflammatory cells (PMN) as designated by red arrows, c and d: Thicken granulation tissue in dermis, neovascularization (black arrows), and intense infiltration of inflammatory cells as shown by red arrows, stained by H&E stain, (the scale bar of photo (a, c) 50mμ, and (b, d) 20mμ).

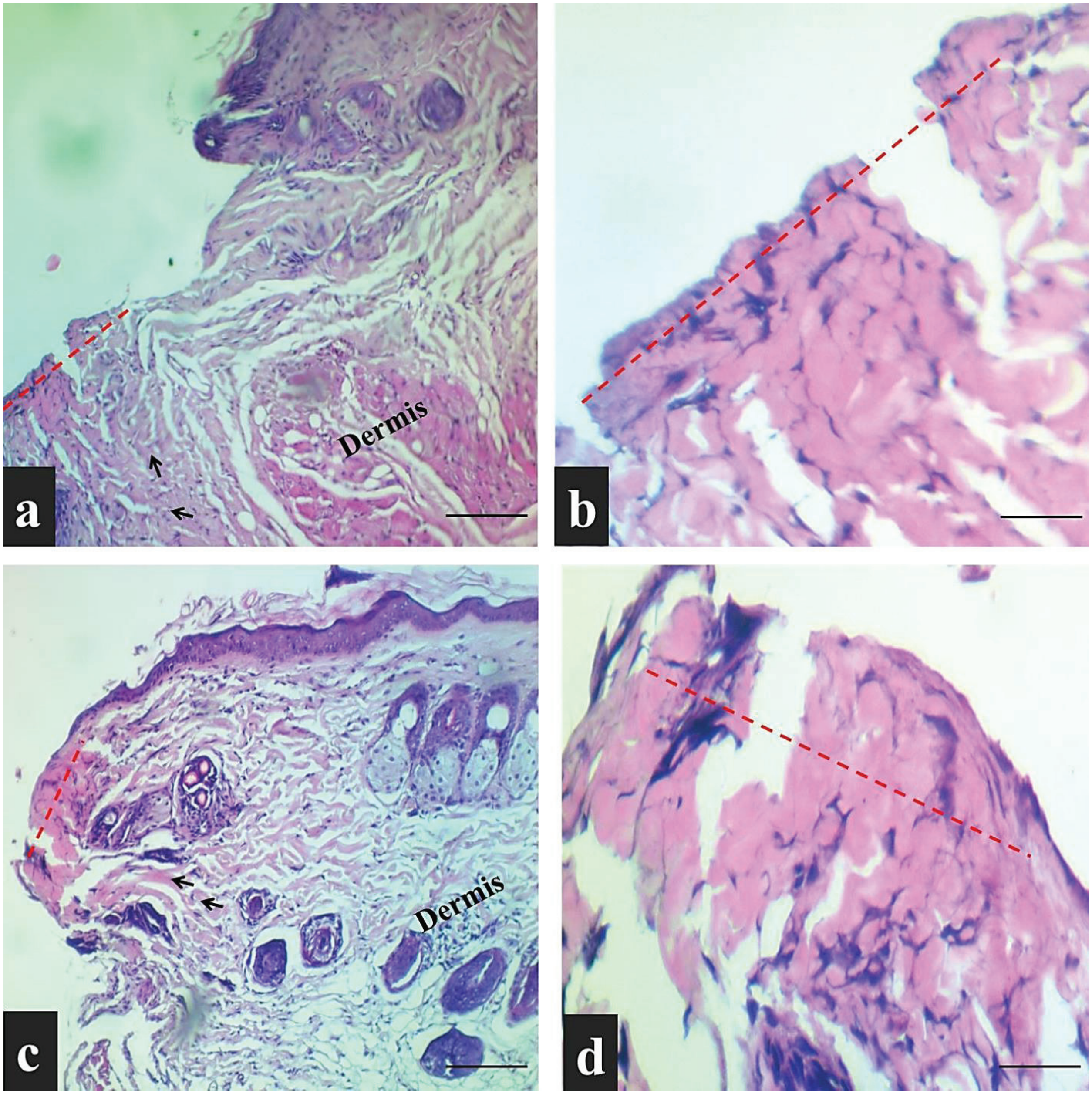

Figure 3: Histological sections of the cutaneous wound site in Treatment groups of II and III at day 8 following wounding showed the middle stage and the late stage of the proliferative phase respectively. b and b: Typical hyperplastic disorganized re-epithelialization formed for bridging the gap as indicated by red dash line, increased in the thickness of the dermal layer by a mature bundle of collagen fibers (black arrows): c and d: Hyperplastic-immature epithelium as designated by red dash lines with an improved in the thickness of the dermal layer by an extreme, mature bundle of collagen fibers (black arrows), stained by H&E stain, (the scale bar of photo (a, c) 50mµ, and (b,d) 20mµ).

