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REVIEW PAPER

Anti-inflammatory influences of royal jelly and melittin and their effectiveness on wound healing

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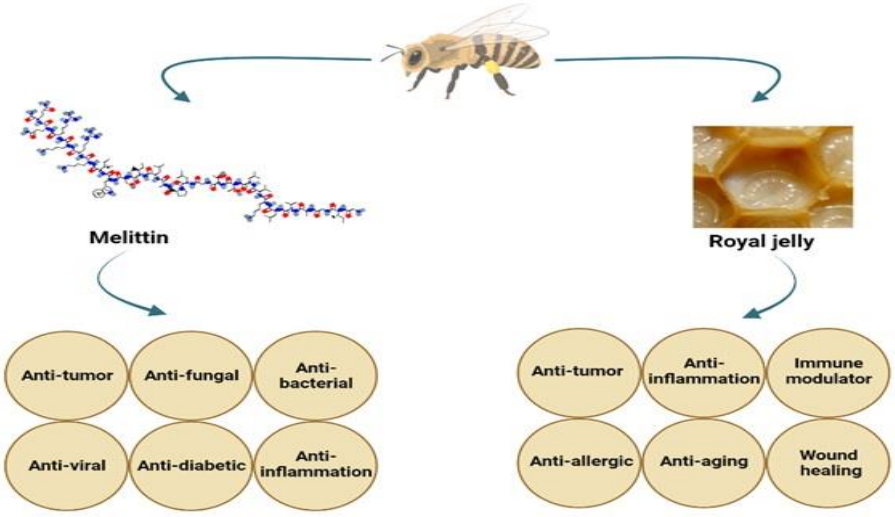
Highlights

- Royal jelly has antioxidant, anti-inflammatory, anti-tumor, and anti-allergy functions.
- Melittin as the main component of bee venom has cytotoxic, antibacterial, anticancer, and anti-inflammatory effects.
- Royal jelly and melittin can play a role in wound healing with different mechanisms.

Graphical Abstract



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Abstract

Royal jelly is a valuable medicinal substance that has different biological functions in various tissues and cells and has many medicinal features including anti-allergic, anti-tumor, antioxidant, and anti-inflammatory activities and also has protective effects on the immune, reproductive, nervous, and vascular systems. Melittin, which is a peptide with 26 residues, is the key element of honey bee venom and has cytotoxic, antibacterial, anticancer, and anti-inflammatory effects. Royal jelly can ameliorate the inflammatory response in microglia through the inhibition of p38 phosphorylation, and by inhibiting the NF-KB nuclear translocation. By decreasing the secretion of pro-inflammatory molecules including TNF-α, IL-1ß, and NO, melittin could apply the anti-inflammatory impacts on several kinds of cells including microglial cells. Royal jelly components may enhance the healing of wound via an anti-inflammatory effect, promotion of the growth factors synthesis, or the fibroblasts or skin keratinocytes migration. Based on multiple biological and pharmacological activities, a kind of formulated melittin is possibly capable to promote the healing of wound. The aim of this review is to narrate the anti-inflammatory effects of royal jelly and melittin and their efficiency on wound healing.

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Introduction

The honey bee produces two types of products, the first category is the products that the bee flies out of the hive to search for and brings back to the hive after identifying and collecting them and including honey, honeydew, flower pollen, and propolis. The second category is those produced by the internal glands of the bee body and used in the hive. Wax, venom, and royal jelly are from this category. Royal jelly, known as RJ, is a thick white to the yellow substance that is the result of the secretions of the glands of salivary in the worker bee and is applied as the main queen food throughout her life and of the bee babies in the initial steps of their development (1). RJ is a valuable medicinal material that has a variety of biological functions in various tissues and cells and has many medicinal features including antioxidant, anti-tumor, and anti-allergic properties and also has protective effects on the immune, reproductive, nervous, and vascular systems (2, 3). The chemical analysis of royal jelly shows that this substance contains 67% water, 16% carbohydrate, 12.5% protein and amino acid, and 5% lipid. Also, enzymes, vitamins, phenols, and minerals are also found in small amounts (4, 5). Melittin, which is a 26-residues peptide, is the key element of honey bee venom and constitutes about fifty percentage of its dry weight. This compound has cytotoxic, anti-bacterial, and anti-cancer influences and also has high cell lysis activity, including red blood cell membrane lysis (6, 7).

