ORIGINAL ARTICLE

LGR6 and β-catenin Expression in Wound Healing of Zinc Oxide and *Curcuma longa* Extract Dressing Application in *Rattus norvegicus*

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ABSTRACT

Introduction: The eugenol component in commonly used wound dressings in dentistry can cause allergies and has a risk of cytotoxicity, necessitating the search for better materials. *Curcuma longa* rhizome, an herbal medicine commonly found in Indonesia, could serve as an alternative material. The wound-healing process relies to epidermal stem cells and two proteins that significantly influence epidermal stem cell growth are β-catenin and LGR6. This study aimed to evaluate the efficacy of zinc oxide and *Curcuma longa* extract combination dressing in promoting wound healing through β-catenin and LGR6 expression. **Materials and Methods:** Forty male Wistar rats were randomly divided into eight groups (n = 5). Excision wounds were made on their back area. The treatment groups (T3, T5, T7, T14) received zinc oxide and *Curcuma longa* extract dressing, while the control groups (C3, C5, C7, C14) did not receive any dressing. Rats were sacrificed on days 3 (T3, C3), 5 (T5, C5), 7 (T7, C7), and 14 (T14, C14) to determine β-catenin and LGR6 expression through immunohistochemical staining. Tukey HSD and one-way ANOVA were used for data analysis. **Results:** Immunohistochemical staining revealed a significant increase ($p<0.05$) in β-catenin expression between the control and treatment groups on days 3 (C3, T3), 5 (C5, T5), and 7 (C7, T7). LGR6 expression was significantly upregulated ($p<0.05$) only on day 14 (C14, T14). **Conclusion:** Zinc oxide and *Curcuma longa* dressing administration increased β-catenin and LGR6 expression in the wound healing process of *Rattus norvegicus*.
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Keywords: β-catenin, LGR6, human and medicine, wound healing, zinc oxide-*Curcuma longa* dressing

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INTRODUCTION

A wound is characterized as a disruption of the tissue's normal anatomical structure brought on by the trauma and the discontinuity of the skin's or mucosa's epithelial lining due to physical or thermal damage [1]. Trauma can cause damage, and it is crucial to ensure the wound is cleaned and covered properly to prevent the spread of illness and additional damage [2]. As an essential physiological process, cutaneous wound healing involves the cooperation of numerous cell types and their byproducts [3]. The wound healing process comprises four overlapping phases: coagulation and hemostasis, inflammation, proliferation, and remodelling [4].

The wound-healing process is driven by the repair and regenerative abilities of cutaneous tissue, which rely on epidermal stem cells [5]. Epidermal stem cells, known as multipotent cell types, play a crucial role in this process by generating β-catenin and LGR6. These proteins are essential for optimal wound healing, ensuring effective tissue repair [6]. The differentiation and proliferation of relevant cells, such as keratinocytes, fibroblasts, and epidermal stem cells (ESC), with the aid of various biological cues, determine the effectiveness of wound healing. These signals have a major impact on how epithelial tissue cells behave biologically during wound healing [7]. In the wound-healing process, β-catenin plays a key role in regulating the expression of genes that promote cell proliferation and migration through the Wnt signaling pathway [8]. Whereas LGR6, a member of

the type B family of LGR proteins, has been thoroughly investigated for its potential as adult stem cell markers and regulators [9].

Wounds require isolation from the non-conducive external environment to accelerate the healing process [10]. Applying dressings to wounds is essential for both wound healing and the prevention of infections [11]. In dentistry, zinc oxide-eugenol dressings are commonly used due to their good anaesthetic and antibacterial properties. However, eugenol can cause allergies, promote tissue inflammation and soft tissue necrosis, and has a risk of cytotoxicity at both low and high doses [12]. Therefore, finding a better therapeutic strategy is necessary.

Humans and medicine are inseparable, and traditional medicine is no exception. Owing to its accessibility and few adverse effects, traditional medicine and herbal remedies are used for healthcare requirements by 80% of the Asian and African populations, according to the World Health Organization [13]. *Curcuma longa* rhizome is one of the rhizomes often used in herbal medicine [14], widely employed for therapeutic purposes in Indonesia. Considering its wide availability and its therapeutic property, the extract of *Curcuma longa* could be proposed as a good alternative to eugenol. Thus, this study aimed to evaluate the efficacy of zinc oxide and *Curcuma longa* extract combination dressing in promoting wound healing by assessing the expression of β-catenin and LGR6

MATERIALS AND METHODS

Animal and ethical approval

Forty male Wistar rats (*Rattus norvegicus*) were acquired from Wistar Farm in Malang. The rats weighed between 200–300 g and were approximately three months old. The Universitas Airlangga Research Ethics Committee of the Faculty of Dental Medicine authorized the experimental methods used in this study (Number 583/HRECC.FODM/VIII/2022).

