

1 ORIGINAL ARTICLE

2 Study of Efficacy of Aqueous and Methanolic Extract
3 of Green Tea on the Process of Opened Skin
4 Wounds Healing in Male (NMRI) Mice Race5 FAEZEH MOSHREFJAVADI^{1*}, PARISA KADANEJADIAN², MOHAMMAD ALI NILFOROOSHZADE³,
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10 ABSTRACT

11 Green tea used for year has a popular cancer preventive activity. Researchers have showed green tea
12 inhibited growth of cancer in the animals. This research has been done with awareness of positives effect
13 of green tea, which is approved by researchers and the importance of treatment of opened skin wound.
14 This work has been done experimentally. There were 56 male mice in 7 different groups. Different dose
15 of water and alcohol such as 50, 150 and 300 μ L were injected. After anaesthetizing the mice, skin
16 wound was created on the back of the mice by a 6-mm punch. While the mice in control group were
17 treated by normal saline, water and alcohol extract of green tea was injected around the wound on the
18 back of each mouse. The dimensions of ulcers and the recovery percent of the wound in the 1st, 3rd, 5th,
19 7th, 10th, 13th and 15th day of study were measured. Furthermore, the needful time for recovery was
20 evaluated. Some histological studies were done as well. Two Specimen of wounds were supplied at 4th,
21 7th and 15th day of the study. In this way, fibroblasts, inflammation, epiteleum and endothelial cell of
22 blood vessels from the wounds were studied. The results show that there are no significant differences
23 among control, water and alcohol groups in recovery processes ($p > 0.05$.) Evaluation of recovery
24 processes showed there were significant differences among these groups on 7th day of study ($p < 0.01$).
25 Evaluation of recovery processes showed there were significant differences among three injected doses
26 of study ($p < 0.001$). The degree of differences in fibroblasts, inflammation and epithelium distortion in
27 different days for 6 groups ($p < 0.05$) was meaningful. According to these findings, although both water
28 and alcohol extracts of green tea speed up the wound healing, there isn't any difference between the
29 uses of water or alcohol extracts.

30 **Keywords:** Green tea, Wound healing, Water and Alcohol extract, Race NMRI

31 Wound healing, or wound repair, is an intricate
32 process in which the skin (or another organ-tissue)
33 repairs itself after injury. The classic model of wound
34 healing is divided into three or four sequential, yet
35 overlapping phases: hemostasis (not considered a phase
36 by some authors), inflammatory, proliferative and
37 remodeling. Upon injury to the skin, a set of complex
38 biochemical events takes place in a closely orchestrated
39 cascade to repair the damage [1].

40 Green tea is made from *Camellia Sinensis* [2].
41 Leaves of this plant are processed with minimal
42 oxidation. It is mainly used in Asia specifically in China
43 [3-4]. There have been extensive researches on the
44 effects of green tea and results have been surprisingly
45 pleasing. Some of the major potential benefits of green
46 tea include; anti-Cancer properties, increases in
47 metabolic rate, anti-diabetes effect, enhancement of
48 mental alertness, improvement of immune system,
49 improvement of quality of life for HIV-infected

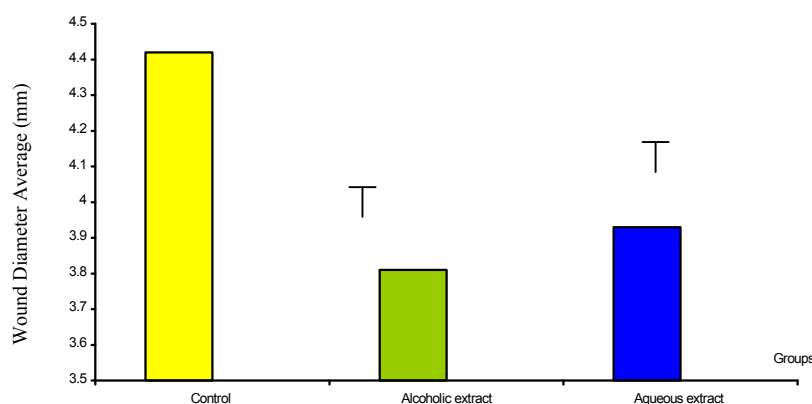


Fig 1. The macroscopic study of wound diameter average between control and treatment group on days 1, 3, 5, 7, 10, 13 and 15. ($p < 0.001$)

50 patients, cardioprotective effects [5-8]. In this study, 51 green tea extracts has been investigated for their effects 52 on the opened skin wound healing.

