

Department of

Yeditepe University

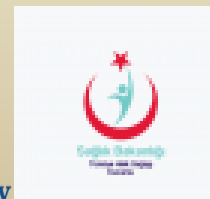


GENETICS & BIOENGINEERING

Development of Boron Containing Antimicrobial Wound Healing Gel

Prof. Dr. Fikrettin ŞAHİN

V. Ulusal Ayak İnfeksiyonları Simpozyumu
03-06 Nisan 2018

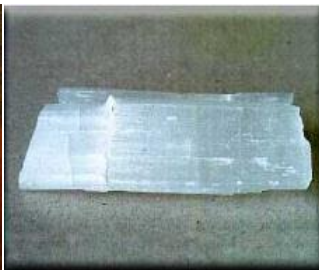


BORON

- **Boron (B)**) is a naturally occurring element, which combine with oxygen and other elements to form boric acid or inorganic salts called borates such as borax (sodium borates), ulexite, colemanite, tincal and kernite.
- Borate minerals were found at the bottom of oceans, sedimental rocks, coal, soils and waters.
- Boron producing countries in the world are Turkey, USA, Argentina, Chile, Russia, China and Peru.
- **Turkey** has **72%** of the world's boron reserves.



$\text{CaB}_3\text{O}_4 (\text{OH})_3 \text{H}_2\text{O}$
Colemanite



$\text{NaCaB}_5\text{O}_9 \cdot 8\text{H}_2\text{O}$
Ulexite



$\text{Na}_2\text{B}_4\text{O}_7 \cdot 10 \text{H}_2\text{O}$
Tincal



$\text{Na}_2[\text{B}_4\text{O}_6(\text{OH})_2] \cdot 3\text{H}_2\text{O}$
Kernite

Boron in Biological Systems/Plants

- Boron is an essential element for plants.
- Boron compounds in small concentrations are used as micronutrients in fertilizers for plant growth and development,
- However, boron compounds in higher concentration can be used as herbicides, algaecides or pesticides.
- Boron has been claimed to be involved in membrane integrity of plant cells.
- Boron deficiency in plant cells is characterized by disruptions of cell wall and membrane unity.
- Boron is involved in the metabolism of calcium in both plants and animals.

Boron in Biological Systems/Mammalian

- Boron compounds in daily diet as micronutrients provides positive contributions to human health
- Boron deficiency is implicated in osteoporosis
- Boron has vital roles in embryogenesis, wound healing, bone growth, and immune and psychomotor functions.
- Recommended boron dose for is 1.2 mg B/day (20 mg B/day upper limit).
- On the other hand, it has been claimed that lack of boron in mammalian can result in abnormal development of bone and brain.

Boron and Human Metabolism

Arthritis

Bone Growth and Maintenance

Cancer

Prostate, Breast, Lung, Cervical

Brain Function

Hormone Facilitator

Immune Response, Inflammation, and Oxidative Stress



Roles and applications of boron compounds in cutaneous acute and chronic wound healing



Wounds

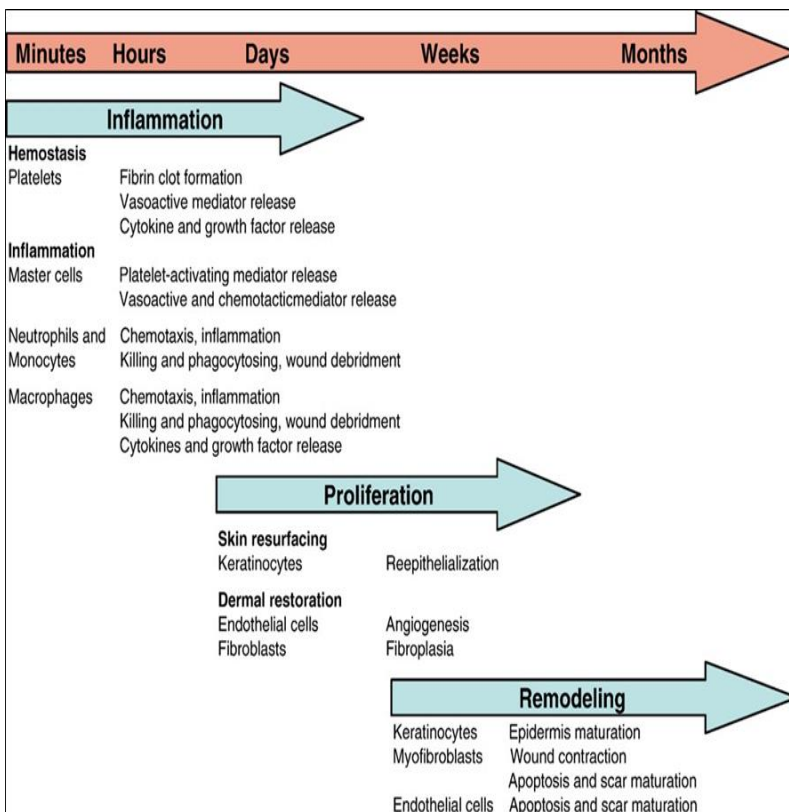


“Wounds are injuries that break the skin or other body tissues by physical, chemical or biological insults such as a gunshot, fall, or surgical procedure; by an infectious disease; or by an underlying condition.

Handoo, S. (2006). A survey of plants used for wound healings in animals. Vet Scan (Online Veterinary Journal), 1(1).

