Review article

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POTENTIAL TREATMENTS OF TOOTH EXTRACTION WOUNDS: A REVIEW

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Wound healing is a complex process occurring in injured tissue with an aim to restore its homeostasis. Depending on the type of wound the closure can be defined as either primary or secondary. The process of wound healing is divided into several precisely programmed (defined) phases that mutually overlap and include (I) hemostasis, (II) inflammation, (III) proliferation, (IV) maturation and in some cases (V) bone regeneration. Tooth extraction represents a very common dental procedure which involves the extraction of decayed, periodontally affected or impacted teeth. After the extraction procedure, the formation of the wound is inevitable, as well as the pain and discomfort that follow it. In this review, we addressed the influence of low-level lasers, polarised light, curcumin and coenzyme Q_{10} on the tooth extraction wound healing process. It seems that there might be potential candidates which might enhance wound healing, after tooth extraction, by modulating different phases in the process. Thus, new and more in-depth clinical and pre-clinical studies need to be conducted in order to estimate the real efficacy and safety levels in humans before introducing them in every day clinical practice.

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The process of extraction wound healing

The wound is defined as the breakage in tissue continuity occurring after either physical, chemical and/or mechanical trauma. Regardless of the etiology of wound occurrence, every mammalian organism is trying to maintain tissue homeostasis, trying to preserve (regenerate) tissue integrity and function, by preventing hemorrhage and infection. Some conditions affecting the human organism, such as diabetes, cachexia, vitamin deficiency, exposure to radiation, etc., can significantly affect the process of wound healing. The wound healing process can be either primary or secondary closure.

Primary closure (*santaio per primam intentionem*) is referred to when the wound edges are smooth, relatively close and when there is no significant tissue damage or infection (1). Thus, one can expect that the primary closure is occurring when the wound is aseptic and fresh, which is mainly related to some small surgical wounds where the edges are sutured together. This type of wound is rarely affected by a significant degree of inflammation and is generally closing in up to 8 days, forming a linear scar and leaving no defect of the surrounding tissue.

Secondary closure (*sanatio per sekundam intentionem*) occurs in wounds with major tissue damage and defect, where it is impossible to bring the wound edges in close contact. The risk of infection, frequently seen immediately after trauma, in this type of closure is significantly higher due to a larger loss of tissue. This type of closure is slower, prolonged and can last up to a few months, and is often followed by a larger amount of granulation tissue and irregular scaring process (2). After surgical intervention in the oral cavity, post-extraction wound or wound involving bone loss, the wound closure is predominantly secondary.

The process of wound healing is divided into several precisely programmed (defined) phases that mutually overlap. They include (I) haemostasis, (II) inflammation, (III) proliferation, (IV) maturation and in some cases (V) bone regeneration. Each change in the line of their occurrence (e.g. prolongation of one of the phases) can lead to significant complications and to chronification of the process, chronic

wound. The changes between the phases are mainly depending on the maturation and differentiation of mastocytes, fibroblasts, keratinocytes, and macrophages, which play a key role in the wound healing process (3).

(I) Hemostasis

Haemostasis occurs after an initial trauma in order to prevent excessive blood loss or capture of blood within the damaged blood vessel. This relatively short phase (lasting around 15 min) involves vasoconstriction, thrombocyte adhesion, and aggregation, as well as coagulum formation. There are numerous systems that are participating in this process, such as injured walls of blood vessels, thrombocytes, all factors involved in the coagulation cascade, as well as fibrinolytic and phagocytic system (4).

Endothelial cells of the blood vessels are playing a key role in clot formation, which under physiological condition secrete thrombomodulin and heparin-like molecule causing prevention of blood coagulation (5). When the trauma of the blood vessel occurs, these endothelial cells decrease the secretion of the before mentioned molecules (coagulation inhibitors) and start to produce/secrete von Willebrand's factor.

Blood vessel damage acts as a switch for thrombin production, which further converts intravascular fibrinogen to insoluble fibrine allowing the formation of a provisory matrix comprised of fibrin, fibronectin (from plasma) and some components of the extracellular matrix (ECM) (4). Minutes after the trauma immune system cell activation occurs, followed by thrombocyte degranulation and bacterial products degradation. These processes cause a release of pro-inflammatory cytokines and numerous growth factors (TGF-β, PDGF, EGF, FGF) from the surrounding tissue and cloth (4).

