

The Effect of Curcumin vs. Curcumin Combined Antibiotic Ointment on the Healing of Skin Wound

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Turmeric is typically used as a spicy food preservative and colorant. It has been proved that curcumin has a wide range of biological effects including anti-inflammatory, antiviral, anti-fungal, and curcumin activity that can improve antibiotic activity on the wounds. To evaluate the effects of Curcumin with and without antibiotics on skin wound treatment. The protocol was approved by the animal house in medical college / Basra university. This study used nine male rabbits aged about 6 months and an average weight of (1.083 g). Each group consists of 3 rabbits: control group (normal saline) A, topical curcumin in group B, topical curcumin, and tetracycline ointment in group C. Regular treatments were given to rabbits in therapeutic groups. The lowest Mean \pm SD of swelling of suturing area was noted in both groups that treated by curcumin alone (9.07 ± 0.97 vs 15 ± 1 mm, p value = 0.002) and that treated with curcumin and antibiotic (9.1 ± 0.9 vs 15 ± 1 mm, p value = 0.002) versus the control group (that treated by normal saline) and the lowest Mean \pm SD of elevation of suture line was noted in both group that treated by curcumin alone (2.63 ± 0.06 vs 4.07 ± 0.21 mm, p value > 0.001) and that treated with curcumin and antibiotic (2.7 ± 0.2 vs 4.07 ± 0.21 mm, p value = 0.001) versus control group. There is no significant statistical difference between the Mean \pm SD neither of swelling of suture area nor of elevation of suture lines of groups that treated by curcumin alone and group that treated with curcumin and antibiotic [(9.07 ± 0.97 vs 9.1 ± 0.9 , p value = 0.97), (2.63 ± 0.06 vs 2.7 ± 0.2 , p value = 0.61) respectively]. The histopathological evaluation is consistent with morphological changes as at day 3 of wound healing in both groups that treated by curcumin with and without antibiotic, there is formation a thin layer of keratin and absence of features that indicate delay wound healing such as hemorrhage, inflammatory cell infiltrate of (Neutrophils, macrophages and lymphocytes) and debris, which are detected in control group. Furthermore, at day 7 of control group, there is decrease of inflammation, presence of gap between the two edges of the wound but no keratin formation. No clear histopathological difference in wound healing between tested groups that treated by curcumin with and without antibiotic. There is no significant clinical and histological evidences that the curcumin not only prevent delay of wound healing but it is also enhanced wound healing. No significant difference in using curcumin alone or combine it with local antibiotic.

Keywords: Antibiotic; Curcuma long; Curcumin; Wound healing.

Wounds are the main cause of physical illness, healing is a method of survival and an attempt to restore normal anatomical structure and function¹. Therefore, the property of living

organisms is wound healing, in addition, wound cure is a process chain needed to extract invaded pathogens from the wounded tissue of the body and to completely or partially restructure the

injured tissue, in general, wound healing takes place in three complex and overlapping interrelated stages, namely inflammation, granulation, and remodeling². Restoring damaged tissue is important for all surgical manipulations³. In general, wound healing is divided into three interconnected complex and overlapping phases: inflammation, granulation, and remodeling, collagen formation occurs at a rapid rate in the early stages of wound healing, accompanied by collagen breakdown in the remodeling process, where collagen cross-linking occurs and tensile strength increases, several factors influence the wound healing process, varying as age to nutritional status and neuropathy after wounding⁴. The cure of the wound is blocked by immune-suppressants, cytotoxins, and non-steroidal anti-inflammatory drugs, antibiotic, analgesic, and herbal medications, however, improve wound healing⁵.

Various natural ingredients, plant ingredients that are composed of active principles such as triterpenes, alkaloids, flavonoids, and biomolecules facilitate the wound healing process⁴.

Turmeric is an ancient spice of *Curcuma longa* rhizomes, which is in the genus of ginger (*Zingiberaceae*), for decades, turmeric has been used for medicinal purposes in India, Turmeric is one of the most effective healers of nature^{6,7}. Curcumin gives turmeric the yellow color and is now known for most medical properties, 2-5 % of turmeric is estimated to be curcumin⁸.