SKIN and WOUND HEALING

Major cells and steps in wound healing (Li et al., 2007)



- When skin is wounded, its stem cells must respond rapidly to restore and repair tissue damage.
- Wound healing involves three overlapping phases: inflammation, tissue formation and tissue remodeling.
- Hemostasis and Inflammation, Following platelet aggregation, various leukocyte lineages, including neutrophils, macrophages, mast cells and T cells, are recruited to the wound site.
 - Clearing dead cells and fighting against infections,
 - Leukocytes secrete cytokines and growth factors such as TGF- β s, IGFs and FGFs that promote angiogenesis, migration and proliferation of keratinocytes and dermal fibroblasts,
- During tissue formation, granulation tissue, consisting of newly formed blood vessels, macrophages and fibroblasts, begins to cover the wound. Epidermal cells then migrate over the granulation tissue to reepithelialize the wound.
- During tissue remodeling, the epidermis and dermal fibroblasts deposit new ECM proteins to strengthen the repaired tissue

Wound Types

Acute Wounds

An acute wound is an injury to the skin that occurs suddenly because of punch, bites, burns, abrasions, surgery or traumas.

Often heal within 3-6 weeks without the need for professional treatment,



Chronic Wounds

A chronic wound is a wound that does not heal in an orderly set of stages and in a predictable amount of time the way most wounds do; wounds that do not heal within three months are often considered chronic wound.

