Wound_healing_induces_vegf.pdf

by

Submission date: 27-Jan-2023 11:34AM (UTC+0700)
Submission ID: 2000327200
File name: Wound_healing_induces_vegf.pdf (318.27K)
Word count: 3894
Character count: 20867

Dental Journal
Majalah Kedokteran Gigi

Dental Journal
(Majalah Kedokteran Gigi)
2023 March; 56(1): 48–52

Original article

Wound healing induces VEGF expression stimulated by forest honey in palatoplasty *Sprague Dawley*

Reine Zhafirah[1], Alifah Nur Aida[1], Helmi Hirawan[2], Tirta Wardana[3,4]
[1]Undergraduate student, Dental Medicine Study Programme, Faculty of Medicine, Jenderal Soedirman University, Purwokerto, Indonesia
[2]Department of Oral Surgery, Dental Medicine Study Programme, Faculty of Medicine, Jenderal Soedirman University Purwokerto, Indonesia
[3]Department of Biomedicine, Dental Medicine Study Programme, Faculty of Medicine, Jenderal Soedirman University Purwokerto, Indonesia
[4]Research Integrity Research Laboratory, Faculty of Medicine, Jenderal Soedirman University, Purwokerto, Indonesia

ABSTRACT

Background: *Cleft palate is a craniofacial disorder with definitive therapy using the V–Y pushback technique palatoplasty, which has the impact of leaving the bone exposed on the palate with long wound healing and a high risk of infection. Forest honey has high antioxidants and the ability to accelerate wound healing.* ***Purpose:*** *This study aims to determine the effect of forest honey on vascular endothelial growth factor (VEGF) expression to accelerate the wound healing process after palatoplasty biopsy.* ***Methods:*** *Posttest only control group design using Sprague Dawley palatoplasty was performed on 15 rats which were divided into three groups, namely the honey treatment (KP), Aloclair as a positive control (KPP), and aquadest as a negative control (KKN). As much as 25 mg of honey was given therapeutically, and VEGF expression analysis post-biopsy palatoplasty was measured using the ELISA test. ANOVA analysis was carried out to determine the significant differences between each treatment, and in silico analysis was conducted to determine the compounds' role in honey on the mechanism of VEGF expression.* ***Results:*** *Statistical analysis of VEGF expression in the KP group was 41.10 ng/ml ± 0.26, the KKP was 39.57 ± 0.27, while the KKN was 33.26 ± 0.62 ($p \leq 0.01$). In silico study, genistein (C15H10O5) targets several signaling pathways such as PI3K-Akt, AMPK, and mTOR, affecting accelerated proliferation and angiogenesis.* ***Conclusion:*** *In wound healing acceleration, forest honey induced VEGF expression through the genistein mechanism of angiogenesis and cell proliferation.*

Keywords: *forest honey; VEGF; palatoplasty; angiogenesis; in silico*
Article history: *Received 24 May 2022, Revised 2 August 2022, Accepted 28 September 2022*

Correspondence: Tirta Wardana, Department of Biomedicine, School of Medicine, Faculty of Medicine, Jenderal Soedirman University, Purwokerto, Indonesia. Email: tirta.wardana@unsoed.ac.id

INTRODUCTION

The cleft palate's abnormal formation causes an abnormal palate cleft, which is usually congenital. The cleft palate is a craniofacial abnormality that occurs in 1:1000 births.[1] The highest incidence occurs in Asians and is dominant in boys compared to girls with a 2.5:1 ratio.[2] One of the therapies used to treat cleft palate is the use of definitive cleft palate therapy.