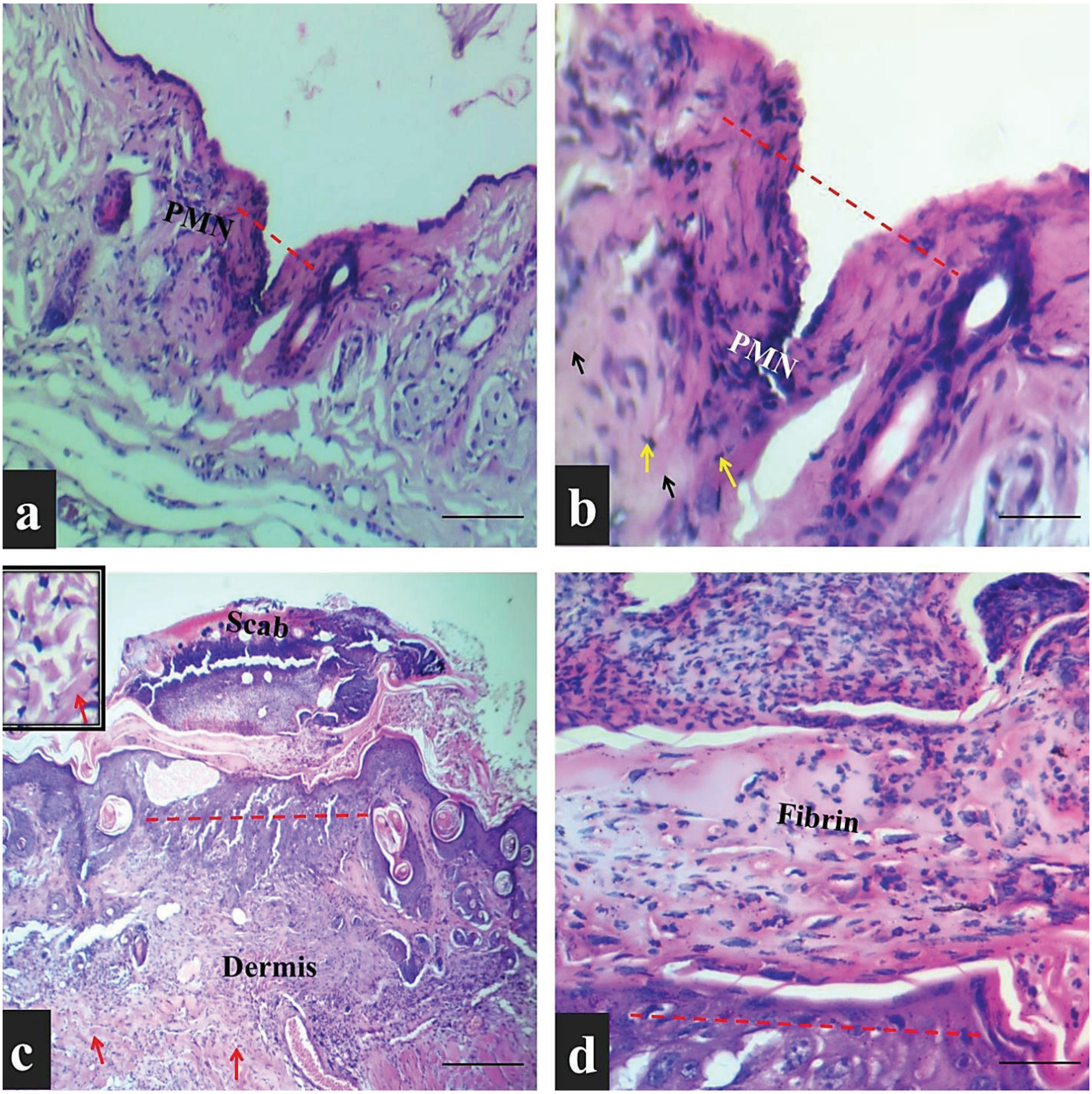

Figure 4: Histological sections of skin wound in Control negative group and Treatment group I at day 21 following wounding. a and b: Immature disorganized epidermis (red dash line). Intense, mature bundle of collagen fibers increased the thickness of the dermal layer (black arrows) with proliferative fibroblasts as designated by yellow arrows. c and d: Small scab that contains fibrin and PMNs completely covered the wound area, epidermis formation (red dash line), thick compact and irregularly arranged collagen fibers as indicated by red arrows and insert. Few numbers of PMN that separate the wound from newly formed epidermis as in section d indicated by red dash line, stained by H&E stain, (the scale bar for photo (a, c) 50 µm, scale bar (b,d) 20 µm).