Inflammation is the immune system response vs. external and internal damaging stimulants. However, inflammation is a double-edged sword and can be harmful if not properly controlled. Royal jelly can ameliorate the inflammatory response in microglia through the inhibition of p38 phosphorylation, and by inhibiting the NF-KB nuclear translocation. Because of its anti-inflammation effects, RJ could be developed as a potential food to enhance the function of immune system to prevent inflammatory diseases (8, 9). In examining the effect of melittin on different organs, it was deduced melittin could apply anti-inflammation influences on several kinds of cells including microglia via reducing the secretion of pro-inflammatory molecules including TNF-α, NO, and IL-1ß. For example, melittin reduces pancreatic inflammation by inhibiting the release of proinflammatory factors by suppressing NF-κB activity (10). Since NF-κB has a key role in regulating the inflammatory genes including cyclooxygenase, inhibition of NF-κB activity can be used to treat inflammatory diseases (11); That is, the anti-inflammatory impact of melittin is caused by the inhibition of inflammatory stimulants including TNF-α, and IL-1B and through the interaction of this compound and the p50 sulfhydryl group, which itself causes the activation of NF-κB (12, 13).

Royal jelly, which has many physiological and biological features, has been applied since ancient times as a treatment for all kinds of wounds. Components of RJ, particularly defensin-1 and 10-hydroxy-2-decenoic acid (10-HDA) may enhance the healing of wound via anti-inflammatory effects, developing the growth factors synthesis, or keratinocytes and fibroblasts migration (14). Based on multiple biological and pharmacological activities, a kind of formulated melittin is possibly capable to promote the healing of wound. In a study that investigated the therapeutic potential of ceftriaxone and melittin nanocomplex (CTX-MEL), embedded in hydrogels to treat the diabetes disease and it has also been investigated in acute wound healing, it was shown that this nanocomplex, after two weeks of daily topical use, improves the procedure of wound healing, in molecular and morphological levels and it could fight oxidative stress by reducing malondialdehyde and elevating the superoxide dismutase and inflammation by reducing the levels of TNF-α and IL-6, like collagen-enhancing functions (increasing the expression of Col1A1 and the levels of hydroxyproline) (15). This study aimed to review the anti-inflammatory effects of royal jelly and melittin and their effectiveness on wound healing.

Royal jelly

Royal jelly is secreted from the cephalic glands of nurse bees and is the main portion of the bee larva's diet. Royal jelly is the only food that is given to all young larvae for the initial two-three days of their maturing process, while RJ is the special food for the queen during the whole life period, and that is why the queen bee has a longer life span than the rest of the bees (16). Royal jelly is also one of the most effective and useful

medicines for humans, and due to its complex combination (natural antibiotics, oligo-elements, water, hormones, enzymes, vitamins, mineral salts, amino acids, protein, carbohydrates, lipids), it is a controversial medicine and a food supplement. Some of the medicinal activities of RJ include antioxidant, neurotrophic, hypoglycemic, hypo cholesterol and liver protective properties, lowering blood pressure and regulating blood pressure, anti-tumor, antibiotic, anti-inflammatory, immune modulator, and anti-allergic, anti-aging, wound healing effects, etc. (Figure 1) (17). The main RJ proteins or MRJPs form about 90% of the overall RJ protein (18). Ten coding loci including mrjp1 to mrjp10 have been identified for MRJ proteins, but there is little information regard to these genes' activity or their peptide products (19).