53 MATERIALS AND METHODS

54 In this experimental research, 56 male mice of 55 NMRI race with average weight of 25-35 grams were 56 studied. The mice were held in 7 cages in Professor 57 Torabi Nejad Research Center in Isfahan with light 58 cycle of 12 hours darkness and 12 hours light in $22 \pm$ 59 2°C . In this period, sufficient water and food were in 60 hand of animals and they were randomly classified to 61 control and experimental groups.

62 Green tea extract was prepared using Soxhlet 63 instrument. The green tea leaves were studied by 64 Isfahan University and were transferred into laboratory. 65 Then using electric mill, they were grinded to a powder. 66 Forty grams of green tea powder was placed into 67 filtration paper and were transmitted to a specific 68 container. In order to produce water extract, 400 69 milliliters of purified water was added and in order to 70 produce alcoholic extract, 400 milliliters of 85% 71 methanol was added. After producing the extract by 72 Soxhlet, it was dried and concentrated in rotary 73 evaporator and then in 48-hour incubation in 70°C 74 Bonna. In next stage, 2 g of each extract (alcoholic or 75 aqueous) was solved in 100 mL normal saline and 76 therefore, 2% aqueous or alcoholic extract was 77 achieved.

78 In order to make a wound in animal, first the mouse 79 became comatose with ether and then its back hair was 80 shaved. After immersing the skin with betiding, with 6- 81 millimeter punch and in accordance to surgery 82 principles, a 6-millimeter wound was developed. The 83 wound depth was full skin thickness and the surgery day 84 was named the day zero. After making the wound, in 85 order to prevent potential putrefaction, 0.2 mg penicillin 86 and 0.2 mg gentamicin were injected.

87 The mice were injected 2% aqueous or alcoholic 88 extract for 7 days, once a day and at 9 am. The amount 89 of 50, 150 or 300 mL of extract were injected in four 90 direction surrounding the wound. All injection were 91 performed by one person. After developing the wound, 92 the mice were classified into 7 groups each 8, as 93 follows:

94 **Group 1 (control):** the wound surface of this group 95 was treated by normal saline;

96 **Groups 2, 3 and 4:** the wound surface was treated 97 by 50, 150 and 300 mL of 2% aqueous extract 98 respectively;

99 **Group 5, 6 and 7:** the wound surface was treated 100 with 50, 150 and 300 mL of 2% alcoholic extract 101 respectively.

102 For macroscopic study, on days 1, 3, 5, 7, 10, 13 and 103 15, the length measurement method of wound and 104 imaging with digital camera was used for all groups. 105 The development of wounds was assessed and the 106 wound stages according to imaging digital camera and 107 size measurement were recorded.

108 For microscopic evaluation, sampling and tissue 109 study was carried out. On days 4, 7 and 15, the mice 110 were killed by smelling ether in air. Then, two samples 111 were taken from wound tissue and surrounding skin 112 which were placed inside 10% Formalin solution. The 113 tissue processing and molding was done by paraffin and 114 wax and the German microtome with firm blade of 115 LEITZ to develop width cuts including skin, bed with the 116 thickness of 4 microns. The cuts were painted by 117 Haematoxylin and Eosin (H&E) coloring methods and 118 edematous cell, fibroblasts and sweating sections were 119 recognized through quality method. The wound 120 improving was determined through rating the pathology 121 parameters as follows:

122 **Rating 1:** The tissues with no repeating 123 epithelisation and fibrosis tissue but with the low 124 numbers of vessels and extreme edema.

Table 1. The microscopic study of aqueous and alcoholic extract of green tea on days 4, 7 and 15 based on the inflammation, fibrosis, epithelium and blood vessels.