Experimental design

Using a posttest-only control group approach, this study was conducted in an experimental laboratory. Eight groups of five rats each were created from the forty rats. The treatment group (T3, T5, T7, T14) received a dressing containing zinc oxide combined with *Curcuma longa*, while the control group (C3, C5, C7, C14) did not receive any dressing. On days 3 (T3, C3), 5 (T5, C5), 7 (T7, C7), and 14 (T14, C14), the rats were sacrificed.
Zinc Oxide and *Curcuma longa* combination dressing preparation and wound treatment.

Curcuma longa was processed in the UPT Laboratory of Materia Medica Batu. *Curcuma longa* powder was extracted by maceration. Zinc oxide and *Curcuma longa* extract were combined on a mixing pad with a stainless-steel spatula for one-part powdered zinc oxide (0.3 grams) and one part extract (0.3 grams) until homogeneous in 60 seconds. The mixture was then applied as a dressing on the excised wound surfaces and left until it hardened.

Preparation of Rat

Each rat in the group was anesthetized using 2 ml of ketamine administered on the right side of the groin. The rat's hair was shaved in the vicinity of the surgical site, and 70% ethanol was used to disinfect it. A full-thickness excision wound measuring 6 mm in length, 6 mm in width, and around 2 mm in depth was made on the dorsal area until the fascia was visible. The wound was cleaned using sterile normal saline (0.9% NaCl). In the treatment group (T), the rats were given a zinc oxide dressing and *Curcuma longa* extract (0.3:0.3 grams) and then covered with hypo-allergenic tape (Hypafix, Germany). In the control group (C), the wound was only covered with hypo-allergenic tape without dressing application. The dressing was applied once and was expected to last until the animal was sacrificed. After sacrifice, the wound area was dissected and processed into formalin-fixed paraffin-embedded (FFPE) slides.

Immunohistochemical staining of β-catenin and LGR6

Samples were stained using immunohistochemistry staining by deparaffinization, rehydration, blocking for non-specific binding, antigen retrieval, antibody staining for the primary and secondary antibody, and counterstaining with hematoxylin staining. The primary antibody used to detect LGR6 was Anti-LGR6 Antibody (F-5): sc-393010 (Santacruz Biotech, USA), while Anti-β-catenin-catenin Antibody (E-5): sc-7963 (Santacruz Biotech, USA) was used to detect β-catenin-catenin. Both antibodies were diluted to a concentration of 1:200 and incubated overnight as per the manufacturer's suggestion. The results were observed under light microscopes at 1000x magnification and documented by Nikon Eclipse E100 (Nikon, Japan).

Statistical analysis

SPSS version 23 (IBM, New York, USA) was used to analyze the collected data. The Levene test was used to determine homogeneity, and the Kolmogorov-Smirnov test was used to determine data normality. Significant differences were analyzed using One-way analysis of variance (ANOVA) and Tukey honestly significant difference (HSD) test, where $p<0.05$ indicated statistical significance.

RESULTS

The effect of a wound dressing containing *Curcuma longa* extract on LGR6 and β-catenin expression under immunohistochemistry evaluation can be seen in Figures 1 and 2, with positive expression shown as a brown color. The number of cells with positive LGR6 and β-catenin expression is shown in Table 1.

Based on Table 1, Figure 3, and Figure 4, both LGR6 and β-catenin were expressed at higher levels in the treatment group than in the control groups at all durations. To determine the significant difference between groups, a one-way ANOVA test was conducted after the Kolmogorov-Smirnov and Levene tests, which showed a normal distribution and homogeneity in both groups. A post hoc test was then performed to identify significant differences between sample groups, as the one-way ANOVA findings indicated significant differences ($p<0.05$) in each of the sample groups. The post hoc method used was Tukey HSD.