Royal jelly has beneficial effects on health of humans and honey bees; it considered as an antibiotic with natural origin and has an effective function in the development of larval steps. In addition, royal jelly influences the size, learning, growth, morphological characteristics, and shape alteration in different organisms including humans, mice, and honeybees (20). One of the distinguishing features of RJ is related to its content of fatty acids and lipids. Also, this part contains phospholipids (0.4-0.8%), steroids (3-4%), wax (5-6%), and phenolic compounds (4-10%). Royal jelly comprises fatty acids with medium-chain, usually eight to twelve carbons, some hydroxylated at the internal or terminal positions as dicarboxy or monohydroxy fatty acids, either unsaturated or saturated at the 2-position (21). Royal jelly can also lower blood sugar levels through insulin-like peptides and other compounds such as chromium, sulfur, and vitamins B3 and H, and is able to maintain optimal blood sugar levels by participating in the glucose oxidation to acquire energy through an insulin-like effect. In insulin-resistant diabetic patients, RJ caused a significant reduction in sugar levels (22).

Bee venom and melittin

Venom of bee comprises various biological activate elements including enzymes, bioactive amines, and peptides that could play beneficial faction in healing of wound. Venom of bee comprises various peptides such as adolapin, apamin, melittin, scapin, and its isomers, MCD peptide, tertiapin, and procamine (23). Peptides comprises the key elements of venom of bee. The peptides and small proteins levels in dry venom is around 48-50%. From the mentioned peptides, melittin has an especially central function in stimulating reactions related to stings of bee (24). Melittin is a 26-resifues peptide and the key biologically activate element in venom of bee (25). It constitutes around half of dry bee venom (26). Because of the hydrophobic terminal amino region and the hydrophobic carboxyl-terminal region of melittin, this compound represents amphipathic features. This feature of melittin lets it to enter membranes through disruption of bilayer of phospholipid (27). Melittin induces membrane permeability and cell lysis. Melittin can create unstable and stable pores in the membrane, which depends on the dose of this substance. Ions and larger molecules, such as glucose, can pass through the small and large pores, respectively. In addition, melittin causes hemolytic pores (28) and in low levels, it displays antifungal, antiviral, antibacterial, and anti-inflammatory impacts, and by increasing blood circulation increases the capillary permeability (29). The biological effects of melittin are summarized in Figure 1.

Bee venom reduces the level of IL-1ß, TNF-α, and IL-6 (30). Venom of bee comprises melittin, which prevents the inflammatory genes expression and is considered the dominant toxic component in the venom and constitutes 50% of its composition. In addition, the venom of bee prevents the expression of COX-2, thus reducing the generation of prostaglandins that participate in the procedure of inflammation (31). The compounds of bee venom have different and sometimes opposite effects and are related to the immune system. The anti-inflammation impact of bee venom is also applied to treat the atopic dermatitis. The amphipathic feature of melittin allows it to solve in H_2O as a tetramer or monomer (29, 32). This polypeptide easily enters membranes and disrupts natural and synthetic phospholipids; indeed, the melittin affinity for membranes consisting of lipids with negative charge is about 100 times greater than that of zwitterionic lipids. The melittin function in membranes exerts via the generation of pores, which non-selectively results in membrane penetration and disrupts eukaryote and prokaryote cells. This function is accountable for the hemolytic, antimicrobial, antifungal, and antitumor activities of melittin (28, 29).

