The Effect of Avocado Seed for Socket Healing after Tooth Extraction on Diabetic Condition (In Silico and In Vivo Research)

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Original Research Article

The Effect of Avocado Seed for Socket Healing after Tooth Extraction on Diabetic Condition (*In Silico* and *In Vivo* Research)

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ABSTRACT

Approximately 2.5% of patients with diabetic complications are experiencing delayed post-extraction healing. In this context, avocado seed (*Persea americana Mill*) content of catechin, chlorogenic acid, procyanidine, and quinic acid compounds can reduce inflammation and increase wound healing after tooth extraction. Therefore, this research aims to explore and provide groundbreaking insights into the potential use of avocado seed compounds as natural therapeutic agents for enhancing post-extraction socket healing, particularly in diabetes mellitus (DM) patients experiencing delayed healing. *In silico* analysis is carried out to predict molecular interactions and therapeutic mechanisms with *in vivo* experimental models for validation, establishing a comprehensive understanding of the impact of avocado seed on healing pathways. Meanwhile, *in vivo* research examined the expression of TNF, RUNX2, and RANKL on tooth socket tissue of mice using the SPSS Mann-Whitney test (α = 0.05). Catechin, chlorogenic acid, procyanidine, and quinic acid from an avocado seed are analysed through *in silico* research using molecular docking. The results showed that there were significant differences in the expression of TNF-α, RUNX2, and RANKL between the control and treatment groups. This is attributed to the compounds in avocado seed, which report binding affinity with receptors in each stage of the inflammation process. According to *in silico* results, quinic acid reports the highest binding affinity with TNF-α, targeting anti-inflammatory activity. Procyanidin and chlorogenic acid show strong binding with RUNX2 and RANKL, targeting the stimulation of proliferation and remodeling processes, respectively.

Keywords: Avocado seed extract, *In Silico*, *In Vivo*, *Persea americana Mill*, Tooth Extraction, Socket healing.

Introduction

The extraction of a tooth from the socket is reported to include soft and bone tissue. In this context, 12.5% of patients with DM complications experienced delayed post-extraction healing. This is because the healing of tooth extractions in diabetes mellitus (DM) patients is slower than in groups without DM.[1] This systemic disease causes the healing process to be delayed and uncoordinated. There was a significant difference in post-extraction complications in DM patients.[2] Achieving the treatment for DM in increasing the healing process is still difficult. The healing process consists of the following phases: (a) coagulation and hemostasis, which happens after the occurrence of trauma. (b) The inflammation occurs in 48 hours and the inflammatory reaction peaks and diminishes after a week. (c) The majority of the healing process is included in proliferation, which starts in the previous days.

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This stage occurs from day-3 until day-14 and granulation tissue starts to form in the wound during the proliferative phase. (d) The restoration of shape and function is the goal of the formation and remodeling phase which occurs for 3 weeks to a year.[3,4] In recent years, research on the biological foundations of medicinal plant treatment qualities has grown in popularity.[5] Avocado seed (*Persea americana Mill*) can reduce inflammation and increase wound healing after tooth extraction.[6] The total antioxidant content is 1350 µmol Trolox Equivalent (TE) per half fruit, or 600 µmol TE per 30 g. This puts avocados in the middle of the fruit phenolic spectrum, possessing the highest capacity for lipophilic antioxidants.[7,8] More polyphenols are found in avocado seed than in flesh or skin.[9,10] Seeds consist of a variety of polyphenols, such as catechin, procyanidin, chlorogenic acid, and quinic acid.[11–14] Avocado seed influences on bone remodeling process and increases osteoblast proliferation in vitro.[15] This seed contains catechin compounds which can increase bone remodeling. Furthermore, catechins can increase bone formation in human cells in vitro with SaOS-2.[16] By promoting osteoclast apoptosis and halting bone resorption in vitro, the derivatives can decrease osteoclastogenesis. Catechins also modulate mesenchymal stem cells (MSCs) or regulate pre-osteoclast stromal cells through activating RANKL and osteoprotegerin (OPG) to affect pre-osteoclasts.[17] Cyanidin can increase osteoblast differentiation,[18] while quinic acid inhibits the pro-inflammatory cytokine TNF-α and increases osteoblast differentiation.[19] Chlorogenic acid, as an antioxidant, increases osteoblast proliferation and differentiation by repairing oxidative stress damaged through high glucose.[20,21] Based on the description above, this research aimed to determine *in silico* composition of the chemicals quinic acid, procyanidine, catechin, and chlorogenic acid in avocado seed. These could have an impact on the regeneration of the extracted tooth socket. Investigation was also conducted to examine TNF, RUNX2, and RANKL expression in tooth socket tissue *in vivo*. Every step of inflammation was determined by using markers, where TNF-α, RUNX2, and RANKL represented inflammatory, proliferation, and remodeling phases, respectively.