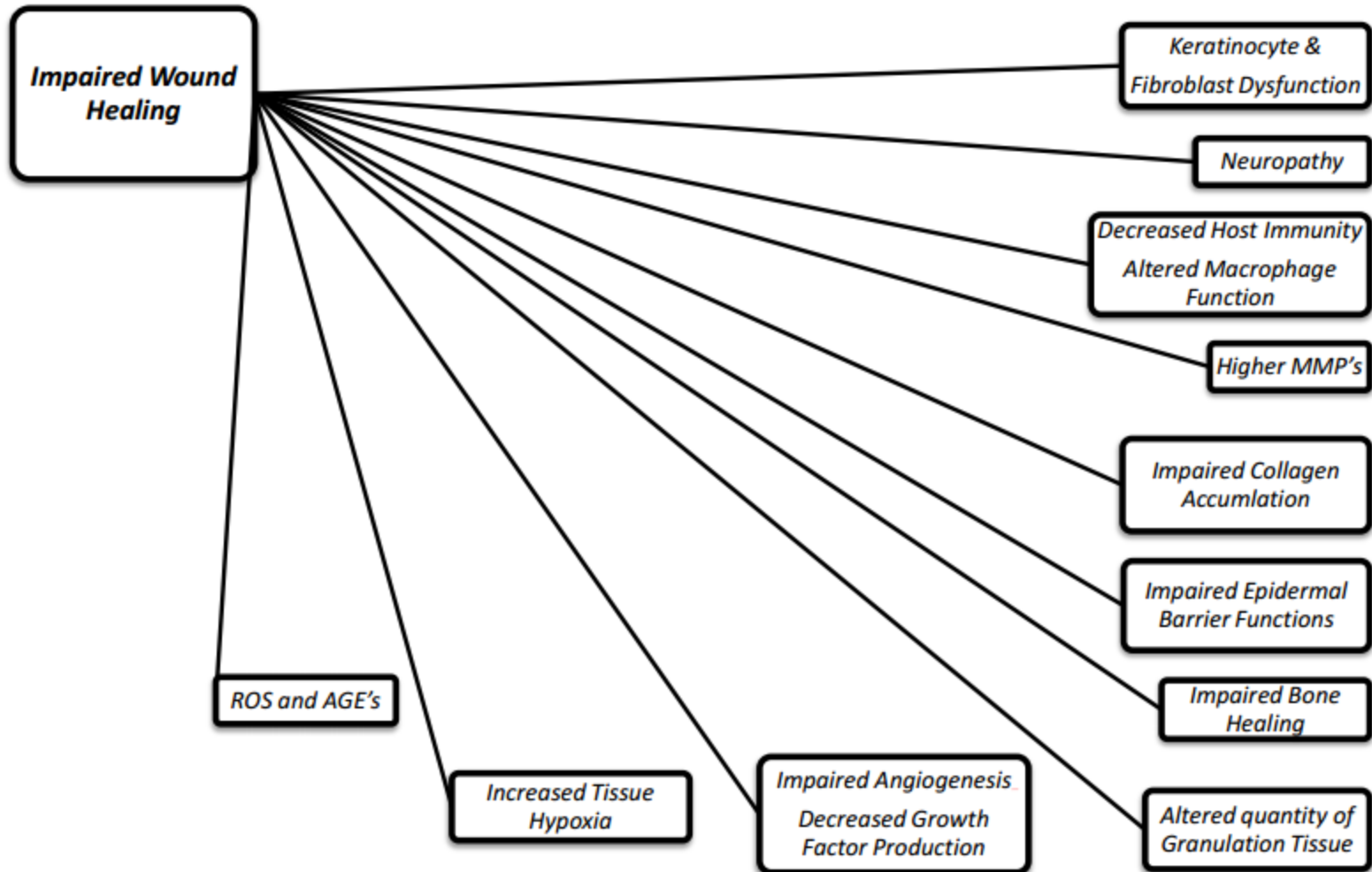


Prevalence of Wounds in the World

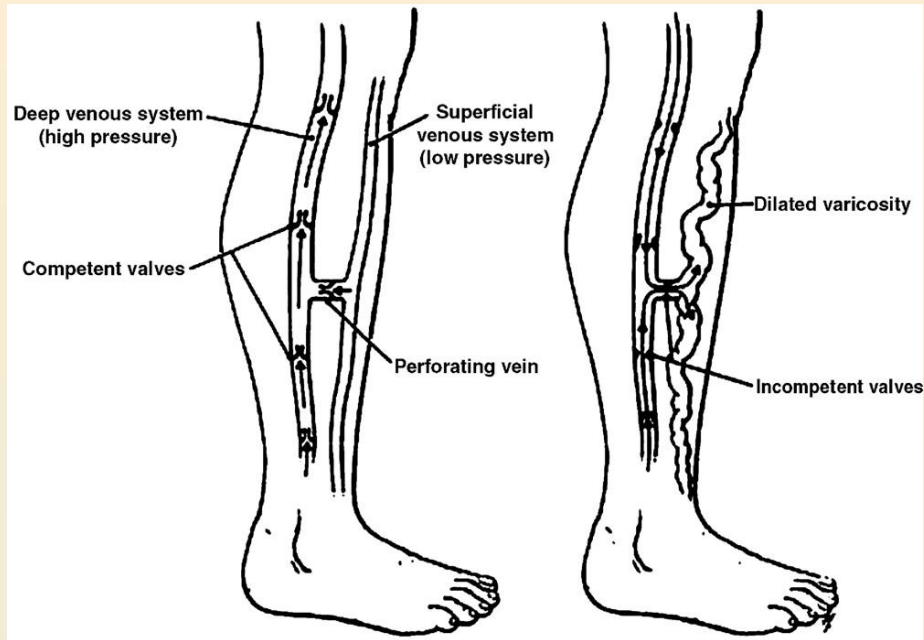
Estimated Prevalence and Healing times of various wound types (Patrick, 2013)

Wound Type	Worldwide Prevalence (Thousands)	Healing Time (Days)	CAGR (2012- 2020)
Surgical wounds	114,271	14	3.6%
Traumatic wounds	1,627	28	1.7%
Lacerations	20,645	14	1.2%
Burn wounds	10,221	21	1.2%
Chronic wounds*	40,400	--	7.6%
Carcinomas	618	14	3.0%
Melanoma	103	14	3.2%
Complicated skin cancer	103	28	3.1%