The characteristics of curcumin are antibiotics and antioxidants⁹. And speed up the re-epithelization of cells such as myofibroblast, fibroblast, and macrophages required for the cure of wounds¹⁰. Curcumin reduces the level of pain and inflammation and promotes homeostasis by selectively inhibiting lipoxy and cyclooxygenase (COX) in the arachidonic acid cascade combination¹¹. Turmeric is considered an easily available antiseptic for cuts, burns, and bruises in Ayurvedic medicine, turmeric is good antibiotic dermatology used in India, the application of turmeric powder eliminates bacterial, fungal infections¹². Combination antibiotic therapy is progressively used to lower the risk of antibiotic resistance in bacteria and to boost antibacterial range throughout therapy¹³. A few experiments have shown that antibacterial efficacy can be enhanced

by combining antibiotics with crude plant extracts^{14,15}.

Skin wound healing is a fascinating process and not just for mammals, it is an evolutionary advantage, due to its essential functions as a physical, chemical, and bacterial barrier, skin wound healing is a significant step for wound survival, while certain interactions during the healing phase are essential, redundancy is high and other cells or mediators may assume roles and signals without significant complications, in preserving the physiological homeostasis of the human body, the integrity of healthy skin is an important factor^[16]. There are many scoring or grading methods for evaluation of wound healing. One of these was used in a study that evaluate ethanolic extract of curcumin (*curcuma Longa*) on wound healing in black Bengal goats⁵, it was precise, clear and simple represented way of wound healing. For these reasons was chosen in this study. This scoring is divided to three grades: Grade I: presence of hemorrhage and debris Grade II: No debris, still there is hemorrhage with inflammatory cell infiltrate inside the tissue such as neutrophils, lymphocytes and macrophages. Grade III: decrease of inflammation, gap between the edges of the wound and then formation of keratin layer.

Aim of this study

To evaluate the effects of Curcumin with and without antibiotics on skin wound treatment.

MATERIAL AND METHODS

Animal modules and diagnostic samples

The protocol was approved by the animal house in medical college / Basra University. This study used 9 male rabbits aged about 6 months and an average weight of (1.083 g). They were kept in an air-conditioned house in stainless steel cages. This study was design to compare and evaluate the effects of curcumin with and without antibiotic on healing of surgical wound in rabbits in three groups Each group consists of 3 rabbits: control that treated with normal saline group A, topical curcumin in group B, topical curcumin, and tetracycline ointment in group C. Regular treatments were given to rabbits in therapeutic groups. The swelling of the suture area was

evaluated at day 3 as the maximum of swelling achieved at the day 3, and the elevation of suture line was evaluated at day 7 which is the day at which skin suture was removed. Measurements of swelling areas were recorded in millimeter (mm) by using slide calipers. T-test was used to evaluate the statistical differences. Skin samples of all rabbits were taken at day 3, 7 and 14 of the injury. Skin biopsy was taken including the wound site and then fixed in formalin for histological examination. After embedding in paraffin, slices were taken and stained by Hematoxylin and Eosin and Mallory Tricom for histological examination a modern Leica light microscope (1000X) magnification provided with a camera (0.5X), as well as a (10X) computerized magnification which provided a high-resolution image.

Turmeric paste preparation

Turmeric roots were collected from the nearby Iraqi market and then grinded by an electrical mill to a fine powder. The paste was prepared by water to (50 g) of turmeric, water was gradually applied to the paste until it was semi-solid and then used on the injury directly.

Tetracycline Ointment: was bought from a pharmacy in Basra and used on the wound.

Surgery procedure

Anesthetized Rabbits use an anesthetic (Lidocaine 2 %) solution to place the rabbit in a prone position and sterilize the lower back skin with a 10 % povidone-iodine solution. The cut was around 1 cm in the skin and sutured with 2-0 non-absorbed silk.