According to the results of the Tukey HSD test presented in Table II, there was an overall higher expression of LGR6 in treatment groups compared to control groups (as shown in Figure 3). However, only the treatment group sacrificed on day 4 (T14) exhibited a significantly higher expression of LGR6 ($p=0.033$) compared to the control group with the same duration (C14). Although the graphical representation in Figure 3 indicates an increasing trend in LGR6 expression on days 3, 5, and 7 in the treatment groups, only the T14 group showed a significantly higher expression compared to T3 group (Table II). No significant difference was observed between T5 and T14 groups.

For β-catenin, the results of the Tukey HSD test (Table II) indicate that all treatment groups exhibited significantly higher expression compared to their respective control groups ($p<0.05$), except between C14 and T14 ($p=0.096$). However, there was no significant increase in β-catenin expression observed among the treatment groups of different durations ($p>0.05$)

DISCUSSION

The intricate process of cutaneous wound healing involves the ability of skin tissue linked to epidermal stem cells to repair and regenerate itself. A multipotent cell type called epidermal stem cells is created to promote wound repair in injured tissue [15]. In this study, we found that the application of zinc oxide and *Curcuma longa* extract combination dressing could stimulate epidermal stem cells to accelerate wound healing, as observed through the expression of β-catenin and LGR6. The expression of β-catenin is significantly upregulated in the wound covered by zinc oxide and *Curcuma longa* extract combination dressing compared to the one without (see Figure 4). The expression is significantly higher from the early wound healing phase on the 3rd day until the 7th day (see Table 2). The upregulated β-catenin expression in the treatment group is due to the *Curcuma longa* extract in the dressing. *Curcuma longa* contains curcumin, which was identified as a potent inhibitor of GSK-3β [16,17]. GSK-3β is a protein that forms the β-catenin destruction complex together with APC, CK, and AXIN in the cytoplasm [18]. This condition prevents the destruction of β-catenin and allows its accumulation in the cytoplasm. In the wound without any dressing, trauma can also inhibit GSK-3β, but through Wnt signaling. Excision trauma causes hypoxia in the tissue, which disrupts tissue homeostasis, thus triggering extracellular Wnt proteins to the injured area [4]. The Wnt protein attaches itself to the cell surface's frizzled (FZD) receptor to start Wnt signaling [18]. This resulted in the increasing trend of β -catenin from day 3 to day 14 in the control group (see Figure 4). But the additional blocking of GSK-3β from curcumin multiplies the β -catenin level and leads to the surge of β -catenin expression since day 3 for the treatment group.

The accumulation of β -catenin in the cytoplasm triggers its translocation to the nucleus, where it initiates the transcription of the Wnt gene by binding to TCF/LEF [18]. This role of β -catenin in Wnt signaling is crucial for growth stimulatory factors that maintain tissue homeostasis, support cell renewal, and aid in regeneration [19]. During the proliferative stage, β -catenin is expressed in dermal mesenchymal cells, enhancing their motility and metabolic movement rate, as well as promoting fibroblast invasion. β -catenin plays a vital role in the development of dermal and epidermal structures, influencing both skin formation and healing processes. Additionally, β -catenin in Wnt signaling is essential for endogenous angiogenesis, enhancing vascular repair [20]. Several target transcription genes in the Wnt signaling pathway, including collagen I, collagen III, EGFR, fibronectin, keratin-14, and LGR6, play key roles in wound healing [21,22]. Collagen I and III act as extracellular matrix (ECM) proteins during the proliferative phase, while EGFR controls keratinocyte migration to the wound site. Keratin-14 and fibronectin contribute to ECM development and reepithelialization [23-26].

The proliferative phase requires β -catenin to regulate fibroblast activity [27]. This required β-catenin is anticipated for the TGF-B/Smad pathway, which emerges in the early stages of wound healing and is a significant signaling route involved in skin wound healing, regulating this process throughout the proliferative phase [28]. Prolonged increase of β-catenin activity beyond normal healing parameters can lead to excessive fibrosis and the production of keloid-like scars [20]. Interestingly, in the treatment group, β-catenin levels remained stagnant from day 5 to 14, contrasting with the control group, where β-catenin expression surged from day 5 to 14, resulting in no significant difference in expression between the control and treatment groups on day 14 (see Figure 4 and Table 2). This finding suggests that curcumin may control β -catenin activity, preventing a prolonged increase that could lead to fibrosis.