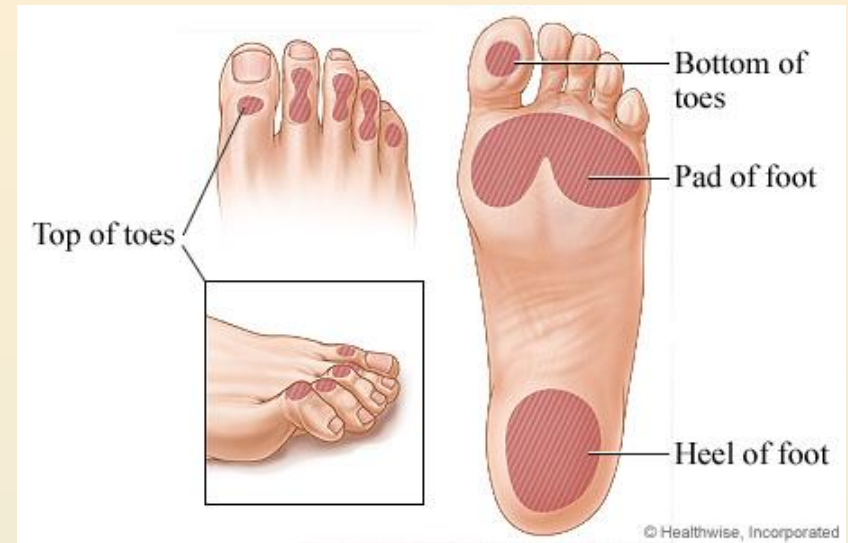
CHRONIC WOUNDS



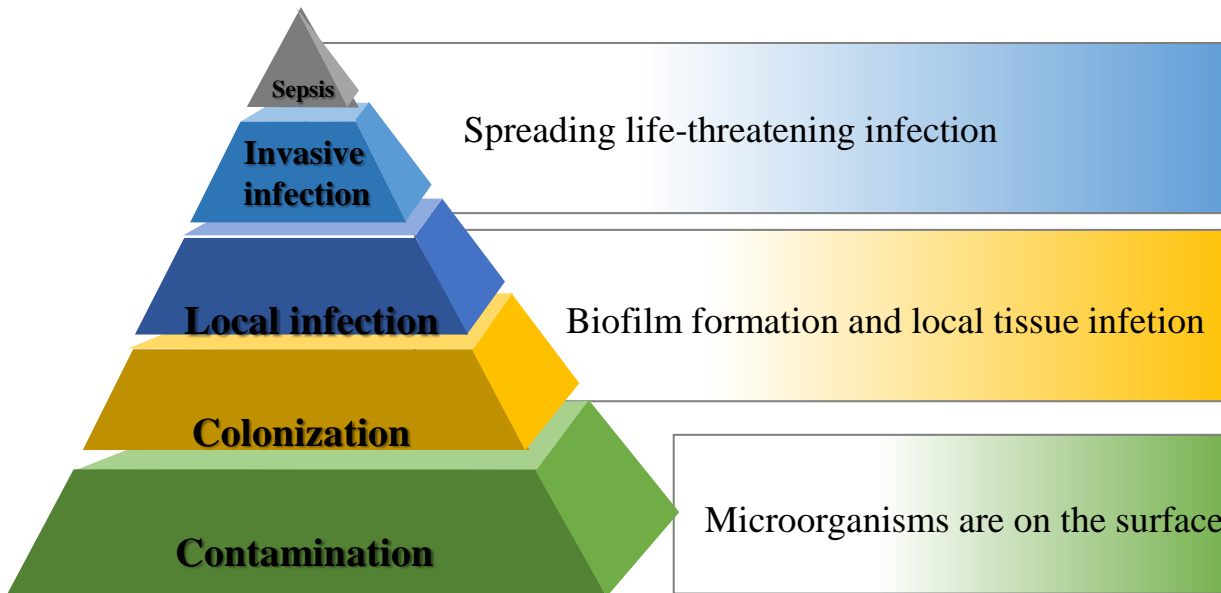
VENOUS ULCERS



DIABETIC FOOT ULCER

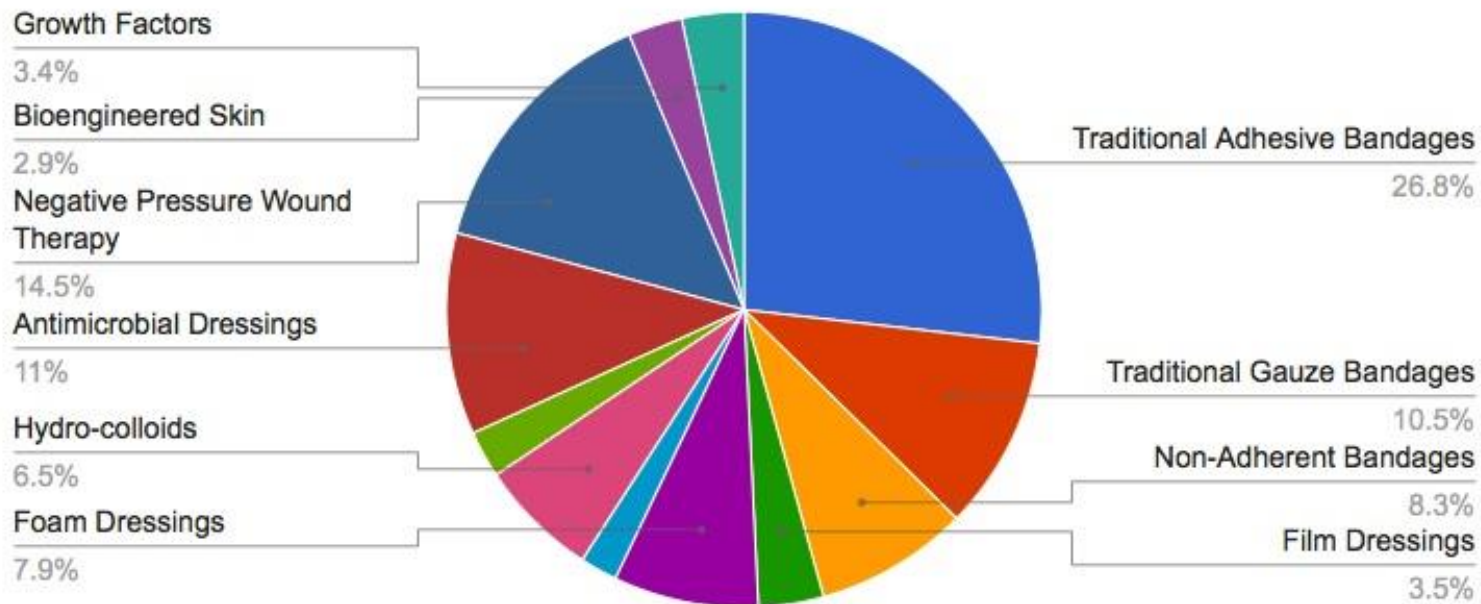


Wound Infection



Current Strategies

Global Wound Care Market, by Segments, 2013



<http://blog.medilience.com/2013/06/10/wound-management-an-18-5-billion-worldwide-market-in-2021/>

Wound Infection



Roles and applications of boron compounds in cutaneous acute and chronic wound healing

Global Market Value of Wound Care Products

- The global wound care market is expected to reach USD 20.4 Billion by 2021 from USD 17.0 Billion in 2016. In Turkey, market value is approx. USD150 Million.
- On the basis of end users, the wound care market is segmented into hospitals and specialty wound care clinics, long-term care facilities, and home healthcare.
- Based on the type of products, the wound care market is segmented into traditional wound care, surgical wound care, and advanced wound management products.
- Factors are driving the growth of the wound care market.
 - rising awareness regarding new technologies for wound care,
 - government support in the form of funding,
 - increasing incidence of chronic diseases such as diabetes and growing obese population,
 - rising aging population

Drawbacks of Wound Care Products Available in the Market

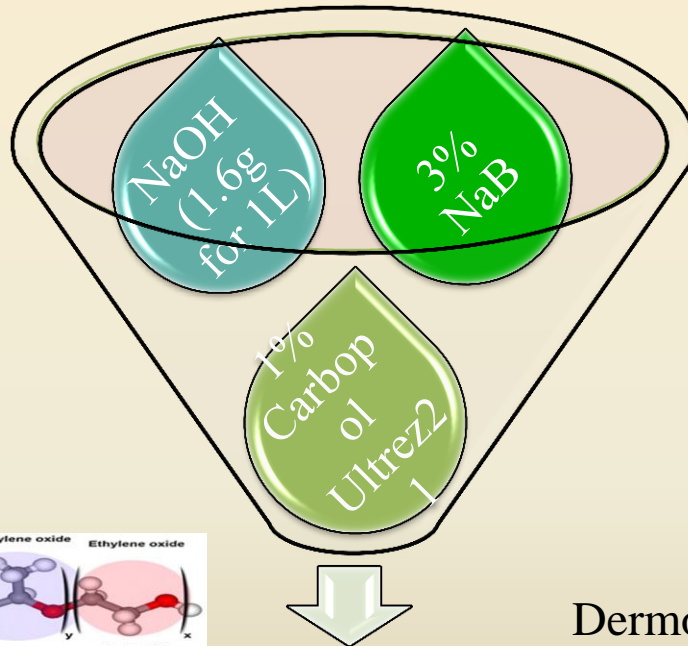
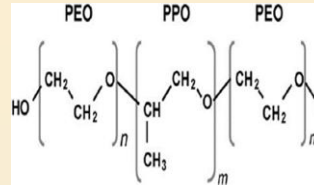
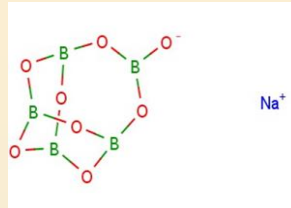
- Most of the products have been being introduced to the market, claiming to provide an ideal wound healing,
- However, they do not meet the expectations
 - being expensive
 - not easily accessible,
 - requiring wound care facilities,
 - having patient-specific response,
 - low efficiency and severe side-effects.
- In this sense, developing new, safe, self-applicable, effective and cheap wound care products with broad-range antimicrobial activity is still an attractive area of international research.