The definitive therapy for cleft palate is reconstructive surgery to close the cleft by connecting existing tissue and is called palatoplasty.[3,4] Palatoplasty is a surgical procedure to repair the cleft palate in the mouth aimed at improving facial appearance, improving swallowing function, helping improve speech function, reducing hearing loss, and reducing the psychological impact on the patient.[5,6] Palatoplasty will cause injury, which will occur in the wound healing process through four phases: hemostasis, inflammation, proliferation, and remodeling. An essential factor in wound healing is the positive regulator and stimulation of the angiogenesis mechanism, which considerably impacts epidermal repair, granulation tissue, and quality repair formation.[7–10]

Vascular endothelial growth factor (VEGF) is an angiogenesis regulatory protein that plays a role in the angiogenic response stage by stimulating the degradation of the extracellular matrix around endothelial cells, increasing the proliferation and migration of endothelial cells, and helping the formation of blood vessel structures.[7,11,12] In addition to its role in angiogenesis, VEGF is also unique

 Available at https://e-journal.unair.ac.id/MKG/index
DOI: 10.20473/j.djmkg.v56.i1.p48–52

in its effects on multiple components in the wound healing cascade, epithelization, and collagen deposition. Therefore, VEGF is one of the potential targets for the surgical wound healing response. After a cleft palate biopsy, postoperative wound care is critical to speed up the healing process. Alternative treatments, especially bee honey, can develop for wound healing along with topical antimicrobial agents obtained from natural ingredients, which have no side effects.[13]

Honey contains energy, carbohydrates, amino acids, proteins, and various active compounds such as alkaloids, flavonoids, steroids, triterpenoids, quinones, and hydrogen peroxide (H_2O_2), which have anti-inflammatory, antibacterial, anti-allergic, antioxidant, and anti-carcinogenic functions.[14] In addition, the contents of honey can stimulate VEGF expression to affect the angiogenesis process. As previously reported, flavonoids could increase VEGF expression in oral aphthous ulcers, new blood cell formation, and pseudotubule formation in the aortic ring test.[8,9,12,15–18] Therefore, we aimed to determine the role of forest honey administration on VEGF expression for wound healing in a palatoplasty model in *Sprague Dawley*.

MATERIALS AND METHODS

True experimental research laboratories in vivo were conducted with the *Sprague Dawley* animal model with posttest only control group design. Fifteen samples from each group, namely the treatment group, were given black honey (KP), the positive control was given Aloclair, and the negative control was given aquadest. The analysis showed the difference in VEGF level against the treatment given. After obtaining the feasibility of all the methods carried out, the study was performed. The ethical approval was issued by the Ethics Committee Faculty of Medicine Jenderal Soedirman University on July 22, 2020, with reference number 127/KEPK/VII/202.

Making animal models of palatoplasty in *Sprague Dawley* rats used a punch biopsy with asepsis on the hard palate using povidone with cotton pellets. Anesthetic ketamine was given at a dose of 1–2 mg/kg intravenously or 5–10 mg/kg intramuscularly. Punch biopsy was performed using a seamless Premier® Uni-Punch width of 3 mm on the hard palate to the exposed periosteum. The bone was seen without any bleeding again, resembling the V–Y pushback technique. Maintenance was carried out in 25 cm x 12 cm x 15 cm / 0.0045 m^3 with sufficient light and air conditions and far from noisy conditions. The environment for rearing experimental animals has a temperature of around 16–27ºC with a humidity of 40%–70%. Animal models are standard fed AD II and drink aquadest ad libitum, with the amount of feed every morning being about 20 g/head/day.

After punch biopsy, applying forest honey treatment to the wound covered the entire area with a laboratory spatula topically. According to previous research, the dosage was done with 25 mg of honey, which is the maximum concentration.[19] The positive control group (KKP) was treated with Aloclair and the negative control group (KKN) with aqueduct at the same dose. Treatment was given routinely in the morning until the fourth day. The tissue around the punch biopsy wound was taken using blade no. 15, as much as 15 mg.

VEGF level analysis was carried out to determine changes in expression using ELISA. Expression level testing was carried out using the indirect sandwich technique using the BT Lab kit (cat no. E0659Ra). A standard dilution buffer was constructed with serial concentration as the horizontal axis, and the optical density (OD) value was taken as a vertical axis. The OD was detected at a wavelength of 450 nm.[20,21] All procedures followed all advice from the company.