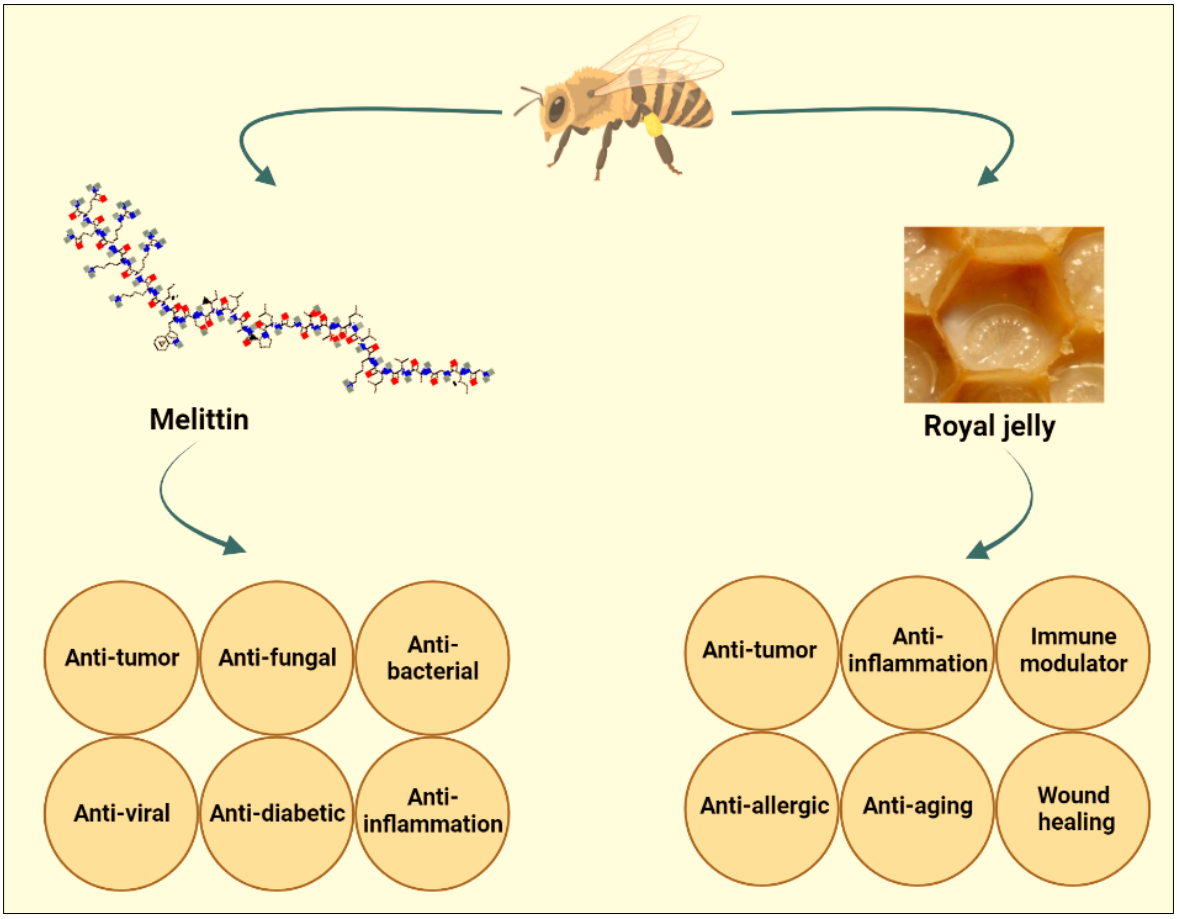

Figure 1. Biological effects of royal jelly and melittin. The royal gel has anti-tumor, anti-inflammatory, immune-modulating, anti-allergic, anti-aging, and wound healing properties. Melittin also has anti-viral, anti-bacterial, anti-fungal, anti-tumor, anti-inflammatory, and wound healing properties.

Anti-inflammatory properties of royal jelly

The inflammation procedure is triggered via a varied cascade of chemical and biological factors such as inflammatory enzymes, cytokines, and compounds with low molecular weight (33). In a dose-dependent way, it inhibits pro-inflammation cytokines including interleukin-1 and tumor necrosis factor-α without cytotoxic impacts on macrophages in vitro. The existence of cytokines levels with anti-inflammatory or pro-inflammatory features including IL-1, IL-18, and TNF-α in the blood and kidney of mice, reflects the anti-inflammation response of royal jelly because of its anti-oxidative and anti-inflammatory influences (34, 35). RJ diet ameliorates the function of skeletal muscle and metabolic function in rats with obese and aged features. In addition, royal jelly improves resistance to insulin and lipotoxicity of muscle in these rats through inhibition of tumor necrosis factor-α in adipose tissues and serum because of its anti-inflammation response. Royal jelly can ameliorate the response of inflammation in microglia via inhibiting the p38 phosphorylation and by inhibiting the NF-KB nuclear translocation (Figure 2). Because of its anti-inflammation features, RJ could be developed as a potential food to enhance the function of immune system to prevent inflammatory diseases (8, 9). The 10-HDA molecule as an excellent matter in royal jelly meaningfully prevents the activity of c-Jun N-terminal kinase/activating protein-1 (JNK/AP-1), p38, and matrix metalloproteinases (MMP1-MMP3). The molecular path which can act as a protective way vs. rheumatoid arthritis (36).