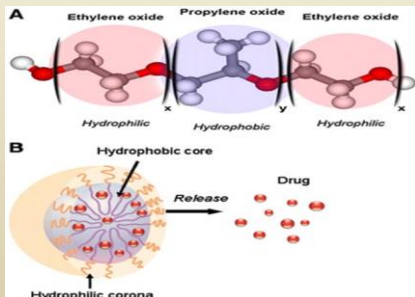
Development of Antimicrobial, Antiaging Carbopol Based Gel Formulation with Wound Healing Property

- **Evaluation of antimicrobial activities *in vitro*;**
- **Investigation of wound healing potential of boron gel *in vivo* ;**
 - Acut and chronic wound animal models
 - Clinical trails

Gel Formulation



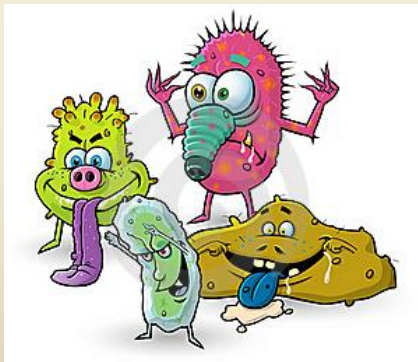
Formulation



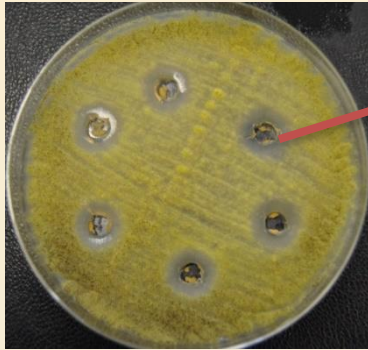
Dermobor is a Chlorhexidine and boron compound (sodium pentaborate pentahydrate-NaB) containing carbopol-based gel composition, co-formulated with poloxamers (F68 and F127).