As one of the Wnt gene targets, LGR6 increases in response to the Wnt signaling pathway activation of β -catenin [22]. This is in accordance with our results, where both the control and treatment groups showed

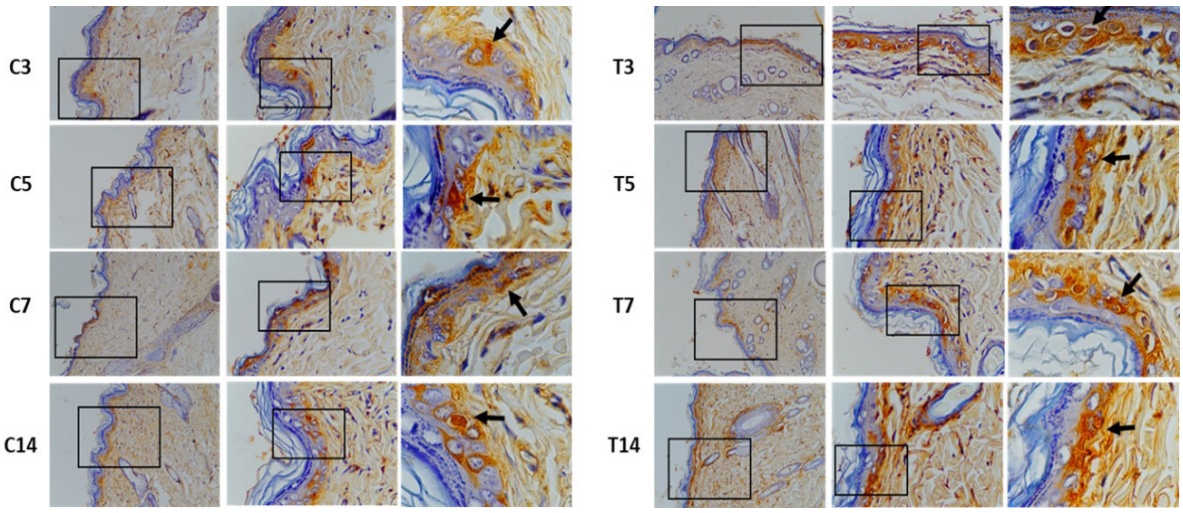

Fig. 1: Histological sections of LGR6 expression in the control group (left) and treatment group (right) on day 3 (C3, T3), day 5 (C5,T5), day 7 (C7,T7), and day 14 (C14,T14) at magnifications of 100x, 400x, 1000x