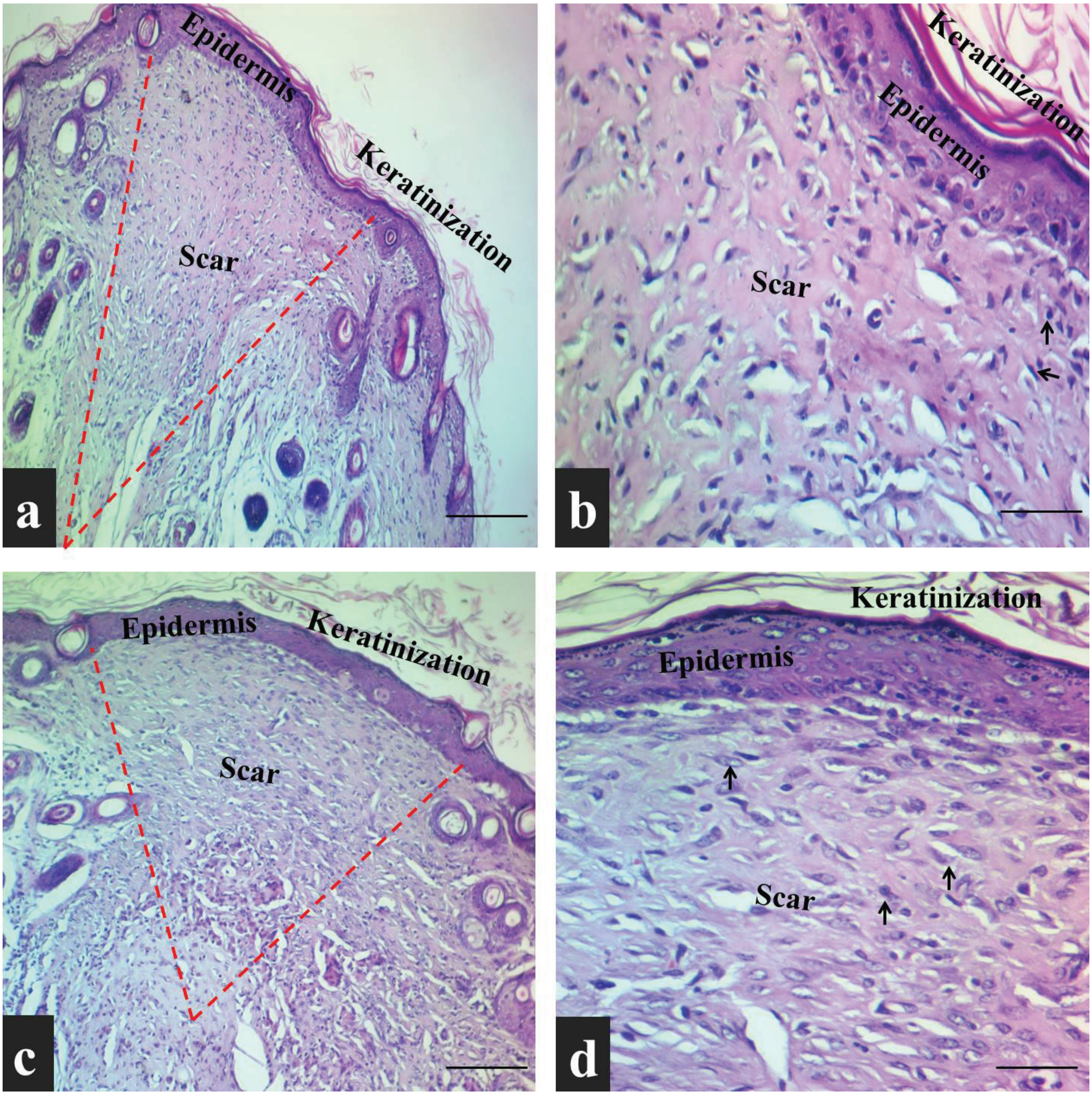

Figure 5: Histological skin wound section in Treatment groups of II and III at day 21 after wounding showed remodeling phase. a and b: Developing of the new epidermis with a mild-moderate keratinization thickness, the center of the wound contain the moderate-marked density of scar tissue (red dash lines) and proliferation of fibroblast (black arrows), well organized thick bundles of collagen fibers observed in the dermis. c and d: Developing of the new epidermis with a mild keratinization thickness, the center of the wound contain the marked density of scar tissue (red dash lines and black arrows), well structured, dense bundles of collagen fibers with inflammatory cell infiltration seen in the dermis as shown by black arrows, stained by H&E stain, (the scale bar of photo (a, c) 50mµ, and (b,d) 20mµ).