(II) Inflammation

One of the first researchers that recognized the importance of inflammation in the wound healing process was John Hunter almost 200 years ago (6). The initial stimulus for this process is trauma itself, where after hemostasis, 5 to 6 h after the trauma, the acute inflammatory reaction is developed in the injured tissue. This reaction is characterized by the release of the different substance from necrotic cells that lead to local, regional and systemic inflammatory response (6). The main feature of the local inflammatory response is inflammatory cell migration mainly neutrophils, macrophages, and lymphocytes (7).

The key role of neutrophils is the removal of the microorganism, necrotic tissue and other cell debris that is formed after tissue damage. However, these cells are also responsible for the generation of reactive oxygen species (ROS) and protease production, which lead to additional tissue damage and potentially can prolong the regeneration process (8).

There are numerous phases in the wound healing process that involve macrophage function. In the early phase, they release cytokines that stimulate an immune response, which is reflected in leukocyte activation and migration to the site of trauma. Addition, macrophages also eliminate necrotic cell material, which mainly consists of necrotic neutrophils, allowing the transition for the inflammatory to the proliferative phase of the wound healing. At the same time, the change in their phenotype stimulates keratinocytes, fibroblast and angiogenesis, which irretrievably leads to the proliferation phase (9).

This phase is a crucial step that further leads to the finalization of the wound healing process and it can directly be related to the development of numerous complications (10). It is obvious that attitude towards inflammation needs to be changed from a simple reaction to injury or infection to a process that can be used in the diagnosis and can represent a therapeutic target (11).

The posttraumatic acute inflammatory response consists of three phases: nerve, immune and endocrine phase.

1. Never phase (immediate, initial, progressive oxygenation)

This phase is dominated by sensory and motoric reactions of the injured tissue. Sensory reactions involve pain which represents an efferent neural response of somatic motoneuron and autonomous nervous system to painful sensation (12). In the earliest phases of the inflammatory response numerous substances are released into the bloodstream and accumulate into the intestinal tissue, these include cortisol, aldosterone, biogenic amines, and glucagon (13). Motoric reactions involve the contraction of smooth muscle cells that are part of blood vessels and their contraction significantly contribute to the development of ischemia and local/systemic blood redistribution. The intensity of tissue ischemia is in direct correlation with a further inflammatory response (14), where the formed edema significantly affects cell metabolism and gene expression and is consider to initialize cell anabolic activity (14).

After ischemia, vasodilation and reperfusion of the injured tissue are responsible for the interstitial edema formation, as well as for the production of ROS and nitrogen reactive species. These molecules increase lipid peroxidation, cause cell membrane permeabilization which further aggravates the edema process (15). Besides the aforementioned roles of edema, this process also affects tissue morphogenesis, cell migration and differentiation, as well as the extracellular matrix (ECM) remodeling during wound healing. Intensified tissue perfusion can also activate fibroblasts, causing ECM remodeling and fibrous tissue formation (16). The role of mast cells should not be neglected as well, where besides vasodilating substance (histamine, serotonin) these cells liberate proteolytic enzymes contributing to the formation of interstitial edema (16). Thus, effective control of edema can be significant for tissue regeneration, since the damaged tissue can't be regenerated without a complete absence of edema.

Cell response to hypoxia leads to the expression of hypoxia-dependent and independent induci-

ble factor (HIF). These two pathways, HIF dependent and independent, allow the cell to survive by inducing the transcription genes that are involved in cell metabolism, migration, invasion, and angiogenesis (17). Damaged tissue is going through the phase of metabolic hypoxia, where although there is a sufficient oxygen concentration they are not able to use it for respiratory processes. The activation of HIF-independent pathway enables the cell to survive extremely low oxygen concentrations and the formation of new tissue, which is necessary for wound healing. On the other hand, the activation of the HIF-dependent pathway, during the states with mild and moderate hypoxia, promotes vascularisation and enable cell survival as well (18).