Material and Methods

In Vivo Research

In vivo research was conducted on diabetic rats. Tooth extraction was conducted on diabetic model rats, followed by treatment with avocado seed extract gel in the treatment group, while the control group did not receive any therapy. The application of avocado seed extract gel was carried out immediately after tooth extraction into socket and continued until days 3 and 7, at which point the samples were sacrificed. Meanwhile, decapitation was performed on the jaws of rats and socket tissues were processed for observation. Immunohistochemical staining was conducted to analyze the expression of TNF-α, RUNX2, and RANKL.

Preparation of Research Animal Test

This research was purely experimental with a posttest-only control group design carried out at Laboratorium Faculty of Dentistry Universitas Hang Tuah Surabaya. Preparation of extracts test was performed at Laboratorium Biologi Pharmacy Institut Ilmu Kesehatan Bhakti Wiyata. Staining and histological observations were carried out in the Research Center Faculty of Dentistry Universitas Airlangga. The study followed standard protocols for the use of experimental animals as declared by Universitas Airlangga Faculty of Dental Medicine Health Research with Ethical Clearance (No. 0063/HRECC.FODM/II/2024). The research samples used 20 healthy and active white male *Rattus Norvegicus*, aged 2–3 months, weighing 200-250 grams. The rats were kept in polycarbonate cages with intense lighting, a temperature of 25–28°C, and a humidity of 40–60%. For seven days, the experimental animals were housed in regular conditions for acclimatization, with unrestricted access to water and a standard diet. A total of 20 rats were divided into 4 groups and sacrificed on days 3 and 7. The control group (C) consists of diabetic rats that did not get any treatment on socket after tooth extraction. The treatment group (T) is diabetic rats administered with gel avocado seed extract after extraction.

DM induction was achieved by a single intraperitoneal (i.p.) injection of streptozotocin (STZ) 60 mg/kg bw in 0.1 M citrate buffer (pH 4.5) in a volume of 0.5 ml/kg/bw. Rats have fasted for 24 hours before the injection of STZ. Furthermore, rats were categorized as positive for DM when blood glucose levels measured using a glucometer were ≥ 250 mg/dL on day 1 post-induction.

Tooth Extraction and Tissue Preparation

The lower left incisors of the samples were extracted with forceps under general anaesthesia with ketamine 0.1 ml/100 g bw and xylazine 0.01 ml/100 g bw intramuscular injection. This was followed with the topical gel application of avocado seed extract every day until the animal was sacrificed on days 7 and 14 according to group division. Meanwhile, the control group was not given medication after tooth extraction. Tissue preparations were made after decapitation under general anesthesia with ketamine-xylazine intra muscular injection on the 3rd, and 7th. In each day interval, the left mandible was cut to the size of a tooth socket fixated with 10% formalin and decalcified to be used as a tissue sample for Immunohistochemical staining for TNF-α, RunX2, and RANKL. The sample slides were observed and assessed under a light microscope (Nikon E-100, Tokyo, Japan) per five-micrometre fields of view on a binocular light microscope with 400x magnification.

Avocado Seed Gel Preparation

This research uses a gel formulation of avocado seed. The formulation consists of avocado seed ethanol extract 10%, CMC Na, Glycerine, Propylene Glycol, and Metil Paraben.

In Silico Research

Protein Preparation

The target proteins included receptor activator of nuclear factor kappa-ligand (RANKL), runt-related transcription factor-2 (RUNX2), and tumor necrosis factor-alpha (TNF-α). The 3D structures of these proteins were retrieved from the PDB codes 1TNF, 6VGG, and 5BNQ RCSB-PDB database.[22] The RCSB-PDB database provided the 3D structures[22] and the receptor is downloaded in pdb format using AutoDockTools. Unused components, such as water molecules, are removed, while nonpolar hydrogen is introduced and filled before adjusting the size and coordinates of the box. The size and coordinates of the box are automatically adjusted to match the ligand position of each receptor by turning the location into the center of the box.

Ligand Preparation

The chemical compounds from avocado seed used in this research include catechin, chlorogenic acid, procyanidine, and quinic acid. The PubChem database provided information on the content with a CID number, formula, physical description, molecular weight, citation, and two-dimensional structure.[23] Data on 3D compound samples were saved using pdbqt format as reported in Table 1.