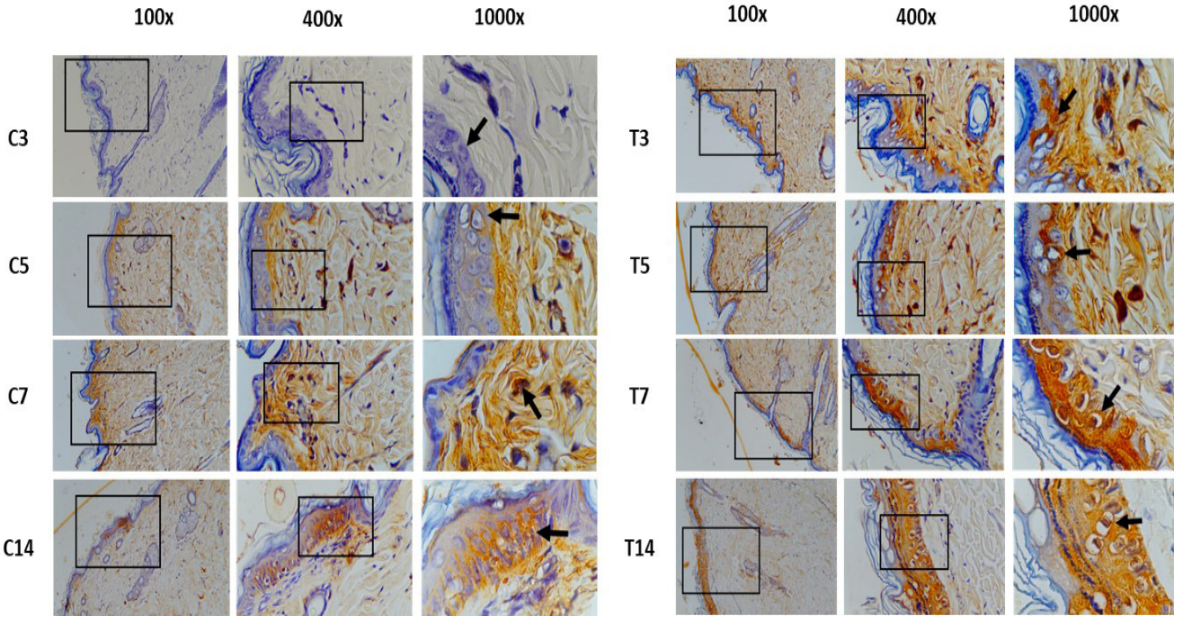

Fig. 2: Histological sections of β-catenin expression in the control group (left) and treatment group (right) on day 3 (C3, T3), day 5 (C5,T5), day 7 (C7,T7), and day 14 (C14,T14) at magnifications of 100x, 400x, 1000x

a significant increase from day 3 to day 14 (see Figure 3 and Table II). However, higher LGR6 expression in wounds covered with zinc oxide and *Curcuma longa* extract combination dressing was noted as a result of GSK-3β blocking by curcumin, which leads to more β -catenin accumulation and results in higher expression of LGR6. LGR6 is the most primitive stem cell protein in the epidermis, contributing to wound healing. Additionally, LGR6 is part of the LGR protein family, which has been investigated in several organs as a marker and regulator of adult stem cells [29]. As one of the most primitive epidermal stem cell proteins, LGR6 initiates proliferation and differentiation [22]. With the zinc oxide and *Curcuma longa* extract combination dressing, the increase of LGR6 observed since day 3 stimulates the proliferation and differentiation phase faster, leading to earlier remodeling and accelerated wound healing.

LGR6 expression should be higher on day 14 because this is the final phase of proliferation before entering the remodeling phase [1]. In the remodeling phase, Wnt signaling is essential for differentiation from myofibroblasts, which cause wound contractures and reduce the wound surface area. Additionally, Wnt has been shown to play a role in angiogenesis and can repair vascular abnormalities. As the angiogenic process diminishes, acute wound metabolism slows, and wound blood circulation declines and eventually stops [30]. The signaling pathway mediated by the Wnt mechanism is crucial in this stage, so LGR6 expression rises dramatically on day 14 (see Figure 3), which

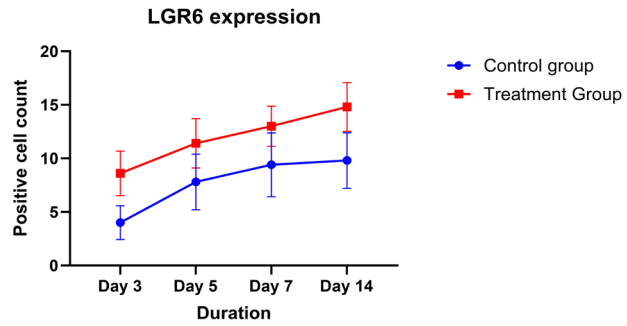

Fig. 3: LGR6 expression in the control group and treatment group on the 3, 5,7, 14 days.

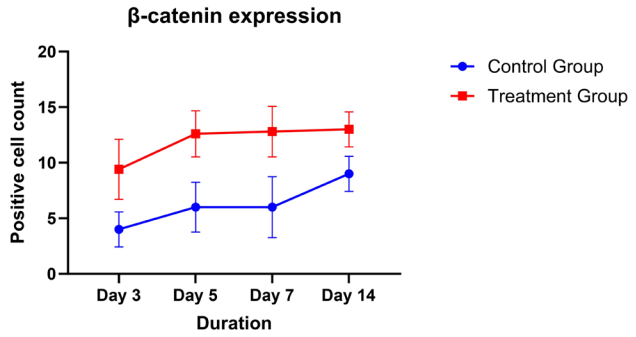

Fig. 4: β-catenin expression in the control group and treatment group on the 3, 5,7, 14 days.