2. Immune phase (leucocytic, intermediary)

Following ischemia and reperfusion phase the infiltration of the damaged tissue by both inflammatory cells and bacteria is occurring. During low oxygen concentration, numerous cells (fibroblasts, macrophages, mast cells, lymphocytes) migrate to the interstitium probably in order to provide the tissue with necessary energy (14). One can say that the "true" inflammatory cells that migrate to the damaged tissue are neutrophils, followed by mast cells and macrophages and some of these cells arrive from blood cloth where they were previously trapped. Activated neutrophils are secreting a large number of substances (ROS, peptides, leukotrienes, prostaglandins) and enzymes (elastase, cathepsin G-proteinase, urokinase), with a role to remove necrotic material. These molecules are one of the reasons why the wound healing can be prolonged since they act on other healthy cells as well.

Before migrating from circulation to tissue monocytes are going through differentiation into tissue macrophages. There are two types of macrophages, M1 (classically activated macrophages) and M2 (alternatively activated macrophages), where the first one secretes inflammatory cytokines (IL-1, -6 and -23) and ROS, while the second ones are involved in angiogenesis and tissue remodeling (19). Additionally, T-helper lymphocytes play a key role in the modulation of macrophages differentiation. Type 1 T lymphocytes (Th1) produce different cytokines (INF-γ and TNF-α) that lead to the transformation of macrophages to M1 subtype, while type 2 T lymphocytes (Th2) induce M2 polarization by secreting IL-4, -5 and -13 (19). Additionally, B lymphocytes are found to be involved in the development of tissue fibrosis (19).

Besides the leucocytes, thrombocytes are found to be enrolled in the initiation and propagation of the inflammatory response as well. Thrombocytes are known to be rich in different secretory granules (alpha, delta and lambda type) and lysozymes (4). These granules contain various signaling molecules that allow other cells adhesion or act as chemokines or growth factors. Among the most recognized growth factors found in these granules is platelet-derived growth factor (PDGF) which even found its potential use as a healing agent (20). Apart from PDGF other growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), haptic growth factor (HGF), etc. could be found (20).

In the inflammatory response, the activation of Toll-like receptor (TLR) plays an important role since they lead to the transcription of nuclear factor kappa B (NF-(k)B), AP-1 and interferon regulating factor (IRF). This TLR (TLR-2 and TLR-4) activation during ischemia and reperfusion phase of the wound healing can be seen during both sterile and unsterile wounds (8). This activation of NF-(k)B, one of the major steps in inflammatory phase, leads to a cascade reaction which results in specific gene expression which in turn cause cytokine and chemokine, as well as their receptor, synthesis (6, 21). Besides its role as immune phase stimulator NF-(k)B is very important for the inflammation resolution and tissue reparation.

In every day clinical practice this phase is followed by wound infection, where a different type of secretions due to bacterial colonization appears. One of the most common pathogens that infect wounds is *Staphylococcus aureus*, which due to the production of numerous enzymes (nucleases, proteases, lipases, collagenases, etc.) prolong wound healing process (22).

3. Endocrine phase (late, angiogenesis)

The formation of new blood vessels (angiogenesis) in this final phase of the inflammatory process appears to be a dominant feature (23). Interestingly newly formed endothelial cells play an important immunomodulatory role at the beginning of the inflammation, thus affecting the final resolution and progression of tissue regeneration (23). The process of angiogenesis is based on endothelial proliferation (microvascular growth) and can be divided into five clear phases (23):

1) disintegration of basement membrane and the formation of new blood vessels that penetrate into perivascular stroma;

2) migration of endothelial cells to the newly formed blood vessel;

3) endothelial cell proliferation;

4) canal formation, branching and formation of vascular loops;

5) perivascular apposition of pericytes and smooth muscles around blood vessels, as well as "de novo" synthesis of basement membrane proteins.

The process of angiogenesis is regulated by numerous factors, such as VEGF, TGF, FGF-2, PDGF, angio-protein, angiotensin II, endothelin, andromeduin, adipokines (leptin, adiponectin), neuropeptide-Y and vasoactive intestinal peptide (24). Angiogenesis is tightly connected to the process of granulation tissue formation since it is necessary to enable cell survival in newly formed tissue (25). The process of granulation (granulation phase) starts three to four days after tissue trauma, and under the impact of macrophages, fibroblast, keratinocytes, and endothelial cells. In parallel to granulation tissue formation, vascular cells react with the provisional matrix comprised of fibrin, fibronectin and vibronectin leading to change in a fibrous matrix.