Molecular Docking Process

AutoDock (The Scripps Research Institute, Inc) program was used to perform a docking process to determine binding affinity and interaction between ligand and receptor. Water molecules and attached ligands were removed from the system during docking simulations. Furthermore, polar hydrogen atoms and Kollman charges were added to the receptor, and the compounds (ligands) were hydrogenated and given Gasteiger charges. In the context of autodock program auto grid settings, ligand binding to the target protein domain was simulated using molecular docking software. A cube with X, Y, and Z axes repositioned in accordance with the research goals is known as a grid. The location can control the binding of ligands to particular domains. The linking type of macromolecule with ligands is reported using the Discovery Studio 2021[23] to determine the capacity to attach to a protein domain and the pattern of interaction.[22]

Statistical Analysis

The data were analyzed using the SPSS version 20.0 (IBM, New York, USA) program, normality with Shapiro-Wilk and Levene test for homogeneity. Mann-Whitney variant test (α = 0.05) was conducted to determine the differences between the expression of TNF-α, RUNX2, and RANKL on the control and treatment groups.

Results and Discussion

Figure 1 shows that the highest expression of TNF-α is on control group days 3. TNF-α is a pro-inflammatory cytokine with the greatest amount during the inflammatory phase and plays a major role in the pathogenesis of bone resorption with an increased expression on day 3.[24] Mann-Whitney test shows that there are significant differences between the expression of TNF-α, RUNX2, and RANKL on days 3 and 7 (Table 2). This is caused by the topical gel application of avocado seed extract on the socket. Avocado seed can reduce inflammation and increase wound healing after tooth extraction.[6]

According to Figure 2, the expression of protein can be observed through immunohistochemical staining. The cytoplasm is stained by brown color through antibodies TNF-α, RUNX2, and RANKL. This protein expression was observed in 1/3 socket apically and the inflammatory process starts from margin to apical before moving to the center and coronal.[25] TNF-α expression on day 3 was greater than on day 7 because TNF plays a role in the inflammatory process and occurs in 48-72 hours. Subsequently, the expression is decreased and RUNX2 plays a role in the proliferation process after inflammation.[25] Healing of a tooth socket starts with a process of inflammation, proliferation, and remodeling. In this research, the inflammatory process is represented by C, which has a role as a pro-inflammatory protein. Group Treatment showed that TNF-α expression on group treatment and control was decreased on days 3 and 7.

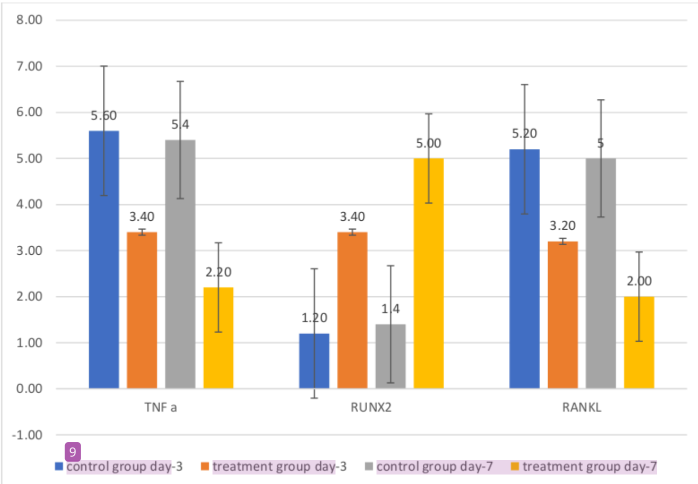


Figure 1: Mean TNF-α , RUNX2, RANKL expression on days 3 and 7

This happens because the quinic acid inhibited TNF-α through the inhibition of MAP kinase and NFKB signaling pathway. The activation of the pathway translocates to the nucleus and binds to DNA in regulating the expression of TNF-α.[25]

Table 1: Structure Ligand

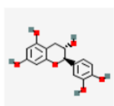
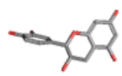
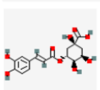
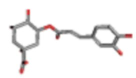
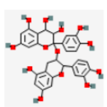
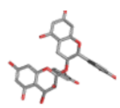
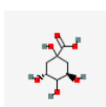
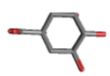
Ligand	2D Structure	3D Structure
Catchine		
Chlorogenic		
Procyanidins		
Quinic		