Statistical data analysis was performed using SPSS version 25 (IBM Inc, Chicago, IL, USA) for Windows. Expression data analysis was carried out based on mean ±SD. One-way ANOVA was conducted to analyze the differences between the treatment groups. A confidence interval (CI) of 95% with $p<0.05$ shows statistical significance, graph and curve performed using GraphPad Prism software version 9.0 for Windows (GraphPad Software, San Diego, CA, USA).

In silico analysis was carried out using web server-based online database software and Pubmed to analyze the content of compounds contained in forest honey.[22] Analysis of compounds and chemical bond structures used http://www.pubchem.ncbi.nlm.nih.gov/ using canonical smiles.[23] The analysis of the compound and target protein mechanism used http://stitch.embl.de/,[24] while the interaction mechanism and the mechanism that was influenced by chemical compounds found in forest honey were analyzed using http:///string.db.org/ in the Kyoto Encyclopedia of Genes and Genomes (KEGG) section pathways.[25]

RESULTS

Animal models of palatoplasty were performed using punch biopsy methods with a seamless Premier® Uni-Punch 3 mm on the palates of the rats. More minor diameter biopsy wounds can heal independently, but a biopsy diameter greater than 3 mm can cause scarring, requiring 1-2 stitches to be sutured. The wound was characterized by exposure to the palate and normal bleeding from the wound and surface. The effect of giving forest honey on VEGF levels in wounds was measured using ELISA by reading the OD value with a wavelength of 450 mm. The absorbance value used is the average of the two repetitions. VEGF levels in the treatment group given forest honey were 41.10 ± 0.26 ng/ml, in the positive control group given Aloclair they were 39.57 ± 0.27 ng/ml, and in the negative control group they were negative 33.26 ± 0.62 ng/ml (Figure 1).

DOI: 10.20473/j.djmkg.v56.i1.p48–52

The Post hoc LSD test conducted expression change analysis to determine significant differences between the groups. The results showed that there was a very significant difference in each group. The negative control group, the positive control group, and the treatment group obtained a significant difference ($p \leq 0.01$). Statistical results analyzed of VEGF level expression were KP (treatment group) = 41.10 ng/ml 0.26, KKP = 39.57 0.27, and KKN = 33.26 0.62 ($p \leq 0.01$).

In a silico study, we analyzed genistein ($C_{15}H_{10}O_5$), as one of the honey's ingredients which has been promising, by targeting several signaling pathways such as PI3K-Akt, AMPK mTOR, prostate cancer, and insulin resistance. Changes in the mechanism can trigger accelerated proliferation and angiogenesis (Figure 2).

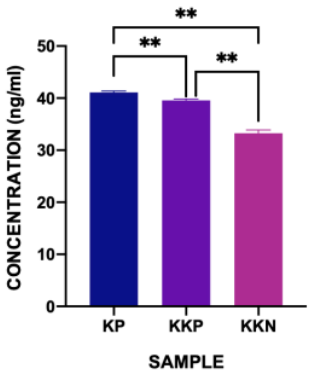


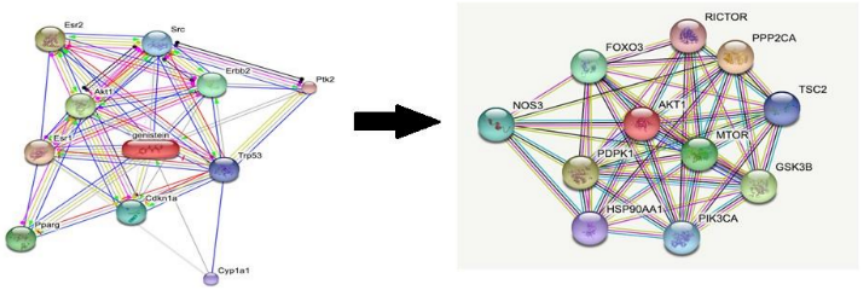
Figure 1. Statistical analysis of VEGF expression. KP (group treatment with honey), KKP (Aloclair/ positive control), KKN (aquadest/negative control) ($p \leq 0.01$).