The resolution of the inflammatory phase is mainly guided by local mediators that are synthe-

sized from fatty acids and these include eicosanoids, docosanoids, resolvins, and lipoxins. They mainly act as ROS production inhibitors, leading to a decrease in blood vessels permeability, blockage of adhesion molecules for leucocytes and endothelial cells, as well as to a decrease in chemokine synthesis (25). The progression of inflammation resolution stimulates the process of epithelization, which occurs only a few days after tissue trauma by migration of keratinocytes to the edge of the wound. This migration and organization of keratinocytes is a complex process that is guided by a number of small mediators such as growth factors (EGF, TGF-α, PDGF), integrins, metalloproteinases (MMP-1, -9 and -10), plasminogen and structural proteins. All these molecules affect the provisional matrix organization and collagen degradation and at the end of this phase the change in keratinocyte phenotype from mesenchymal to epithelial (26).

Fibroblasts also play an important role in inflammation resolution, where besides ECM formation they can influence the process of angiogenesis by secreting different growth factors. Some growth factors, such as PDGF and TGF-β, can influence the differentiation of fibroblast to myofibroblasts, thus helping the wound to contract (27, 28). Also, these cells mainly influence the formation of ECM by synthesizing collagen, elastin, glycoproteins, etc. During this phase, many cells, macrophages, endothelial cells, myofibroblasts are going through apoptosis which leaves the tissue comprised mainly of collagen fibers and ECM proteins. The remodulation phase starts 2-3 weeks after tissue injury and sometimes lasts up to a year, while in some cases this phase can last much longer (19, 27, 28).

(III) Proliferation

The proliferation phase is taking place between the 4th and 21st day after the trauma, and since it overlaps with inflammatory phase, there is a thin line between them, it makes it almost impossible to clearly separate one phase from another. This phase is characterized by fibroblast and keratinocyte proliferation, which will further lead to growth factor secretion, angiogenesis stimulation, ECM formation and epithelization (27, 29). The formation of ECM is mainly depending on fibroblast presence and their ability to produce collagen (maximum deposition seen 21 day after trauma), glycosaminoglycans and proteoglycans (27). Besides these roles' fibroblasts act as one of the main cellular components of granulation tissue formed at the bottom of the wound. Keratinocyte differentiation is also a very important step in the wound healing process since the change in creatine production enables tissue elasticity and easier migration (30).

(IV) Maturation

Following proliferation and ECM synthesis the wound healing process in entering its final phase of remodeling, which starts 2-3 weeks after initial tissue trauma and can last up to a year (27). Complete reepithelization stimulates fibroblast, myofibroblasts and keratinocytes to produce fibrin, fibronectin and collagen III. Fibroblasts are the key cells of this phase since they are responsible for transformation from collagen type III to collagen type I (Tracy et al., 2016). This process is lasting for around 30 days, while the maximum is expected somewhere between 42 and 60 days after an initial injury (27). The change in ECM is occurring in order to form a new tissue (27) and represent a change in provisional ECM into the mature matrix, comprised mainly of collagen type I fibers and molecules such as actin and myosin within the cells (31).

The scar tissue is going through the physiological contraction, that is dependent on myofibrils, which is occurring through the process of wound healing (27). In the end stage of successful tissue reparation apoptosis of cells that contain myofibrils is starting, followed by deactivation and differentiation of keratinocytes (27). Maturation phase is also characterized by regression of newly formed capillary vessels and the density of the vessels within the tissue is returning to the level before the injury.

(V) Bone regeneration

Some wounds, such as those after tooth extraction, are going through an additional phase which involves bone tissue regeneration. This rather complex mechanism acquires the involvement of different types of cells and biological agents that stimulate cell proliferation, differentiation and tissue organization (32). The most important cells in this type of regeneration are osteoblast which is responsible for the migration of bone cells (33). An additional characteristic of this regeneration is the process of ECM mineralization which starts around 7th day which starts from the edge of the defect and goes towards the middle, while in the case of extraction defects from the apical third and edge of the alveolar ridge. The newly formed bone tissue and trabeculae are resorbed 14 days after the injury and this is considered the begging of the bone remodeling and maturation (34). Around 21 day after tissue injury, the number of young blood vessels is drastically lower, and the defect is a field with bone trabeculae (35). The final step of mineralization begins after 4 weeks and involves consolidation of bone tissue and formation of regular bone trabecules, as well as differentiation of osteoblasts into osteocytes. This phase is known to last for the very long time period and in most cases, it is finished after a year.