Anti-inflammatory properties of melittin

In examining the effect of melittin on different organs, they deduced that melittin could exert anti-inflammation impacts on several kinds of cells including microglial cells by reducing the secretion of molecules with pro-inflammation features including TNF-α, NO, and IL-1ß. For example, melittin reduces pancreatic

inflammation through suppressing the release of pro-inflammatory factors via suppressing NF-κB function (Figure 2) (10). Since NF-κB has a key role in the control of inflammatory genes including cyclooxygenase, suppression of NF-κB function could be employed to treat inflammatory disorders (11); that is, the inhibition impact of melittin on inflammation caused by inhibition of inflammatory stimulants including TNF-α, and IL-1B through the interaction of melittin and the p50 sulfhydryl group, which in turn stimulates NF-κB (12, 13). In fact, melittin might change a sulfhydryl group of p50, thus preventing the affinity of p50 to binding element of NF-κB and inhibiting this pathway (37). In another study, it was observed that melittin in a high affinity could interact with IKK (a and b) (38).

On the other hand, the induction of COX-2 results in an increase in formation of prostaglandin and contributes to the pathophysiology of inflammation in both chronic and local conditions (39) and selective COX-2 suppressor have strong anti-inflammation effects (40). For example, NO acts as a pro-inflammatory molecule and results in tissue damage in inflammatory arthritis (41); The NO molecule could modulate the expression of COX-2 and react with reactive oxygen species to create further greatly reactive intermediate named peroxynitrate, which damages the tissue (42). So, the treatment potential of the combined suppression of nitric oxide synthesis systems and prostanoid through the suppression of IKK function has been determined as an efficient anti-inflammation therapeutic approach vs. the arthritis progression (38, 43).