Parameter	Days	Groups						
		Control	Aqueous extract			Alcoholic extract		
			50 μ L	150 μ L	300 μ L	50 μ L	150 μ L	300 μ L
Inflammation	4	4.50 \pm 0.07	0.01 \pm 4.10	0.02 \pm 3.50	0.05 \pm 3.52	0.02 \pm 4.0	0.01 \pm 3.70	0.001 \pm 3.11
	7	3.21 \pm 0.05	0.2 \pm 2.80	0.02 \pm 2.50	0.09 \pm 2.10	0.01 \pm 2.70	0.01 \pm 2.30	0.03 \pm 2.0
	15	1.81 \pm 0.01	0.03 \pm 1.50	0.01 \pm 1.2	0.001 \pm 0.09	0.01 \pm 1.40	1.0 \pm 0.01	0.001 \pm 0.07
Fibrosis	4	4.81 \pm 0.01	0.02 \pm 4.51	0.01 \pm 4.20	0.05 \pm 3.91	0.02 \pm 4.52	0.01 \pm 4.52	0.0 \pm 3.70
	7	1.21 \pm 0.01	0.001 \pm 1.0	0.081 \pm 0.02	0.01 \pm 0.06	0.90 \pm 0.06	0.001 \pm 0.70	0.50 \pm 0.002
	15	2.31 \pm 0.01	2.0 \pm 0.02	0.01 \pm 1.62	1.21 \pm 0.02	0.05 \pm 2.11	0.05 \pm 0.70	0.001 \pm 1.25
Epithelium	4	5	5	5	5	5	5	5
	7	4.80 \pm 0.01	0.01 \pm 4.11	0.02 \pm 3.80	0.05 \pm 2.52	4.0 \pm 0.01	3.20 \pm 0.02	0.04 \pm 2.32
	15	2.0 \pm 0.001	0.02 \pm 1.42	0.01 \pm 1.0	0.04 \pm 0.51	0.02 \pm 1.50	0.05 \pm 1.0	0.03 \pm 0.51
Blood Vascular	4	5.0 \pm 1.13	1.10 \pm 4.92	1.0 \pm 4.90	1.0 \pm 4.89	1.2 \pm 4.93	1.0 \pm 4.90	0.01 \pm 4.88
	7	4.5 \pm 1.10	1.12 \pm 4.25	1.12 \pm 4.23	0.01 \pm 4.210	1.12 \pm 4.25	1.10 \pm 4.21	1.02 \pm 4.22
	15	0.01 \pm 3.5	0.01 \pm 3.25	1.10 \pm 3.0	1.10 \pm 3.01	0.01 \pm 3.28	0.01 \pm 3.01	1.10 \pm 3.0

125 **Rating 2:** The tissues with repeating epithelisation, 147 treatment group on the days 1, 3, 5, 7, 10, 13, and 15
 126 low quantity fibrotic tissue, low number of vessels and 148 has been illustrated in Fig 1. There is a meaningful
 127 extreme edema 149 difference between groups ($p < 0.001$).

128 **Rating 3:** The tissues with epithelisation and 150 The microscopic results show that edema, fibroblast
 129 fibroblast in small limit and also low number of vessels 151 and epithelium amount in mice received aqueous or
 130 and low edema. 152 alcoholic extract did not have a meaningful difference.

131 **Rating 4:** The tissues with no edema and the 153 The edema, fibroblast and epithelium amount were
 132 medium number of epithelisation and fibroblast 154 significantly different in groups received aqueous or

133 **Rating 5:** The tissues with complete epithelisation, 155 alcoholic extracts when compared with control group (p
 134 complete fibrotic tissue development, high number of 156 < 0.001). In contrast, the blood vascular amount were
 135 vessels and no edema. 157 not significantly different in groups received aqueous or

136 All the data were analyzed using one-way ANOVA 158 alcoholic extracts when compared with control group
 137 by SPSS statistical software. The p values < 0.05 were 159 (Table 1).

138 considered significant.