Antimicrobial effects of the gel formulation

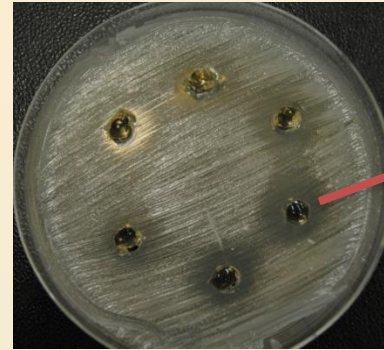


Antimicrobial effects of the gel formulation



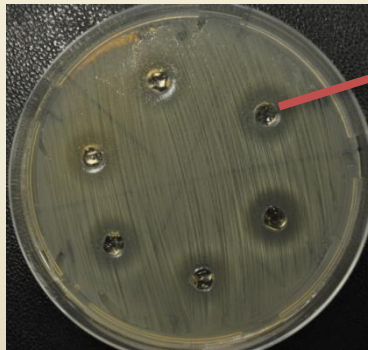
OPTIMIZE JEL

Aspergillus niger



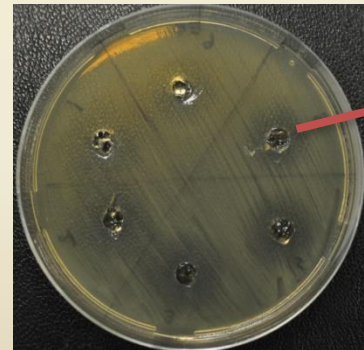
OPTIMIZE JEL

Candida albicans



OPTIMIZE JEL

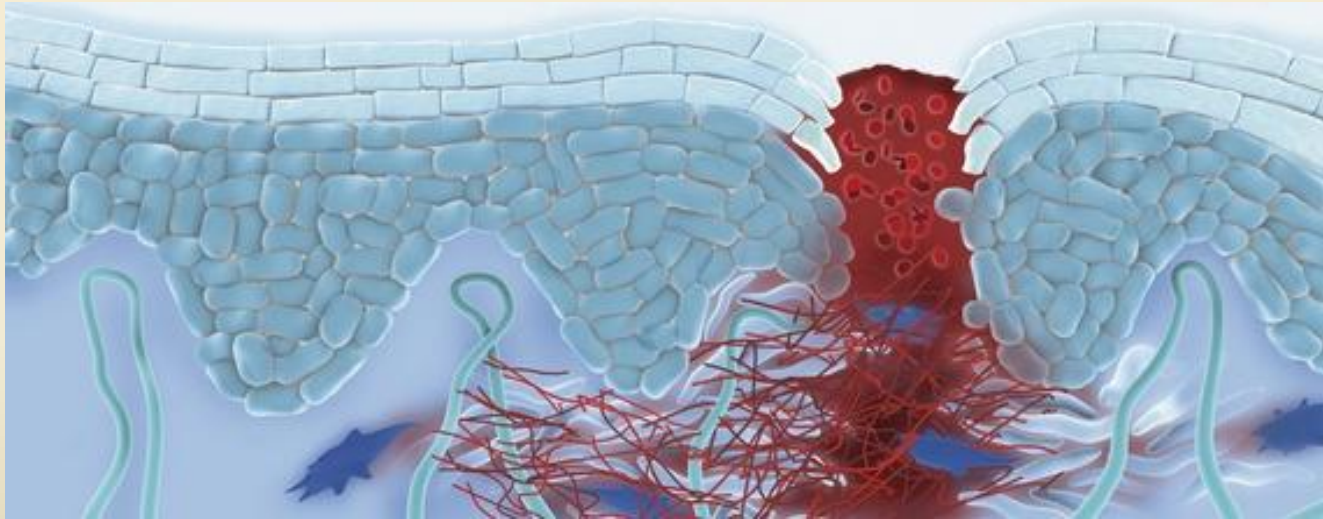
Staphylococcus aureus



OPTIMIZE JEL

Escherichia coli

Wound healing activities of Boron

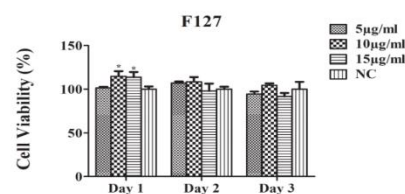
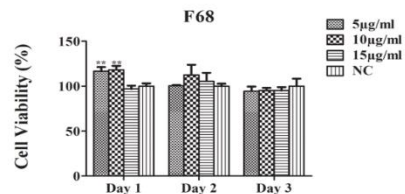
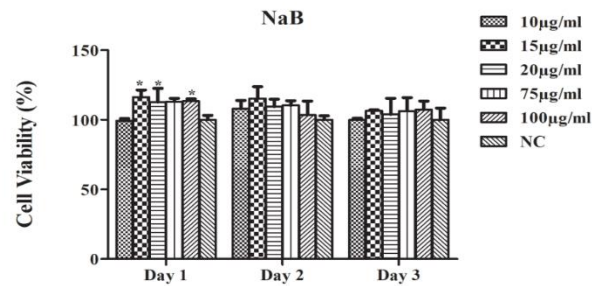
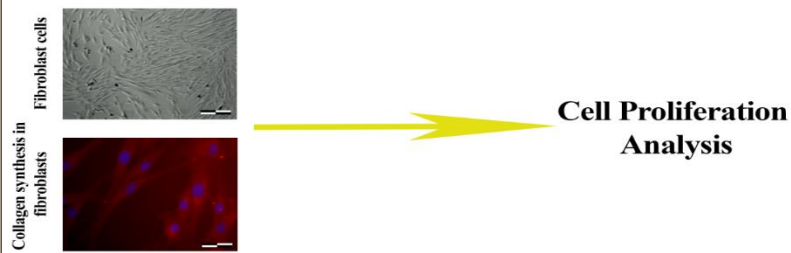


Cell Culture Experiments



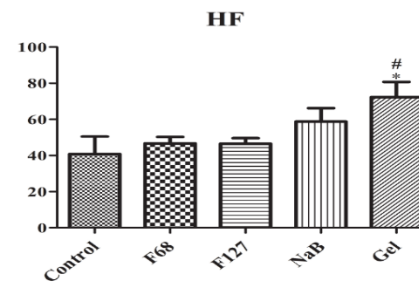
Effects of boron on dermal human fibroblast (HF) cells

Dermobor increases the cell viability, the cell migration rate, the antioxidant enzyme activity of fibroblast cells



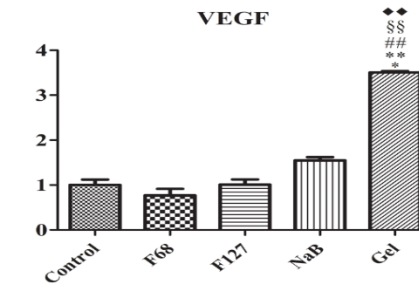
A

Cell Migration (%)