RESULT AND DISCUSSION

The lowest Mean ± SD of swelling of suturing area (at day 3) was noted in both groups that treated by curcumin alone (9.06 ± 0.97 vs 15±1 mm, p value = 0.002, table 1) and that treated with curcumine and antibiotic (9.1 ± 0.9 vs 15±1 mm, p value = 0.002, table 1) versus the control group that treated by normal saline and the lowest Mean ± SD of elevation of suture line (at day 7) was noted in both group that treated by curcumin alone (2.63 ± 0.06 vs 4.07±0.21 mm, p value > 0.001, table 1) and that treated with curcumin and antibiotic (2.7 ± 0.2 vs 4.07±0.21 mm, p value = 0.001, table 1),

Table 1. Represent Mean ± SD of the morphological difference (swelling of the suturing area and elevation of suture line) in three groups (A control group, B treated with curcumin and C treated with Curcumin and tetracycline Ointment)

Group	Mean ± SD of swelling of suturing area at Day 3 (mm)	Mean ± SD of elevation of suture line at Day 7 (mm)
Group A	15± 1	4.06±0.21
Group B	9.06±0.97	2.63±0.06
Group C	9.1±0.9	2.70±0.2

Table 2. Represent histological grade of wound healing in three groups that mentioned above

Group	Day	Grade of healing
Group A	3	Grade I to II
	7	Grade II to III
	14	Grade III
Group B	3	Grade III
	7	Grade III
	14	Grade III
Group C	3	Grade III
	7	Grade III
	14	Grade III

and this could indicate less inflammation in group B and C as compared with group A. This result could support the reports that describe the wound healing is a complex process depend on many cell types and many mediators^[2] and the role of curcumine could be through different mechanisms as will described below. Another interesting result was, no significant statistical difference between the Mean ± SD neither of swelling of suture area nor of elevation of suture lines of groups that treated by curcumin alone and group that treated with curcumin and antibiotic [(9.06 ± 0.97 vs 9.1 ± 0.9, p value=0.97), (2.63 ± 0.06 vs 2.7 ± 0.2, p value=0.61) respectively, table 1].

Another essential result of this study, as shown in the (Table 2 and Figure 2) at day 3 of group A (control group), the grade of healing was between grade I and II because there is hemorrhage, inflammatory cell infiltrate mainly neutrophils, macrophages, lymphocytes and still there is debris while at day 3 of group B and C, the grade of healing was grade III (there is no hemorrhage and no debris and no inflammatory cell infiltrate and there is mature keratin layers formation (Figure 2) that indicate complete healing was achieved within 3 days in group B and C.

Furthermore, at day 7 of group A (control group), the grade of healing of was between grade

II and III because there is decrease of inflammation, presence of gap between the two edges of the wound but no keratin layer formation (Table 2 and Figure 3). This indicate complete healing still was not achieved within 7 days after injury. While at day 7 of both group B and C, the grade of healing was grade III because mature keratin layer was formed (Figure 4).

Moreover, at day 14 of group A (control group), the grade of healing was grade III because there is mature keratin formation (Table 2 and Figure 5). While at both group (B and C), the process of healing was already reached the last

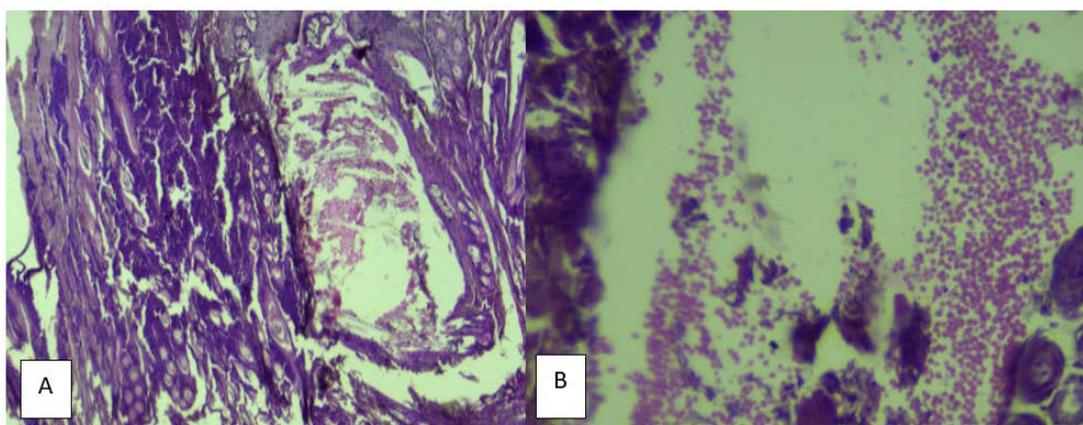


Fig. 1. A-Representative section of day 3 of wound healing at group A (100X-Haematoxylin and eosin stain). There is debris, dilated blood vessels contain red blood cells with haemorrhage and slight inflammatory cell infiltrate. B- Representative section of day 3 wound healing at group A (400X-Haematoxylin and eosin stain). There is hemorrhage, red blood cells with slight inflammatory cell infiltrate.