139 RESULTS

140 The average wound diameter in control group was 162 studies in the effects of green tea on skin. The primary
 141 4.42 \pm 1.66 mm, in the group which received the 163 focuses of these studies are the chemical carcinogens or
 142 alcoholic extract of green tea was 3.81 \pm 1.74 mm, and 164 photo carcinogens in animals [9]. Generally, The
 143 in the group which received aqueous extract of green 165 polyphenols which are present in teas are categorized as
 144 tea, it was 3.93 \pm 1.69 mm. No meaningful difference 166 catechins. Green tea leaves contain six primary catechin
 145 between 3 groups was observed (not significant). The 167 compounds: catechin, gallaogatechin, epicatechin,
 146 average of wound diameter among control and 168 epigallocatechin, epicatechin gallate, as well as

160 DISCUSSION

apigallocatechin gallate (also referred to as EGCG). healing [11]. The other researchers showed that glycoproteins have different biological activities like polyphenols cause the infusion, contrast and anti-tumor, anti-edema, anti-virus, anti-ratification, anti-propagation in epidermis Keratinocytes [9]. Catkins are oldness, and lowering the blood sugar [7-10]. Chemical also from polyphenol group that have anti-oxidant and structure of these molecules is the polyphenol of green anti-ratification property and have role in prevention of tea which is the beginner of antioxidant theory [11]. bleeding and reducing thrombosis [9]. From seventh EGCG is the primary combination of green tea day on, is the propagation stage [17]. On seventh day, in polyphenolitic that has properties like antioxidant, anti-treatment group, the wound surface is reducing in tumor, and anti-mutagenic [9]. The biological and contrast with control group that this shows the epidemiological studies in the past 10 years show that reconstruction stage commencement [14] or in other EGCG can be the preventer of tumor growth in chest, word, the earlier start of revival phase of collagen lung, liver, sweetbread, stomach, pancreas, skin, cyst, synthesis take place in this stage and collagen groups and prostate [11]. EGCG is the preventer of secretion of with more diameter are constructed and the width link chymotrypsin, tumor necrosis factor alpha and glucose between molecules also change [18]. The collagen yarn 6-phosphate dehydrogenase in liver [11-12].

In this study, there is not a meaningful difference before wounding and prevents the white and ugly scar. between the alcoholic and aqueous extract of green tea In addition, increasing blood and oxygen availability to in studied groups. This finding is important for two wound location takes place through widening the veins reasons. Firstly, using green tea extract doesn't have [19]. Researches show that green tea reduces blood any relationship with aqueous or alcoholic treatment. sugar, blood lipids, blood pressure, heart disease Secondly, in this study, the effect of aqueous and reduction, heart bit and also vein widening [11,20]. This alcoholic variables is excluded. In the current study, on influences on the practical capacity of fibroblasts, fourth day, as the edema stage indicator is considered as synthesis increase in collagen fibers and increase in the wound treatment process [13], the excess of edema wound insistence because of increase in collagen in treatment group is meaningfully less that of control content and because fibroblasts are responsible for group ($p < 0.001$). This shows that the green tea makes developing collagen. So we can conclude that green tea the edema stage of treatment process faster and (polyphenol, catechin and EGCG) cause the propagation therefore the wounds heal faster. In addition, injecting of fibroblasts and influence the practical capacity of the 2% extract of green tea into mice wound caused fibroblasts and increase the synthesis of fibro Collagen meaningful increases in fibrous tissue and reduction in [20]. The higher the injection dose (300 mL), the higher the edema in seventh day of study in comparison to the the meaningful number of fibroblasts [9]. The research control group. This meaningful increase of treatment of Madham *et al.* show that catechin polyphenol and group fibrous in considering their role in following EGCG prevent the collagenase activity against 202 issues are important and indicate the positive effect of Collagens [18]. In fact, Catkin and EGCG prevent the green tea on distribution phase of wound treatment action through linking with hydrogen and reaction with process.

1. Fibroblasts are responsible for synthesis of the a role in collagens registration [18]. Research of Young matrix components of primary outer cell of wound bed *et al.* also shows the prevention of collagen destruction including fibronectin and proteoglycans that provide and collagenase activity through setting reactions of proper substrate for immigration and propagation of cellular signal by EGCG [19]. cells [14].

2. The fibroblasts then synthesize the collagens that healing process of wound through general and localized develop tension power in wound substrate [15].