2. Hematological Study:

In this study, the hematological results of all treated mice shown in table 1; A significant mild-moderate increasing in the mean value of WBC (*P= 0.02*), and Platelets (*P= 0.005)* were found in Treatment group II, as well as a decrease in the mean values of HGB (*P =0.01*), MCV (*P =0.01)* and MCH (*P =0.01*) also detected, while in Treatment group III, significant elevation only detected in the mean value of Platelets (*P =0.000)* besides, to decrease in MCH (*P =0.01*) and

MCHC (*P= 0.05*) mean values, additionally, the result revealed a significant decrease in the mean values of PCV% (*P =0.01*) and MCH (*P =0.000*) in Treatment group I, when compared with a control negative group. On the other hands the result of hematological analysis in table 1 showed non-significant effects in the following parameters in each groups; For instance in Treatment group II, there were an increase in RBC (*P =0.68*), LYM (*P =0.6*), and GRAN (*P =0.67*) means, whereas in the same group PCV% (*P= 0.5*), MCHC (*P =0.1*), and MPV (*P =0.6*) showed non-significant reduction in there means, while in Treatment group III there was decrease in the means of RBC (*P =0.06*), LYM (*P =0.2*), HGB (*P* =0.*16*), PCV% (*P =0.36*), and MCV (*P =0.3*) in addition to increase in WBC (*P =0.7*), GRAN (*P =0.52*) , and MPV (*P=0.5*) means, furthermore, there was non-significant decrease in the means of RBC (*P= 0.34*), MCV (*P* =0.1), MPV (P=*0.2*), and HGB (*P =0.38*) besides elevation in the means of WBC (*P =0.91*), LYM (*P =0.3*), GRAN (*P =0.32*), Platelet (*P =0.2*), and MCHC (*P =0.32*) in Treatment group I in comparison to the control negative group.

Table 1: The hematological profile among different experimental groups.

Hematological parameters	Control negative	**Treatment I *Lawsonia Inermis***	**Treatment group II *Mustic Gum Resin***	**Treatment group III *Quercus Brantii***
Total RBC **(10^{12}/L)**	7.79±0.21	7.32±0.34	7.85±0.21	7.18±0.22
Total WBC **(10^9/L)**	3.34±0.21	3.40±0.26	4.92±0.28**	3.68±0.43
LYM (10^9/L)	2.92±0.49	3.56±0.41	3.56±0.41	2.50±0.41
GRAN (10^9/L)	0.52±0.08	0.61±0.13	0.65±0.11	0.65±0.12
HGB (g/dl)	12.94±0.24	10.87±0.74	10.24±0.10*	12.39±0.17
PCV (%)	39.96±0.64	33.72±1.75**	38.98±0.99	38.93±0.74
MCV (fl)	52.58±0.59	50.56±1.31	48.79±0.81**	51.78±0.84
MCH (Pg)	53.71±0.37	13.76±1.19***	15.42±0.45***	14.91±0.67***
MCHC (g/dl)	32.38±0.23	32.98±0.37	31.52±0.47	31.36±0.52**
Platelets (10^9/l)	155.30±8.09	204.20±34.05	209.60±14.31***	258.38±17.02***
MPV (fl)	6.52±0.14	6.28±0.22	6.46±0.17	6.64±0.17

Within each row, values expressed by Mean±SE, values with small superscripts star vary from each other ** P≤0.05 and *** P≤0.05 vs. Control (n=10).

Discussion

In the current study we reported the wound healing potential of the *Mustic Gum Resin (MGR), Quercus Brantii (QB), and Lawsonia Inermis*, applied on wounds in *BALB/c* mice. *MGR* is a natural constituent and has many biological impacts such as analgesic, antioxidant, anti-inflammatory, and antimicrobial activities [14,15]. *Henna (LI)*, has antiseptic, anti-inflammatory [16,17] and antimicrobial possessions [18]. Along these lines, if any plant material has antimicrobial, pain-relieving, and anti-inflammatory effects together, this substance may likewise be required to help advance injury healing and lead to skin renewal [19]. We observed that after 8 days of the topical application of Treatment group I (*LI)* enhanced late phase of granulation tissue and healing more progressed than in mice of control negative group. While in Treatment group II and III (*MGR* and *QB*) respectively, the healing became more pronounced and showed an early phase of the re-epithelization process.