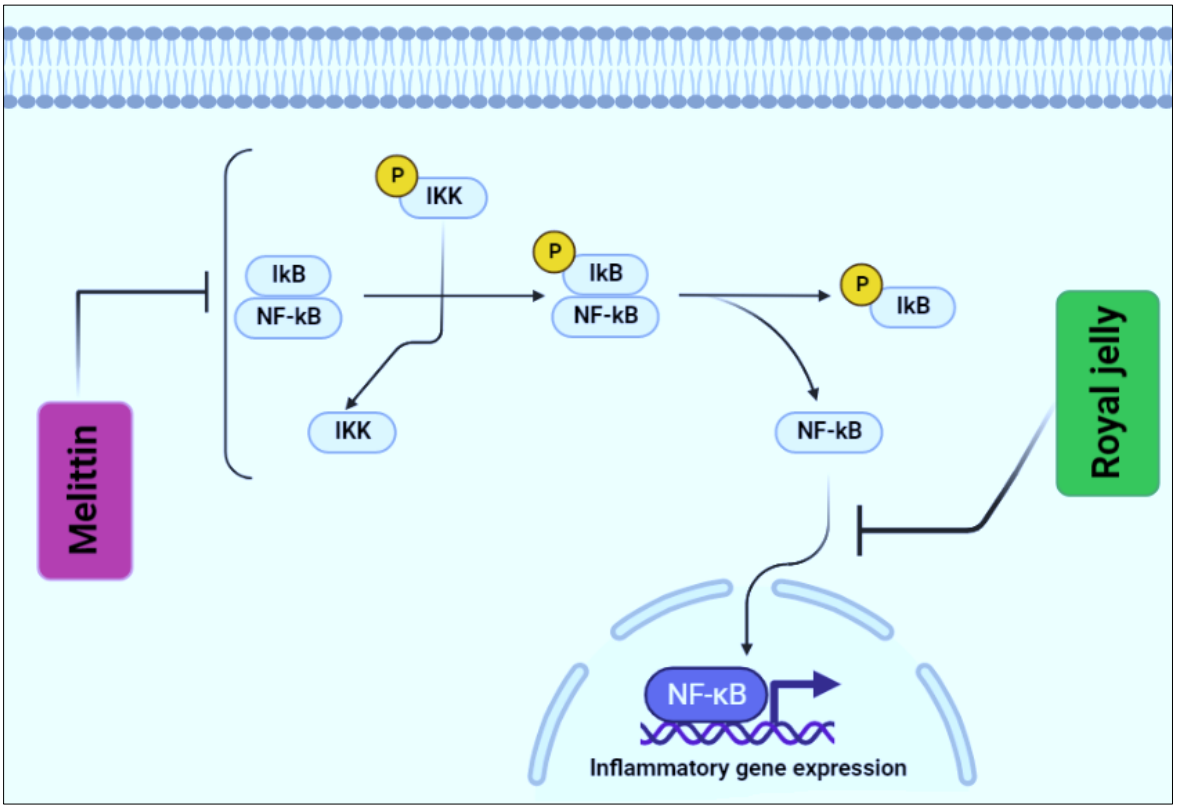

Figure 2. Anti-inflammatory mechanism of royal jelly and melittin. Royal jelly can stop the nuclear translocation of nuclear factor kappa β. The inhibitory effect of melittin on inflammation caused by inhibition of inflammatory stimuli through the interaction NF-κB pathway.

Molecular mechanism of wound healing

Immediately after clot formation, cell signals are produced, which lead to neutrophil response. Usually, about 48 to 96 hours after injury, with the accumulation of inflammation mediator molecules, prostaglandins are produced and adjacent vessels dilate to permit elevated cell transit. Neutrophils are stimulated by IL-1, TNF-α, TGF-ß, and products of bacteria are drawn to the injured area (44). Monocytes in the tissue and blood adjacent to the region are absorbed and become macrophages. Activation of inflammatory cells is especially critical for macrophages; an activate macrophage promotes angiogenesis process through synthesis of VEGF,

TNF-α, and FGF as well as fibroplasia through synthesis of EGF, IL-1, TGF-ß, TNF-α, and PDGF (45) and synthesizes NO from the activation of inducible nitric oxide synthase (iNOS) via TNF-α and IL-1, which reacts with radicals of peroxide ion oxygen to produce the further toxic radicals of peroxynitrite and hydroxyl (46). Finally, when neutrophils arrive in the wound area, it cleans the area from cell debris and invader bacteria. Neutrophils release proteolytic enzymes that kill bacteria and digest non-living tissues (47).

Melittin and wound healing

Melittin is a small linear cationic peptide soluble in water without a bridge of disulfide, which is the key element and the main painful substance of venom of bee. This molecule has treatment function vs. apoptosis, oxidative stress, and pain, like infection of bacteria (48). Based on multiple biological and pharmacological activities, topically formulated melittin is possibly capable to promote healing of wound. In a study that investigated the therapeutic potential of ceftriaxone and melittin nanocomplex (CTX-MEL), embedded in hydrogels for the diabetes therapy and it has also been investigated in acute wound healing, it was shown that this nanocomplex, after two weeks of daily topical use, improves the procedure of healing of wound at the molecular and morphological level and it could fight oxidative stress by reducing malondialdehyde and elevating the SOD and inflammation by reducing the levels of and TNF-α IL-6, like collagen-enhancing activities (increasing expression of Col1A1 and levels of hydroxyproline). It was also found that the nanocomplex of CTX-MEL truly elevates the tissue levels of TGF-1 and VEGF-A, two factors that have a key role in the recovery of tissue related to the procedure of wound healing in diabetic rats (49).