3. Miofibroblasts that are exclusive fibroblasts Neuron and hormonal like cell and vein factors or participate in wound shrinkage through providing motion and secretary activities influence the wound contraction force [14].

During granulation, fibronectin develops a proper EGCG and the properties of antibacterial and antivirus substrate for immigration and growth of cells and of green tea in order to fasten the healing of wound therefore links with miofibroblasts so that wound [20]. EGCG causes the propagation, division, and contraction is developed influentially. In addition, this motivation of natural cells growth and does this through fibronectin is a support for fibrilligenesis [16]. cell division and anti apoptosis division. Also, it Regarding the above-mentioned results, it was indicated increases the Keratinocytes survival and influences on that the green tea extract has improved the wound the propagation and fixing of fibroblasts [20]. The treatment at seventh day that these influences are preventing effect of green tea is related to its anti- observed in reduction of wound surface and increase of oxidant power. Polyphenols and glycoprotein play the healing percent and also in reduction of required time role of scavenger in special conditions and thus it for complete healing. Reduction in edema resulted in implements its preventing effects on bacteria and virus speeding the wound stage. In 2004, Bayer and colleges growth. In this regard, preventing effect of green tea show that polyphenols prevent the discharge of gamma- (Camellia Sinensis) and black tea on the bacteria growth interferon and have anti edema, anti oldness, anti wound has been shown [21]. It is possible that green tea

improve the healing speed of wound. It has been reported that antibiotic medicine speeds the healing of wound by infection control [21]. But in this study the amount of collagen synthesis will exceed the exterior symptoms of infections are not observed in control group. Therefore, it seems to be actions other required for construction of veins, immigration of that preventing the wound infection for green tea for macrophages and correct function of nutrients [30]. fastening the wound improvement. Bayat *et al.* explain the ultrasound treatment effect and gel on healing the vitamin C and includes 18 amino acids including lysine wound section and they believe that wet wound is the speeding factor of wound healing process. In current study, the wounds were daily wetted by the alcoholic and aqueous extract.

The experimental studies on animals show that the localized usages of epidermal growth factors have an important influence on speed of epidermal healing in wounds with relative thickness and burnings. The usage of this material on human wounds also has similar effects and its usefulness has been proved [22]. The speeding the healing process in treatment group.

epidermal healing is a complex phenomena from which the rest epidermal cells are propagated so there will be another healthy epidermis. The molecular actions that set the natural epidermal healing are not completely known, but it seems that the peptide growth factors that act through autocrin or paracrin mechanisms have an important role on them [23-25]. In 2003, *Chung et al.* showed that the green tea extract (EGCG) cause epidemic creationists survival in human. In 2003, *Bollag et al.* proposed cellular propagation and healing of wound through polyphenols of green tea. Many numbers of growth factors are known including the epidermal growth (EGF). This factor is a polypeptide of 53 amino acids that DNA and protein is activated by the mRNA [25]. It has been shown that the peptide growth factors increase significant proliferation of cells in wounds with relative wounds and also increase traction influence on Mesenchyme cells [26]. In fact, the growth factors of exterior peptide will increase other production of growth factors like transforming growth factor which is revealed from platelets and macrophages, indirectly activates the healing and improving the wound [27]. Without considering the structure, immediate facing of cells during healing with growth factors of epidermal, increases the epithelial [28]. *Kwon et al.* stated that EGCG motivates the growth of human hair through proliferation and has Anti-apoptosis effects on DPCs cells [28]. The histology of wound showed that proliferation of cells increase that is probably because of chemical combination of green tea and epidermal growth factors.

In addition, role of vitamins on wound healing process and the relationship of green tea contents with them can be considered. Lack of vitamin C is important in delay of wound healing. In such patients, wound healing in fibroplasia stage is stopped. In this state, even when the number of fibroblasts is natural, they do not produce sufficient collagen. Vitamin C is required for ion link of (OH) with amino acid of proline and lysine and hydroxyl of them inside fibroblast cell. Without hydroxy-lysine, fibrils of collagens will not obtain width links. In extreme Scurvy, not only the new

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