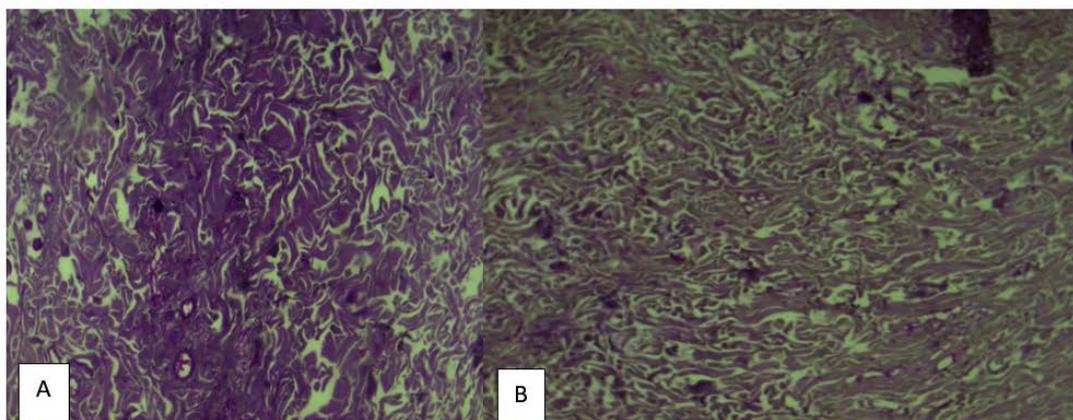


Fig. 2. A-Representative section of day 3 of wound healing at group B (400X-Haematoxylin and eosin stain). There is full layer of keratin formation. B- Representative section of day 3 of wound healing at group B (40X-Haematoxylin and eosin stain). There is full layer of keratin formation.

stage of grade III at day 7 as there is formation of mature keratin (Table 2 and Figure 6).

This indicates that the histopathological evaluation is consistent with morphological changes because there is hemorrhage, inflammatory cell infiltrate mainly neutrophils, macrophages, lymphocytes and still there is debris at day 3 of control group. Furthermore, at day 7 of control group there is decrease of inflammation, presence of gap between the two edges of the wound but no keratin formation. While at day 3 of both groups that treated by curcumin with and without antibiotic the wound healing was achieved and reach to

thin layer of keratin at day 3 and then to mature keratin at day 7. There is no clear histopathological difference in wound healing between tested groups that treated by curcumin with and without antibiotic. This indicates that curcumin alone (independent on adjuvant antibiotic) play a core role in the enhancement of wound healing. As the wound healing is a complex process². The role of curcumin in enhancement of wound healing is more complex⁵.

Many individual factors could affect healing such as age, nutritional factors, presence of neuropathy and others and as mentioned above⁴, but in