Table I: The expression of β-catenin and LGR6 (Mean + SD

Group	LGR6	β-catenin
C3	4.00 ± 1.58	4.00 ± 1.58
C5	7.80 ± 2.59	6.00 ± 2.24
C7	9.40 ± 2.97	6.00 ± 2.74
C14	9.80 ± 2.59	9.00 ± 1.58
T3	8.60 ± 2.07	9.40 ± 2.70
T5	11.40 ± 2.30	12.60 ± 2.07
T7	13.00 ± 1.87	12. 80 ± 2.28

Table II: Tukey HSD test result

C	C3	T3	C5	T5	C7	T7	C14	T14
C3		0.008*	0.815	0.000*	0.815	0.000*	0.000*	0.000*
T3	0.063		0.229	0.295	0.229	0.229	1.000	0.174
C5	0.196	0.999		0.001*	1.000	0.000*	0.372	0.000*
T5	0.001*	0.555	0.251		0.001*	1.000	0.174	1.000
C7	0.017*	0.999	0.954	0.866		0.000*	0.372	0.000*
T7	0.001*	0.086	0.024*	0.954	0.251		0.130	1.000
C14	0.008*	0.991	0.866	0.954	1.000	0.388		0.096
T14	0.001*	0.004*	0.001*	0.315	0.017*	0.917	0.033*	

LGR6

β-catenin

* denotes significant difference (p<0.05)

corresponds to our findings in wounds covered by zinc oxide and *Curcuma longa* extract combination dressing. Based on the results of this study, combining zinc oxide and *Curcuma longa* extract as a wound dressing can boost the Wnt/β -catenin signaling pathway. This, in turn, can accelerate the healing process by increasing β-catenin accumulation and stimulating the expression of LGR6.

CONCLUSION

In the wound-healing process of *Rattus norvegicus*, there was an increase in the expression of β-catenin and LGR6 following the application of zinc oxide and *Curcuma longa* extract combination of wound dressings, which can accelerate the healing process and promote the wound healing. Thus, this wound dressing has the potential as an alternative to the usual zinc oxide eugenol dressing used in daily practice.

REFERENCES

1. Gonzalez AC, Costa TF, Andrade ZA, Medrado AR. Wound healing – A literature review. An Bras Dermatol. 2016;91(5):614-20. doi:10.1590/abd1806-4841.20164741
2. Coalson E, Bishop E, Liu W, Feng Y, Spezia M, Liu B, et al. Stem cell therapy for chronic skin wounds in the era of personalized medicine: From bench to bedside. Genes Dis. 2019;6(4):342- 58. doi:10.1016/j.gendis.2019.09.008
3. Cacedo-Dorantes L, Cacedo-Ayala M. Skin Acute wound healing: A comprehensive review. Int J Inflam. 2019;2019:3706315. doi:10.1155/2019/3706315
4. Houschyar KS, Momeni A, Pyles MN, Maan ZN, Whittam AJ, Siemers F. Wnt signalling induces epithelial differentiation during cutaneous wound healing. Organogenesis, 2015;11(3):95–104. doi:10.1080/15476278.2015.1086052
5. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound healing: A cellular perspective. Physiol Rev. 2019;99(1):665-706. doi: 10.1152/physrev.00067.2017
6. Wang PH, Huang BS, Horng HC, Yeh CC, Chen YJ. Wound healing. J Chin Med Assoc. 2018;81(2):94-101. doi: 10.1016/J.JCMA.2017.11.002
7. Bielefeld KA, Amini-Nik S, Alman BA. Cutaneous wound healing: recruiting developmental pathways for regeneration. Cell Mol Life Sci. 2013;70:2059–81. doi: 10.1007/s00018-012-1152-9
8. Sorg H, Tilkorn DJ, Hager S, Hauser J, Mirastschijski U. Skin wound healing: An update on the current knowledge and concepts. Eur Surg Res. 2017;58(1-2):81-94. doi:10.1159/000454919.
9. Van Hiel MB, Vandersmissen HP, Van Loy T, Vanden Broeck J. An evolutionary comparison of leucine-rich repeat containing G protein-coupled receptors reveals a novel LGR subtype.