Therapeutic approaches in tooth extraction wound healing

Having in mind all previously described processes, as well as factors that can influence them, one cannot oversee a number of places for different therapeutic approaches. Standard, everyday clinical approaches involve the removal of local causes, wound revision and addressing of systemic disorders. Faster wound healing leads to pain elimination, decrease in swelling and infection, as well as to an increase in life quality in patients (22, 36).

A great number of studies evaluated the course of the wound healing process, where the experimental model in rats represents a perfect model for

the evaluation of this process and the obtained results give a clear insight into processes happening in humans (28). Different studies applied various procedures (chemical and physical) in order to estimate their potential in accelerating the wound healing process.

(I) Physical procedures

Among the most popular physical procedures applied for the treatment of wounds after tooth extraction are low-level lasers (LLL) (37). In a group of subjects, LLL therapy was reported to remarkably decrease trismus, swelling and intensity of pain on the first and the seventh postoperative days after third molar extraction (38). The LLL (helium-neon and argon laser) were found to be able to increase collagen synthesis, estimated based on hydroxyproline concentration in scar tissue (39). Also, LLL induce the formation of new blood vessels (angiogenesis) and modulate the expression of MMP-2 in the newly formed granulation tissue (40). In patients with extracted molars, LLL increased salivary IgA and albumin concentrations and decreased subjective feelings during treatment (41). Besides the effects of LLL on soft tissue healing it also enhances the bone tissue regeneration by increasing cell proliferation and the number of osteoclasts (37), while other studies found no effect of LLL on ossification process (41). However, one should not neglect the possible carcinogenic potential of laser radiation therapy (39).

On the other hand, polarised light, which involves more wavelengths (polychromatic), with small energy as well, found its application for the treatment of almost all complications that follow tooth extraction wound (37, 42-44). This light is obtained through the system of specially designed crystals which transduce light at wave lengths between 400 and 2000 nm (42). The results of several studies conducted suggest that polarised light treatment affects all phases of wound healing that follow tooth extraction (42-44). In the inflammatory phase, polarized light increases the number of lymphocytes present in wound tissue and induces a faster transition from monocytes to macrophages. The function of macrophages is also affected and it is found that this type of treatment increases their number, as well as the release of biologically active substance (42). In an animal model six-day exposure to this type of light lead to a faster epithelisation process of extraction wound, where narrower defect with two-layered cubicle epithelium was found in treated animals while in those from the control group only granulation tissue was seen at this time point (43). Up to know no undesired effects were observed during the usage of polarised light.

(II) Chemical procedures – pharmacological treatment

There is a large number of compounds both synthetic and naturally occurring ones that were assayed for their potential in enhancing the tooth extraction wound healing process. However, due to the inability to include all the research conducted we will focus our attention on two well-studied antioxidants curcumin and coenzyme Q_{10}.

Curcumin (Cur) is a naturally occurring compound, found in *Curcuma longa*, which has a long history of ethnomedicinal usage (45). Besides its antitumor, antibacterial, antiviral, antifungal, antiulcer and anti-inflammatory properties, it is proven to possess a wound healing property as well (45-47). Its traditional usage suggests that it can be applied to wounds in a form of ointment (46), where it enhances the process of healing. The proposed mechanism of action involves the inhibition of inflammatory processes, which leads to faster and better healing of acute and chronic wounds (47). These include downregulation of TNF-α, IL-1, NF-kB and MMP-9 transcription and upregulation of IL-10 and catalase, superoxide dismutase and glutathione peroxidase (21, 47). In a model of tooth extraction wound healing, it is found that Cur enhances epithelization process and increases the density of newly formed blood vessels in soft tissue that surrounds wound. Also, measured biochemical parameters that reflect tissue inflammatory reaction (NO and myeloperoxidase (MPO)) were found to be decreased (suppressed) in the group that received Cur (45). In other models of inflammation Cur inhibited cyclooxygenase and 5-lipooxygenase, decreased histamine liberation and production, enhanced the activity of cortisol and increased tissue blood flow (47).