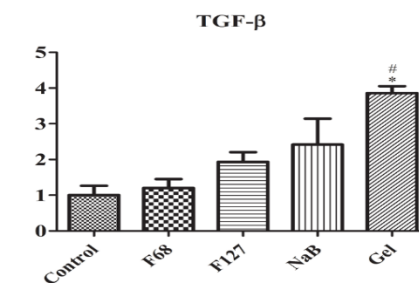
C

Relative mRNA expression



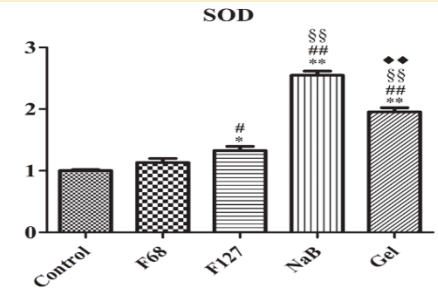
E

Relative mRNA expression



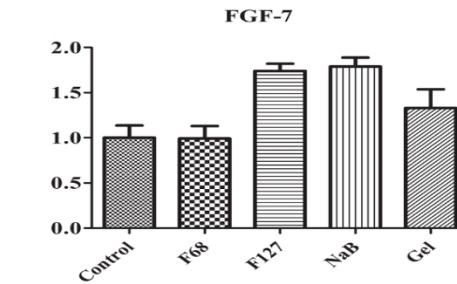
B

Relative enzyme activity



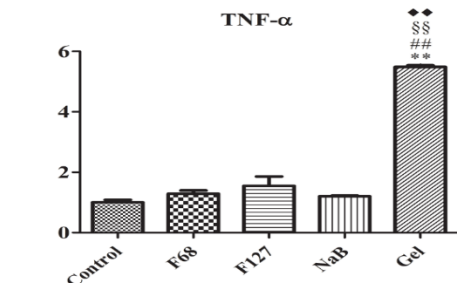
D

Relative mRNA expression



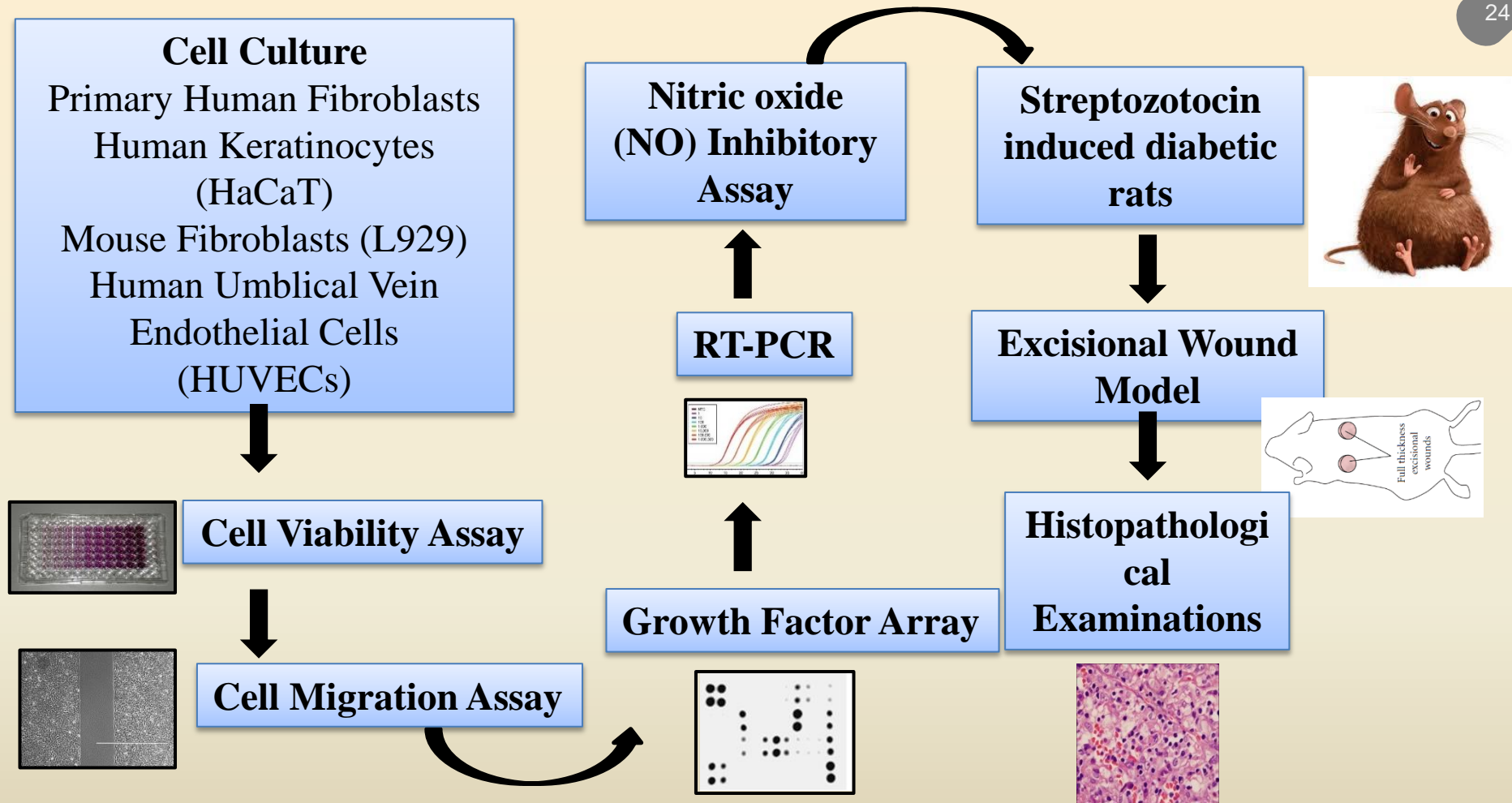
F

Relative mRNA expression

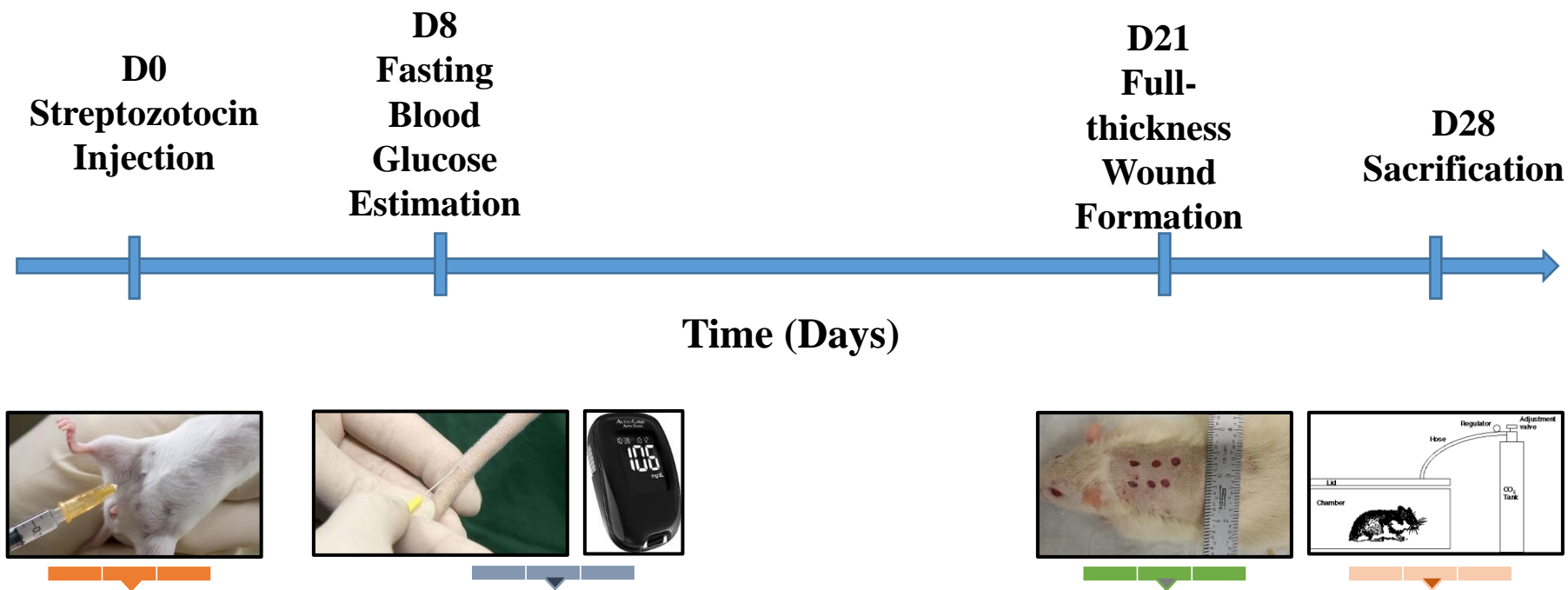


Preclinic Study: Wound Healing Effect of Boron in Diabetic Rat

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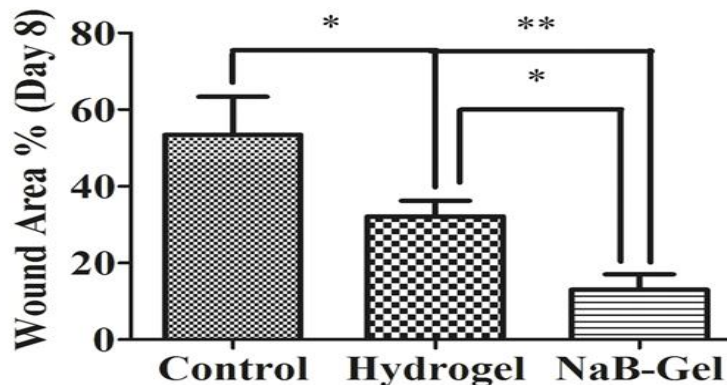
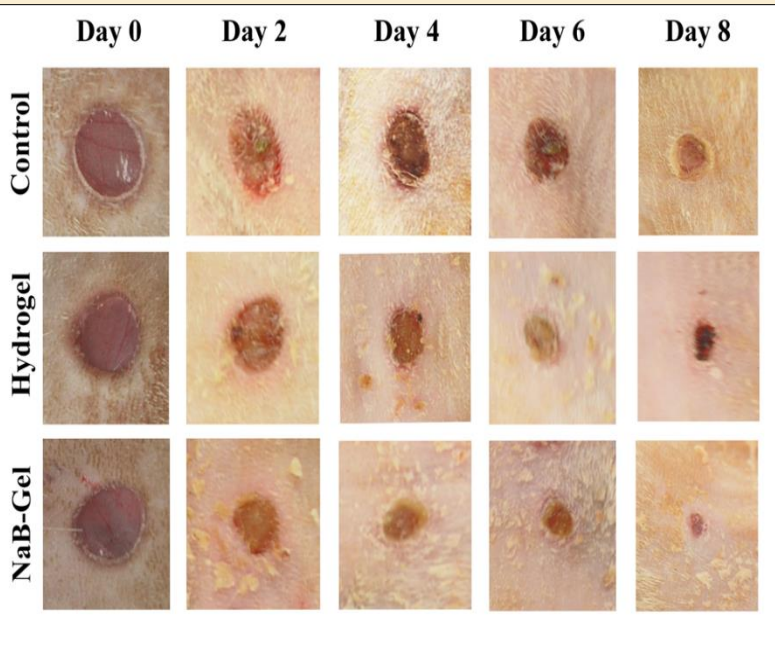


In vivo Experimental Design



SZT-induced Diabetic Wound Animal Model

Our results showed that boron-containing gel formulation could be a useful option for the management of diabetic ulcer.



Mol Cell Biochem
DOI 10.1007/s11010-016-2719-9



Boron promotes streptozotocin-induced diabetic wound healing: roles in cell proliferation and migration, growth factor expression, and inflammation

Selami Demirci¹ · Ayşegül Doğan¹ · Safa Aydın¹ · Esra Çikler Dülger² · Fikrettin Şahin¹

Clinical Trials



Summary and Future Perspectives

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ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Home > Find Studies > Study Record Detail

Wound Treatment With 3% Sodium Pentaborate Pentahydrate

This study is currently recruiting participants. (see Contacts and Locations)