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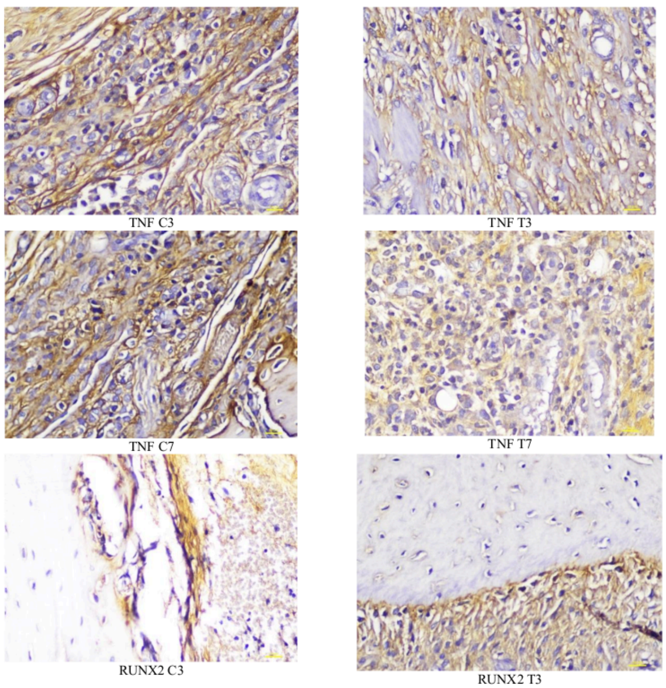
Table 2 : Mann-Whitney test

		TNF a (groups C-T)	RUNX2 (groups C-T)	RANKL (groups C-T)
Days 3	Sig	0.007	0.006	0.033
Days7		0.008	0.007	0.008

This research is in line with previous results that quinic acid can reduce TNF-α expression.[26] The proliferation phase is represented by RUNX2 and this protein has a role in stimulating preosteoblasts.[2] RUNX2 increases in the treatment groups than the control group as reported in Figure 1. Meanwhile, procyanidin has the greatest binding to the RUNX2 receptors. *In vivo* research showed that the number of RUNX2 in treatment groups was increased than the control group. Procyanidin increases RUNX2 activity and regulates osteoblast proliferation and differentiation under experimental conditions in relation to the ERK1/2 pathway proliferation.[14] The remodeling process is represented by RANKL and this protein released by osteoblasts, binds RANK to osteoclasts, assisting in the process of osteoclastogenesis.[22] The number of RANKL is reduced in the treatment group compared to control. The highest binding in the remodeling stage is on binding affinity between RANKL and Chlorogenic acid (Table 3), inhibiting RANKL-Mediated Osteoclast Differentiation. RANKL induced osteoclast differentiation in remodeling process while[27] chlorogenic acid decreased bone resorption by increasing the ratio RANKL/OPG.[28]

The docking interaction result is shown in Figure 3 and the bond between the ligand and the receptor is depicted in Table 4. Hydrogen and hydrophobic bonds (Van der Walls, unfavorable donor, Pi Alkyl, Pi- Cation, Pi- Anion, Pi-Pi Ti Shaped, etc) exist between ligand and receptor (Table 4). In this context, hydrogen bonds play an important role in ligand-receptor interactions to stabilize interactions by forming stable complexes and increasing receptor-ligand affinity. The function of hydrophobic bonds is to stabilize the interaction by bringing non-polar molecules closer together, excluding water or an aqueous environment. The bonds are equally important for receptor-ligand binding, depending on the context used.[29] Finding the energy of a ligand with a favorable binding to the target receptor is the goal of molecular docking.[30] Weak bonds are formed between ligand and target protein domain during contact to activate biological response.[31]



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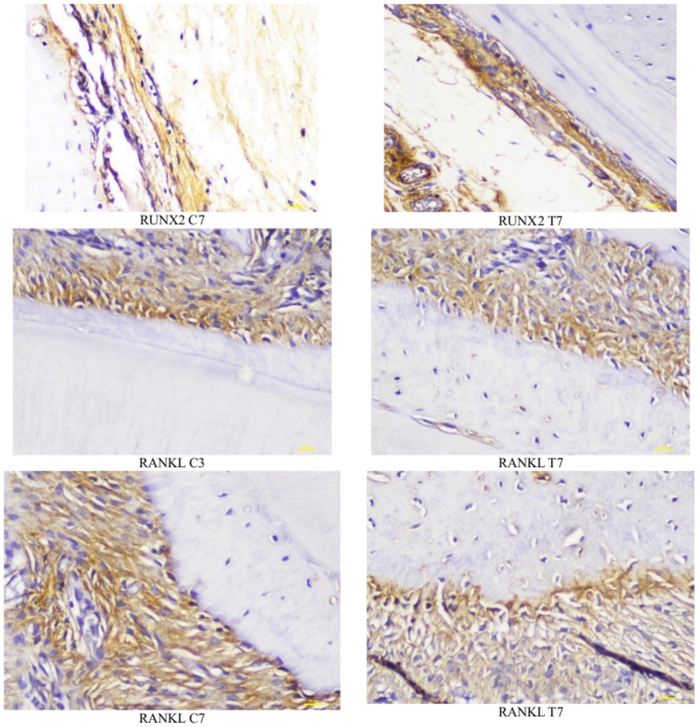