DISCUSSION

Cleft palate craniofacial deformity or palatoschisis affects the sufferer because it will cause eating disorders, speech disorders, psychological disorders, and impaired tooth growth. The cause of cleft palate is due to the interaction between genetic and non-genetic (environmental) factors. Surgical treatment (palatoplasty) is performed to treat palatoschisis. One of the techniques is called a punch biopsy, which is simple and easy, and the diameter of the biopsy is small, so there is no need for suturing the wound.[26] However, palatoschisis needs to be treated as early as possible and antibacterial properties used to speed up wound healing.

The increased expression of VEGF in the administration of honey indicated an increasing amount of neovascularization compared to the control group. Honey is considered one of the candidates among natural ingredients, which the data shows accelerates wound healing after palatoplasty surgery due to its high content of flavonoids and H_2O_2.[27–29] The content of flavonoids in wild honey shows a rate of 20.43%. Flavonoids are known to have anti-inflammatory and antioxidant properties and induce VEGF. The dynamic content of flavonoids in honey, such as quercetin,[30] apigenin,[31] genistein,[32] and kaempferol,[33] can activate hypoxia-inducible factor-1 (HIF-1), which then induces VEGF.[34]

The content of flavonoids in honey such as quercetin, apigenin, genistein, and kaempferol has been widely reported to have a role in wound healing. Quercetin is often recommended as a drug for oral ulcers to increase collagen in wounds and accelerate angiogenesis.[32,35] Quercetin is known to increase VEGF by activating HIF-1. In addition, apigenin and genistein pass through the phosphatidyl-inositol-3-kinase (PI3K) pathway by binding to protein kinase 1 (AKT1), and increasing endothelial nitric oxide



KEGG Pathways			
pathway	*description*	*count in gene set*	*false discovery rate*
hsa04151	PI3K-Akt signaling pathway	10 of 348	4.95e-15
hsa04152	AMPK signaling pathway	7 of 120	8.19e-12
hsa04150	mTOR signaling pathway	7 of 148	2.26e-11
hsa05215	Prostate cancer	6 of 97	2.57e-10
hsa04931	Insulin resistance	6 of 107	3.62e-10

Figure 2. In silico analysis of the role of genistein, which is one of the ingredients in forest honey and plays an essential role in the mechanism of angiogenesis and cell proliferation.

DOI: 10.20473/j.djmkg.v56.i1.p48–52

synthase (eNOS) to increase VEGF expression.[36–40] This plays an essential role in the mechanism of angiogenesis and cell proliferation. In a previous study, Hu reported that the kaempferol content in honey could increase the activation of VEGF receptor-2 (VEGFR-2) receptors to increase VEGF protein expression and keratinocyte cell migration so that re-epithelialization occurs.[33]

In this study, to determine the role of honey on VEGF expression through in vivo and in silico analysis, we found that genistein compounds directly target PI3K and AKT, thereby influencing the angiogenesis pathway. The process of the angiogenesis mechanism is mainly mediated through the interaction of VEGF-A with VEGFR-2. Other VEGF ligand and receptor variants play a secondary role in this process.[7] One of the wound healing process effects is hypoxia due to the lack of oxygen in the cells around the wound. Hypoxia stimulates the VEGF Flt-1 receptor, and then hypoxia can regulate the expression of VEGF and its receptors so that angiogenesis occurs through HIF-1 by inducing VEGF.[41]

This study proved that forest honey had increased VEGF expression in palatoplasty of wound healing in animal models. The 25 mg of forest honey increased VEGF expression higher than the positive and negative controls with a fold change of 1.038 times higher (41.10 ng/ml) than the positive control given Aloclair (39.57 ng/ml), and the control negative in the form of aquadest (33.26 ng/ml). Thus, we recommend alternative natural treatment using forest honey to support the acceleration of post-biopsy wound healing. Forest honey affects the increased expression of VEGF protein in punch biopsy wounds of the palate in *Sprague Dawley* rats. The use of 25 mg of honey affected VEGF protein expression with a fold change of 1.038 times compared to the positive control and 1.235 times that of the negative control group.