The first reaction of wound healing is inflammation, which serves as a tissue protection mechanism that can withstand microbial contamination [20]. Therefore, the significant wound healing activity of *MGR* and *QB* substances might be identified with its amazing anti-inflammatory impact. For the injury repairing period, the antimicrobial effort is significant because the injury that is presented to the external circumstance is progressively powerless against microbial assaults which ordinarily lead to delays in the healing procedure. Threat factors like pathogens can thus jeopardize the repair process. The most common pathogen responsible for infection of skin wounds is *S. aureus* and *P. aeruginosa* [21].

Complete wound healing seen in 21 days post-operation more specifically in Treatment group II and III (*MGR* and *QB*) respectively, the histological findings showed normal epidermis covered the wound area and unique tissue recovery was a lot more prominent in skin wounds rewarded with Treatment group II and III (*MGR* and *QB*) correspondingly, than in wounds of control negative and even Treatment group II (*LI*). The wound healing effects of (MGR) fruit oil have previously been studied in a rabbit burn model and its ability to increase in re-epithelialization has been established and it's in agreement with our study [22]. The oil exhibited improved wound healing efficacy, which could be attributable to the synergistic effect of all the components found in *Pistacia lentiscus* oil, especially fatty acids, tocopherols, and sterols. Such phytochemicals showed desirable wound healing functions and beneficial behaviors through different methods at the various stages of the wound healing cycle involving antimicrobial, anti-inflammatory, antioxidant, collagen synthesis enhancement, cell proliferative and angiogenic impact [23]. In accordance to our results, other studies proposed that the oak can enhance the angiogenesis phase, reepithelialization and wound recovery process in male adult albino rats [24,25], Because of the antimicrobial, antioxidant, and inflammatory effects of most plant extracts, wound healing can aid [26].

Some research reported the influence of henna on wound healing, which is compatible with the recent report, suggesting that henna's antibiotic and anti-inflammatory properties are generally effective in wound healing, also demonstrated that henna extract decreased the mean cutaneous wound diameter and improved dramatically healing up to 12 days. [27,28].

The contraction of wounds is facilitated by specialist myofibroblasts located in the granulated tissue [29]. The increase in wound contraction in in mice of Treatment group II and III (*MGR* and *QB*) correspondingly, in our finding might be a result of the enhanced activity of fibroblasts and agrees with the previous report, who has shown that the injury reaction includes the proliferation and migration of cells such as fibroblasts, endothelial and epithelial cells and the deposition of connective tissue and wound contraction [30].

The results of the hematological evaluation of the blood samples in table 1 showed significant changes in the following parameters; For example in the Treatment group II (*MGR*) increasing in the mean value of WBC these discoveries associate very well with a past report [31], this was overwhelmingly accounted by an intensification in the circulating neutrophil infiltration [31], perhaps as a result of recruitment or demarcation of neutrophils from bone marrow [32]. Also in the *MGR* treated group there was a significant increase in the mean value of blood platelets count, in agreements with former studies that found the increase in megakaryocytes may lead to increased blood platelets [33], or platelet production can increase due to inflammatory disease [34]. As well as a slight decrease in the mean of HGB, MCV, and MCH which is corroborated similar findings reported by [35,36] in mice**.** While in Treatment group III *(QB*) significant elevation only detected in the mean value of Platelets, besides, to decrease in MCHC and MCH mean values which is in agreements with that found by [37,38], The decrease in the MCHC value that results from the toxic impact on red blood cell count and hemoglobin concentration of these natural ingredients, as the validity of these indexes is determined by the red cell count, hemoglobin concentration and packaged cell volume values [38]. Additionally, the result revealed a significant decrease in the mean values of PCV% and MCH in Treatment group I (*LI)* treated group when compared with control negative group similarly decrease in PCV was observed by [39,40], which can be disclosed as because of a huge reduction in Hb, this would prompt reduction in the size of RBCs and thus the last decline in PCV [41,42]**.** PCV regards are likewise noteworthy in estimating anxiety on animal health and demonstrate the limit of the blood to convey oxygen [34]. Reducing the WBC and PCV values in the treated mice indicates stress [36]

Conclusion

The present study demonstrated that the *Mastic Gum Resin*, *Lawsonia Inermis,* and *Quercus Brantii* plant extracts were more effective in wound healing when used for 21 days after incision; further studies will also be required to study these effects and their mechanism of action in detail.

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