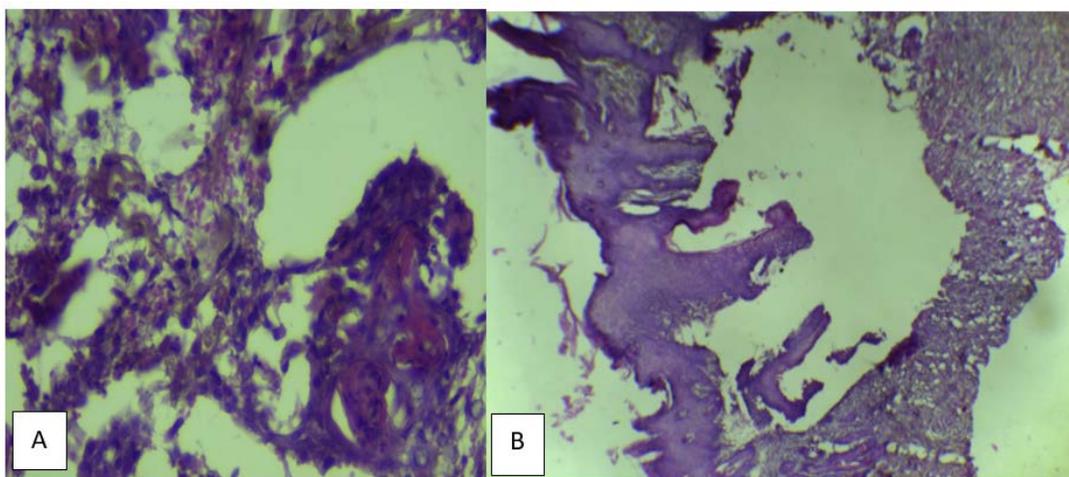


Fig. 3. A-Representative section of day 7 of wound healing at group A (40X-Haematoxylin and eosin stain). There is gap formation with slight inflammatory cell infiltration but no keratin formation. B- Representative section of day 7 wound healing at group A (400X-Haematoxylin and eosin stain). There is gap with slight inflammatory cell infiltration (lymphocytes, plasma cells and neutrophils) but no keratin formation

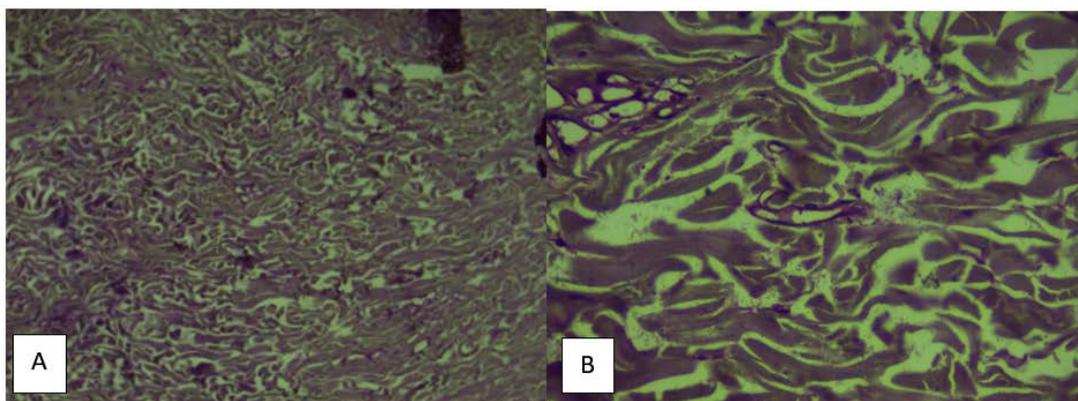


Fig. 4. A-Representative section of day 7 of wound healing at group B (40X-Haematoxylin and eosin stain). There is full layer of keratin formation. B- Representative section of day 7 of wound healing at group B (400X-Haematoxylin and eosin stain). There is full layer of keratin formation

the current study all these factors are standardized because all nine rabbits that submitted in this study have the same individual features. Therefore, the effects of curcumin on wound healing could be due other mechanisms like anti-inflammatory, anti-bacteriological effect of curcumin^{9,11,12} and antifungal¹³. The current study reveals an interesting finding that, the role of curcumin not only due to prevention of factors that delay wound healing such as anti-inflammatory, antifungal and antibacterial effect, it also enhance wound healing through different mechanism such as enhancement of granulation tissue formation, contraction of

the wound, enhancement tissue re-modeling , releasing of chemotaxic agents, releasing of growth factors and re-epithelization of cells such as myofibroblast, fibroblast and macrophages required for the cure of the wound¹⁰. Therefore, might be all or more than one mechanism could be performed by curcumin. Although, some microbiological study, postulated the synergistic effect of some antibiotic with extract of some plants (curcumin was not used)¹⁵. One of an interesting finding of this study is that, there is no additive role of combination of tetracycline ointment with curcumin as compare with curcumin alone on histopathological and