In conclusion, we have confirmed the role of forest honey in accelerating wound healing in a palatoplasty animal model—the ability of forest honey to increase VEGF protein expression. Analysis in silico indicated the role of genistein in forest honey that has affected the cell's angiogenesis and proliferation mechanism.

REFERENCES

1. Bennun RD, Harfin JF, Sándor GKB, Genecov D. Cleft lip and palate management. Bennun RD, Harfin JF, Sándor GKB, Genecov D, editors. Cleft Lip and Palate Management: A Comprehensive Atlas. Hoboken, NJ, USA: John Wiley & Sons, Inc; 2015. p. 1–267.
2. Vyas T, Gupta P, Kumar S, Gupta R, Gupta T, Singh H. Cleft of lip and palate: A review. J Fam Med Prim Care. 2020; 9(6): 2621.
3. Raj N, Raj V, Aeran H. Interim palatal lift prosthesis as a constituent of multidisciplinary approach in the treatment of velopharyngeal incompetence. J Adv Prosthodont. 2012; 4(4): 243.
4. Rossell-Perry P, Cotrina-Rabanal O, Barrenechea-Tarazona L, Vargas-Chanduvi R, Paredes-Aponte L, Romero-Narvaez C. Mucoperiosteal flap necrosis after primary palatoplasty in patients with cleft palate. Arch Plast Surg. 2017; 44(03): 217–22.
5. Oliveira MHM de F, Rezende AL de F, Ibiapina C da C, Godinho RN. Hearing impairment in children with cleft lip and cleft palate. Rev Médica Minas Gerais. 2015; 25(3): 400–5.
6. Gongorjav Na, Luvsandorj D, Nyanrag P, Garidhuu A, Sarah Eg. Cleft palate repair in Mongolia: Modified palatoplasty vs. conventional technique. Ann Maxillofac Surg. 2012; 2(2): 131.
7. Johnson KE, Wilgus TA. Vascular endothelial growth factor and angiogenesis in the regulation of cutaneous wound repair. Adv Wound Care. 2014; 3(10): 647–61.
8. DiPietro LA. Angiogenesis and wound repair: when enough is enough. J Leukoc Biol. 2016; 100(5): 979–84.
9. Greaves NS, Ashcroft KJ, Baguneid M, Bayat A. Current understanding of molecular and cellular mechanisms in fibroplasia and angiogenesis during acute wound healing. J Dermatol Sci. 2013; 72(3): 206–17.
10. Gonzalez AC de O, Costa TF, Andrade Z de A, Medrado ARAP. Wound healing - a literature review. An Bras Dermatol. 2016; 91(5): 614–20.
11. Kumar P, Kumar S, Udupa EP, Kumar U, Rao P, Honnegowda T. Role of angiogenesis and angiogenic factors in acute and chronic wound healing. Plast Aesthetic Res. 2015; 2(5): 243.
12. Neve A, Cantatore FP, Maruotti N, Corrado A, Ribatti D. Extracellular matrix modulates angiogenesis in physiological and pathological conditions. Biomed Res Int. 2014; 2014: 756078.