Figure 2: Imunohistochemical staining TNF-α , RUNX2, RANKL expression on days 3 and 7

C3= Control groups day-3
C7= Control groups day-7
T3= Treatment groups day-3
T7= Treatment groups day-3

Table 3: Binding Affinity and Inhibition Constant

Protein Receptor	Cathecine		Chlorogenic		Procyanidins		Quinic	
	Binding Affinity (kcal/mol)	RMSD/IB (Ä)	Binding Affinity (kcal/mol)	RMSD/IB (Ä)	Binding Affinity (kcal/mol)	RMSD/IB (Ä)	Binding Affinity (kcal/mol)	RMSD/IB (Ägstrom)
TNF-α	-2.2	0.0 uM	-0.7	0.0 nM	-6.2	0.0 uM	-7.4	0.0 uM
RuNx2	-7.3	0.0uM	-6.9	0.0 uM	-8.7	0.0 uM	-5.8	0.0 mM
RANKL	-6.0	0.0 uM	-6.4	0.0 uM	-5.0	0.0 mM	-4.9	0.0 mM

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Figure 3: Docking Interaction Result

Table 4: The Kind of Binding Ligand-Receptor

	Hydrogen Bond	Hydrophobic Bond
TNF **α**- Catechin	TYR A:119	PRO B: 117, ALA A:96, ILE A:118
TNF **α**- Chlorogenic		PRO B: 117
TNF **α**- Procyanidine	LYS A:98, TYR A:119	ILE B:118, PRO B:117, ALA:96, ILE A:118, GLU A:116, PRO B:117, PRO A: 117
TNF **α**- Quinic		ILE A:118, TYR B: 119, PRO B: 117, LYS B:98,LYS C:98, ILE B:118,PRO A:117, TYR C:119, ILE C:118, TYR C:119, LYS A:98, TYR A: 119
RunX2- Catechin	LEU D:168	ARG G:33, LEU D:168
RunX2- Chlorogenic		SER D:165, MET D: 157, ALA D:166, LEU D:168.
RunX2- Procyanidine		ALA D:171
RunX2- Quinic		SER D:165, GLU D:167, LEU D:168
RANKL- Catechin		TYR A: 217, HIS A:167
RANKL- Chlorogenic	ASN A:276, TYR A:307, HIS A:167	TYR A:217
RANKL- Procyanidine	LYS A:181, SER A:252, SER A:252	GLU A: 292, LYS A:205, PRO A:250
RANKL- Quinic		ILE A:175

The values of the hydrogen bond interactions, inhibition constant, and binding affinity between the ligand and the receptor can evaluate the outcomes of docking. The stability and spontaneity of the bond are indicated by binding affinity energy between the ligand and the target. A lower binding affinity number shows a more spontaneous and stable relationship.[30] The docking result showed that the highest binding on the inflammation stage was on the affinity between TNF-α and Quinic acid. The compounds of quinic acid can influence the processes of inflammation by inhibiting cytokine proinflammation of TNF-α. Avocado seed has the potential to enhance the healing process following tooth extraction at every stage through *in silico* and *in vivo* experiments.

Conclusion

Avocado seed reported the ability to reduce the inflammatory process and promote the remodeling process by decreasing TNF-α and RANKL expression, as well as increasing RUNX2 expression. Docking results showed that avocado seed-derived compounds, such as catechin, chlorogenic acid, procyanidin, and quinic acid played a role in socket repair after tooth extraction *in silico*. These bioactive compounds could be developed into natural therapeutic agents for post-extraction socket healing, particularly for diabetic patients experiencing delayed healing processes, by targeting inflammation, proliferation, and remodeling pathways.

Conflict of Interest

The authors declare no conflict of interest.

Author's Declaration

The authors declare that the work presented in this research is original and will borne any liability for claims relating to the content of this article.

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