In another investigation, the wound healing features of a nanoformulation of melittin and diclofenac (MEL-DCL), in rats, were studied to evaluate whether these two compounds could synergistically apply the preclinical influence in a rat model of wound. And finally, it was observed that, in rats, DCL and MEL synergistically improved healing of wound, and it is interesting to note that the optimized formula achieved elevated and substantial function regarding the closure of wound, proliferation of fibroblast, inflammatory cell infiltration, deposition of collagen, and wound healing phase. This formula also has the ability to increase the production of hypoxia-inducing factor 1 alpha and the TGF-β1 synthesis, an anti-inflammation cytokine that plays a main role in the processes of wound healing, and levels of it reduces in patients with diabetes disorder. In impaired wound healing condition, DCL and MEL interact synergistically in an optimal formulation of MEL-DCL to promote healing of wound in mice via antioxidant, anti-inflammation, and collagen-enhancing activities (50, 51).

Royal jelly and wound healing

In daily life, skin damage is unavoidable. Recently, with the growing number of disorders including metabolic diseases and diabetes, chronic wounds have turned into a main problem in clinical processes. RJ, which has many physiological and biological features, has been applied since ancient times as a treatment for all kinds of wounds. The components of royal jelly, particularly defensin-1 and 10-HDA may enhance the healing of wounds via anti-inflammatory effects, developing the growth factors synthesis, or fibroblasts or keratinocytes migration (14). MRJPs can induce various human cell proliferation in vitro. Keratinocytes are accountable for epidermal repair after damage via a process called epithelialization. The proliferation, migration, and differentiation of keratinocytes and fibroblasts like the interaction among these cells are essential for effective re-epithelialization and healing of wound (52). In immature keratinocytes, the matrix metalloproteinases, such as MMP-2 and MMP-9 are expressed, and also plasmin is produced, which allows them to separate from the basal membrane and enables their migration (53). Gelatinase B (MMP9) is an endopeptidase, a zinc-dependent enzyme, contributed to the proteolytic degradation of proteins in the extracellular matrix including elastin and collagens III and IV. The mentioned endopeptidase has a main role in regular healing of wound, especially in extracellular matrix remodeling and epithelial regeneration. Healing of wound is disrupted in condition of MMP-9 inhibition. RJ induces the secretion of MMP-9 and increases the

dermal fibroblasts migration, changes the several lipids levels involved in the process of healing of wound, and elevates the generation of procollagen type I and TGF-β in fibroblasts. Moreover, 10-HDA, a special fatty acid present in royal jelly, stimulates the production of filaggrin protein and transglutaminase-1 in humans (54). Also RJ by changing the level of different lipids, increases the fibroblasts migration in humans and elevates the sphingolipids level that promote wound healing (55). The defensin-1 protein in royal jelly helps the regeneration of skin and closure of wound in skin via elevating the secretion of MMP-9 and migration of keratinocyte (56, 57).

Conclusion

Recently, with the growing number of disorders including metabolic diseases and diabetes, chronic wounds have turned into a main problem in clinical processes. Royal jelly, which has many physiological and biological features, has been applied since ancient times as a treatment for all kinds of wounds. Royal jelly components may enhance wound healing via an anti-inflammatory effect, promoting the growth factors synthesis, or the fibroblasts or keratinocytes migration. Bee venom has traditionally been employed in traditional eastern medicine as a drug for treatment of rheumatoid arthritis and relieve joint pain. In addition, in the past years, there have been many reports on the therapeutic effects of venom of honey bee in various diseases. One of the main elements of venom of bee is melittin, which has been reported to have many properties. Among these properties, we can mention the properties of pain relief, anti-inflammatory, and wound healing. With further investigations, we can hope that this compound will replace the current methods with high side effects as a useful compound in the treatment of wounds.

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