13. Eteraf-Oskouei T, Najafi M. Traditional and modern uses of natural honey in human diseases: a review. Iran J Basic Med Sci. 2013; 16(6): 731–42.
14. Miguel M, Antunes M, Faleiro M. Honey as a complementary medicine. Integr Med Insights. 2017; 12(2): 117863371770286.
15. Guo D, Wang Q, Li C, Wang Y, Chen X. VEGF stimulated the angiogenesis by promoting the mitochondrial functions. Oncotarget. 2017; 8(44): 77020–7.
16. Daaboul HE, Dagher C, Taleb RI, Bodman-Smith K, Shebaby WN, El-Sibai M, Mroueh MA, Daher CF. β-2-Himachalen-6-ol inhibits 4T1 cells-induced metastatic triple negative breast carcinoma in murine model. Chem Biol Interact. 2019; 309: 108703.
17. Varoni EM, Lodi G, Sardella A, Carrassi A, Iriti M. Plant polyphenols and oral health: Old phytochemicals for new fields. Curr Med Chem. 2012; 19(11): 1706–20.
18. Ma J, Zhou X. Pro-angiogenic and anti-angiogenic effects of small molecules from natural products. In: Nutraceuticals and Natural Product Derivatives. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2018. p. 81–109.
19. Ibnu YS. Potensi madu sebagai terapi topikal otitis eksterna. J Ilm Kedokt Wijaya Kusuma. 2019; 8(2): 7–22.
20. Zhu L, He J, Cao X, Huang K, Luo Y, Xu W. Development of a double-antibody sandwich ELISA for rapid detection of Bacillus Cereus in food. Sci Rep. 2016; 6(1): 16092.
21. Wang S, Liu J, Yong W, Chen Q, Zhang L, Dong Y, Su H, Tan T. A direct competitive assay-based aptasensor for sensitive determination of tetracycline residue in honey. Talanta. 2015; 131: 562–9.
22. National Library of Medicine. NCBI PubMed Overview. National Center for Biotechnology Information. 2021.
23. National Center for Biotechnology Information. PubChem database NCBI. 2021. Available from: https://pubchem.ncbi.nlm.nih.gov/docs/about/.
24. Szklarczyk D, Santos A, von Mering C, Jensen LJ, Bork P, Kuhn M. STITCH 5: Augmenting protein-chemical interaction networks with tissue and affinity data. Nucleic Acids Res. 2016; 44(D1): D380-4.
25. Hermawan A, Putri H. Bioinformatics studies provide insight into possible target and mechanisms of action of nobiletin against cancer stem cells. Asian Pacific J cancer Prev. 2020; 21(3): 611–20.
26. Levitt J, Bernardo S, Whang T. How to perform a punch biopsy of the skin. N Engl J Med. 2013; 369(11): e13.
27. Almaz AI, Purnawati RD, Istiadi H, Susilaningsih N. The effect of honey in second degree burn healing on Wistar rats (overview of angiogenesis and the number of fibroblasts). Sains Med. 2020; 11(1): 27–32.
28. Martinotti S, Ranzato E. Honey, wound repair and regenerative medicine. J Funct Biomater. 2018; 9(2): 34–40.