Peptides. 2012;34(1):193–200. doi: 10.1016/j.peptides.2011.11.004.
10. Freedman M, Stassen LFA. Commonly used topical oral wound dressing materials in dental and surgical practice--a literature review. J Ir Dent Assoc. 2013;59(4):190–5.
11. Teng M, Huang Y, Zhang H. Application of stems cells in wound healing – An update. Wound Repair Regen. 2014;22(2):151-60. doi:10.1111/wrr.12152
12. Monje A, Aranda L, Diaz KT, Alarcyn MA, Bagramian RA, Wang HL, et al. Impact of maintenance therapy for the prevention of peri-implant diseases. J Dent Res. 2016;95(4):372–9. doi:10.1177/0022034515622432.
13. Al Akeel MM, Al Ghamdi WM, Al Habib S, Koshm M, Al Otaibi F. Herbal medicines: Saudi population knowledge, attitude, and practice at a glance. J Family Med Prim Care 2018;7:865-75. doi:10.4103/jfmpc.jfmpc_315_17.
14. Martнnez CC, Diaz GM, Oh MS. Use of traditional herbal medicine as an alternative in dental treatment in Mexican dentistry: a review. Pharm Biol. 2017;55(1):1992-8. doi:10.1080/13880209.2017.1347188.
15. Fьllgrabe, A. Epidermal stem cells in physiological tissue regeneration, wound healing and cancer [Internet]. Stockholm: Karolinska Institutet. 2017. [cited 2023 May 21) Available from:https://openarchive.ki.se/xmlui/bitstream/handle/10616/44962/Thesis_Anja_F%C3%BCllgrabe.pdf.
16. Reshad RAI, Alam S, Raihan HB, Neem KN, Rahman F, Zahid F, et al. In silico investigations on curcuminoids from *Curcuma longa* as positive regulators of the Wnt/β-catenin signalling pathway in wound healing. Egypt J Med Hum Genet 2021;22:65. doi:10.1186/s43042-021-00182-9
17. Steinhart Z, Angers S. Wnt signalling in development and tissue homeostasis. Development. 2018;145(11):199. doi:10.1242/dev.146589.
18. Jargalsaikhan BE. Deciphering the roles of LGR6 in WNT and EMT signalling in pancreatic cancer. Molecules. 2019;9(1):148–62. doi:10.1007/978-3-319-76.
19. Valenta T, Hausmann G, Basler K. The many faces and functions of O 2-catenin. EMBO J. 2012;31(12):2714–36. doi:10.1038/emboj.2012.150
20. Duscher D, Shiffman MA. Regenerative medicine and plastic surgery. Philadelphia: Springer International Publishing; 2019.
21. Choi S, Yoon M, Choi KY. Approaches for regenerative healing of cutaneous wound with an emphasis on strategies activating the Wnt/β -catenin pathway. Adv Wound Care. 2022;11(2):70-86. doi:10.1089/wound.2020.1284.
22. Doherty L, Sanjay A. LGRs in skeletal tissues: an emerging role for Wnt-associated adult stem cell markers in bone. JBMR Plus. 2020;4(7):e10380. doi:10.1002/jbm4.10380.
23. Xue M, Jackson CJ. Extracellular matrix reorganization during wound healing and its impact on abnormal scarring. Adv Wound Care, 2015:4(3);119–36. doi:10.1089/wound.2013.0485
24. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature. 2008;453(7193):314-21. doi:10.1038/nature07039.
25. Repertinger SK, Campagnaro E, Fuhrman J, El-Abaseri T, Yuspa SH, Hansen LA. EGFR enhances early healing after cutaneous incisional wounding. J Invest Dermatol. 2004;123(5):982-9. doi:10.1111/j.0022-202X.2004.23478.x.
26. Meizarini A, Aryati A, Rianti D, Riawan W, Puteri, A. Effectivity of zinc oxide-turmeric extract dressing in stimulating the reepithelization phase of wound healing. Vet World. 2020;13(10):2221–5. doi:10.14202/vetworld.2020.2221-2225
27. Baghani Z, Kadkhodazadeh M. Periodontal dressing: a review article. J Dent Res Dent Clin Dent Prospects. 2013;7(4):183–91. doi:10.5681/joddd.2013.040
28. Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: a review of preclinical and clinical research. Altern Med Rev. 2009;14(2):141-53.
29. Kwon MS. Park BO, Kim HM, Kim S. Leucine-rich repeat-containing G-protein coupled receptor 5/GPR49 activates G12/13-Rho GTPase pathway. Mol Cells. 2013;36(3):267–72. doi: 10.1007/s10059-013-0173-z.
30. de Lau W, Peng WC, Gros P, Clevers H. The R-spondin/Lgr5/Rnf43 module: 860 regulator of Wnt signal strength. Genes Dev. 2014;28(4):305-16. doi:10.1101/gad.235473.113.