Coenzyme Q_{10} (CoQ_{10}) is a ubiquitous lipophilic molecule mainly present in its *trans* form (48). In cells it is located in the membrane of different organelles, especially in mitochondria, in two forms: oxidized and reduced (49). Its concertation depends on cell type, where cells which have higher energy (cardiomyocytes, hepatocytes, skeletal muscle cells) needs the concentration of CoQ_{10} is higher. It acts as a radical scavenger in cells and is incorporated in several mitochondrial enzymes (respiratory chain enzymes), thus its deficiency is tightly related to a decrease in tissue oxidative defenses (49). Among others, CoQ_{10} protects ROS-induced DNA damage and together with tocopherol protects lipids from peroxidation (50). In gingival biopsies obtained from patients with damaged periodontal tissue, researchers found a decrease in CoQ_{10} and it is suggested that its application in oral mucosa, in a form of different supplements, lead to faster wound healing (51). Local application of CoQ_{10} on rat tooth extraction wounds significantly faster lead to wound healing, possibly by decreasing tissue inflammation estimated through NO and MPO levels (48). Also, the same work showed that encapsulation of CoQ_{10} in nanoparticles increases the effectiveness of this compound by increasing its solubility, concentration and delivery in target tissue after its application (48). On a molecular level, the application of CoQ_{10} to oral cavity wounds was proven to decrease proinflammatory cytokines expression (IL-1 and TNF-α), as well as of some molecules involved in inflammation (NF-kB and hypoxia factor-1) (52). Here again, besides soft tissue CoQ_{10} was shown to be able to affect bone regeneration in a similar animal model of tooth extraction (52).

Conclusion

It seems that there is a number of potential candidates which might enhance wound healing, after tooth extraction, by modulating different phases in the process. Over the years researchers collected a vast amount of information regarding the potential mechanisms by which these candidates modulate the wound healing process and it is not so clear which of them might be the best one for the treatment. Thus, new and more in-depth clinical and preclinical studies need to be conducted in order to estimate the real efficacy and safety levels in humans before introducing them in every day clinical practice.

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POTENCIJALNI TERAPEUTSKI PRISTUPI U TRETMANU RANA NAKON EKSTRAKCIJE ZUBA: PREGLEDNI RAD

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Zarastanje rana je kompleksan proces koji se dešava nakon povrede tkiva sa ciljem povraćaja njegove homeostaze. U zavisnosti od tipa rane, može biti primarno ili sekundarno zarastanje. Sam proces zarastanja rane podeljen je u nekoliko precizno definisanih faza koje se međusobno vrlo često preklapaju, a one uključuju: (I) hemostazu, (II) inflamaciju, (III) proliferaciju, (IV) maturaciju, a u nekim slučajevima i (V) koštanu regeneraciju. Ekstrakcija zuba je veoma česta procedura u stomatologiji i predstavlja ekstrackiju pokvarenih, periodontalno izmenjenih ili impatkiranih zuba. Nakon ekstrakcije, nastanak rane je neizbežan, a vrlo često je ovaj proces praćen bolom i osećajem nelagodnosti. U ovom revijalnom radu osvrnućemo se na mogućnost primene lasera male snage, polarizovane svetlosti, kurkumina i koenzima Q_{10} u terapiji rana nastalih ekstrakcijom zuba. Na osnovu pregleda literature može se zaključiti da postoje potencijalni kandidati koji mogu da poboljšaju zarastanje rane nakon ekstrakcije zuba, jer moduliraju različite faze u procesu zarastanja. Takođe, smatramo da su neophodne nove i detaljnije kliničke i pretkliničke studije koje bi odredile pravi uticaj i potencijalne neželjene efekte ovih terapeutskih mogućnosti kod ljudi pre no što se krene sa njihovom primenom u svakodnevnoj kliničkoj praksi.

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Ključne reči: *rana, ekstrakcija zuba, laseri male snage, polarizovana svetlost, kurkumin, koenzim Q_{10}*