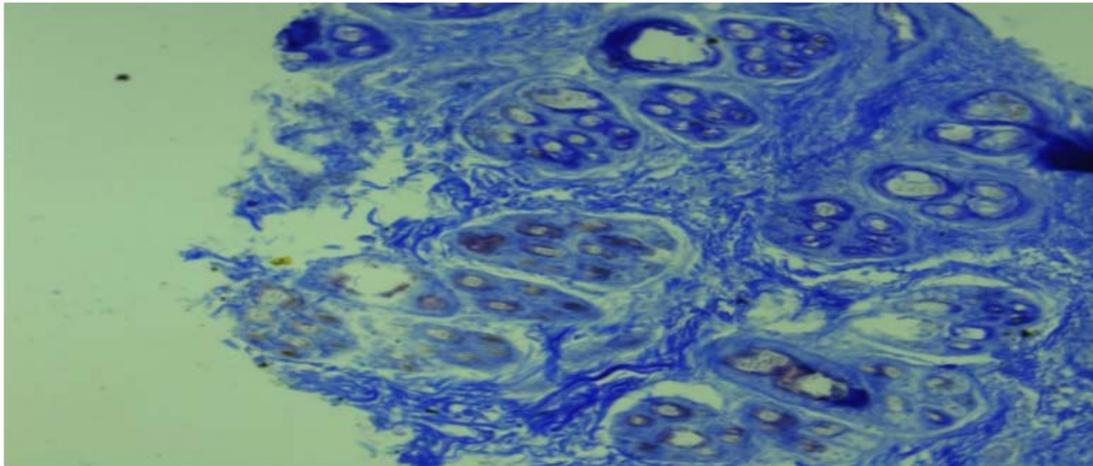


Fig. 5. Representative section of day 14 of wound healing at group A (100X-Mallory triple stain). There is full layer of keratin formation

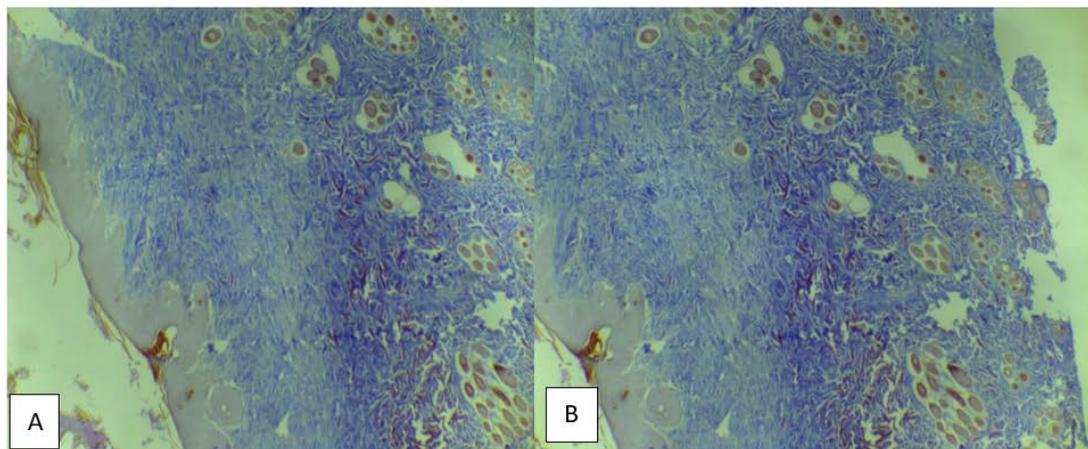


Fig. 6. A -Representative section of day 14 of wound healing at group B (100X- Mallory triple stain). There is full layer of keratin formation. B -Representative section of day 14 of wound healing at group C (100X-Mallory triple stain). There is full layer of keratin formation

morphological healing of the wounds. The result of this study was comparable to the result of other study as Sukandar *et al.* (2016) postulated that combination of penicillin or ampicillin with curcumin could have synergistic effect against *Staphylococcus aureus*, but this synergistic effect was not detected with tetracycline¹⁴.

It is well known that combination of antibiotic therapy is progressively used to lower the risk of antibiotic resistance in bacteria and boost antibacterial range throughout therapy^{14,15}. Therefore, the result of current study could indicate that curcumin could have more than one broad spectrum anti-bacterial agents or could contain new anti-bacterial agent that didn't used before. Then the bacteria cannot resist the antibacterial effect. Therefore, the fundamental finding of this study is the curcumin alone (independent of adjuvant antibiotic) play a core role in the enhancement of wound healing.

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