DOI: 10.20473/j.djmkg.v56.i1.p48–52

29. Oryan A, Alemzadeh E, Moshiri A. Biological properties and therapeutic activities of honey in wound healing: A narrative review and meta-analysis. J Tissue Viability. 2016; 25(2): 98–118.
30. Gopalakrishnan A, Ram M, Kumawat S, Tandan S, Kumar D. Quercetin accelerated cutaneous wound healing in rats by increasing levels of VEGF and TGF-β1. Indian J Exp Biol. 2016; 54(3): 187–95.
31. Tu F, Pang Q, Chen X, Huang T, Liu M, Zhai Q. Angiogenic effects of apigenin on endothelial cells after hypoxia-reoxygenation via the caveolin-1 pathway. Int J Mol Med. 2017; 40(6): 1639–48.
32. Sergiel I, Pohl P, Biesaga M. Characterisation of honeys according to their content of phenolic compounds using high performance liquid chromatography/tandem mass spectrometry. Food Chem. 2014; 145: 774–8.
33. Hu W-H, Wang H-Y, Xia Y-T, Dai DK, Xiong Q-P, Dong TT-X, Duan R, Chan GK-L, Qin Q-W, Tsim KW-K. Kaempferol, a major flavonoid in ginkgo folium, potentiates angiogenic functions in cultured endothelial cells by binding to vascular endothelial growth factor. Front Pharmacol. 2020; 11: 526–38.
34. Nugroho AM, Elfiah U, Normasari R. Pengaruh gel ekstrak dan serbuk mentimun (Cucumis sativus) terhadap angiogenesis pada penyembuhan luka bakar derajat IIB pada tikus Wistar. e-Jurnal Pustaka Kesehat. 2016; 4(3): 443–8.
35. Fu J, Huang J, Lin M, Xie T, You T. Quercetin promotes diabetic wound healing via switching macrophages from M1 to M2 polarization. J Surg Res. 2020; 246: 213–23.
36. Favaro E, Granata R, Miceli I, Baragli A, Settanni F, Cavallo Perin P, Ghigo E, Camussi G, Zanone MM. The ghrelin gene products and exendin-4 promote survival of human pancreatic islet endothelial cells in hyperglycaemic conditions, through phosphoinositide 3-kinase/Akt, extracellular signal-related kinase (ERK)1/2 and cAMP/protein kinase A (PKA) signalli. Diabetologia. 2012; 55(4): 1058–70.
37. Eller-Borges R, Batista WL, da Costa PE, Tokikawa R, Curcio MF, Strumillo ST, Sartori A, Moraes MS, de Oliveira GA, Taha MO, Fonseca F V., Stern A, Monteiro HP. Ras, Rac1, and phosphatidylinositol-3-kinase (PI3K) signaling in nitric oxide induced endothelial cell migration. Nitric oxide Biol Chem. 2015; 46: 40–51.
38. Abhinand CS, Raju R, Soumya SJ, Arya PS, Sudhakaran PR. VEGF-A/VEGFR2 signaling network in endothelial cells relevant to angiogenesis. J Cell Commun Signal. 2016; 10(4): 347–54.
39. Alzoubi A, Ghazwi R, Alzoubi K, Alqudah M, Kheirallah K, Khabour O, Allouh M. Vascular endothelial growth factor receptor inhibition enhances chronic obstructive pulmonary disease picture in mice exposed to waterpipe smoke. Folia Morphol (Warsz). 2018; 77(3): 447–55.
40. Salehi B, Machin L, Monzote L, Sharifi-Rad J, Ezzat SM, Salem MA, Merghany RM, El Mahdy NM, Kılıç CS, Sytar O, Sharifi-Rad M, Sharopov F, Martins N, Martorell M, Cho WC. Therapeutic potential of quercetin: new insights and perspectives for human health. ACS Omega. 2020; 5(20): 11849–72.
41. Lugano R, Ramachandran M, Dimberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities. Cell Mol Life Sci. 2020; 77(9): 1745–70.

DOI: 10.20473/j.djmkg.v56.i1.p48–52

Wound_healing_induces_vegf.pdf

ORIGINALITY REPORT

5%	%	5%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Priscila Schilrreff, Ulrike Alexiev. "Chronic Inflammation in Non-Healing Skin Wounds and Promising Natural Bioactive Compounds Treatment", International Journal of Molecular Sciences, 2022 Publication	2%
2	Ade Wulandari, Ni Putu Sumartini, H Ahmad. "Model of Anticipation Guidance Through Family Centered Care (FCC) to Increase Family Competence in Newborn Baby", Jurnal Kesehatan Prima, 2020 Publication	2%
3	Jingshu Wang, Lina Yang, Fan Liang, Yaping Chen, Gong Yang. "Integrin alpha x stimulates cancer angiogenesis through PI3K/Akt signaling-mediated VEGFR2/VEGF-A overexpression in blood vessel endothelial cells", Journal of Cellular Biochemistry, 2018 Publication	2%

Exclude quotes	On	Exclude matches	< 2%
Exclude bibliography	Off		