Verified September 2014 by SB Istanbul Education and Research Hospital

Sponsor:
SB Istanbul Education and Research Hospital

Collaborator:
Bezmialem Vakif University

Information provided by (Responsible Party):
Erhan Aysan, SB Istanbul Education and Research Hospital

ClinicalTrials.gov Identifier:
NCT02241811

First received: September 13, 2014
Last updated: NA
Last verified: September 2014
History: No changes posted

Full Text View

Tabular View

No Study Results Posted

Disclaimer

? How to Read a Study Record

► **Purpose**

Chronic foot wounds which is very difficult to treat are common especially in diabetic and peripheral arterial or venous insufficiency. Recovery with 3% Sodium pentaborate pentahydrate hydrogel.

Diabetic Foot Ulcer



3 Weeks treatment-Control gel

Diabetic Foot Ulcer

1st Day



2nd Day



3rd Day



4th Day



5th Day



6th Day



Roles and applications of boron compounds in cutaneous acute and chronic wound healing

Diabetic Foot Ulcer

8th Day



9th Day



10th Day



11th Day



Diabetic Foot Ulcer

1st Day



20th Day



Diabetic Ulcer



3 Weeks treatment-Boron gel

Diabetic Ulcer



3 Weeks treatment-Boron gel

Diabetic Ulcer

9 Weeks treatment-Boron gel



Bed sore

Day 0



3. week



5 week



7. week



11. week



Radiodermatitis



**5th week of Radiotherapy.. Patient #10
(Placebo Group)**



**6th week of Radiotherapy.. Patient #6
(Placebo Group)**



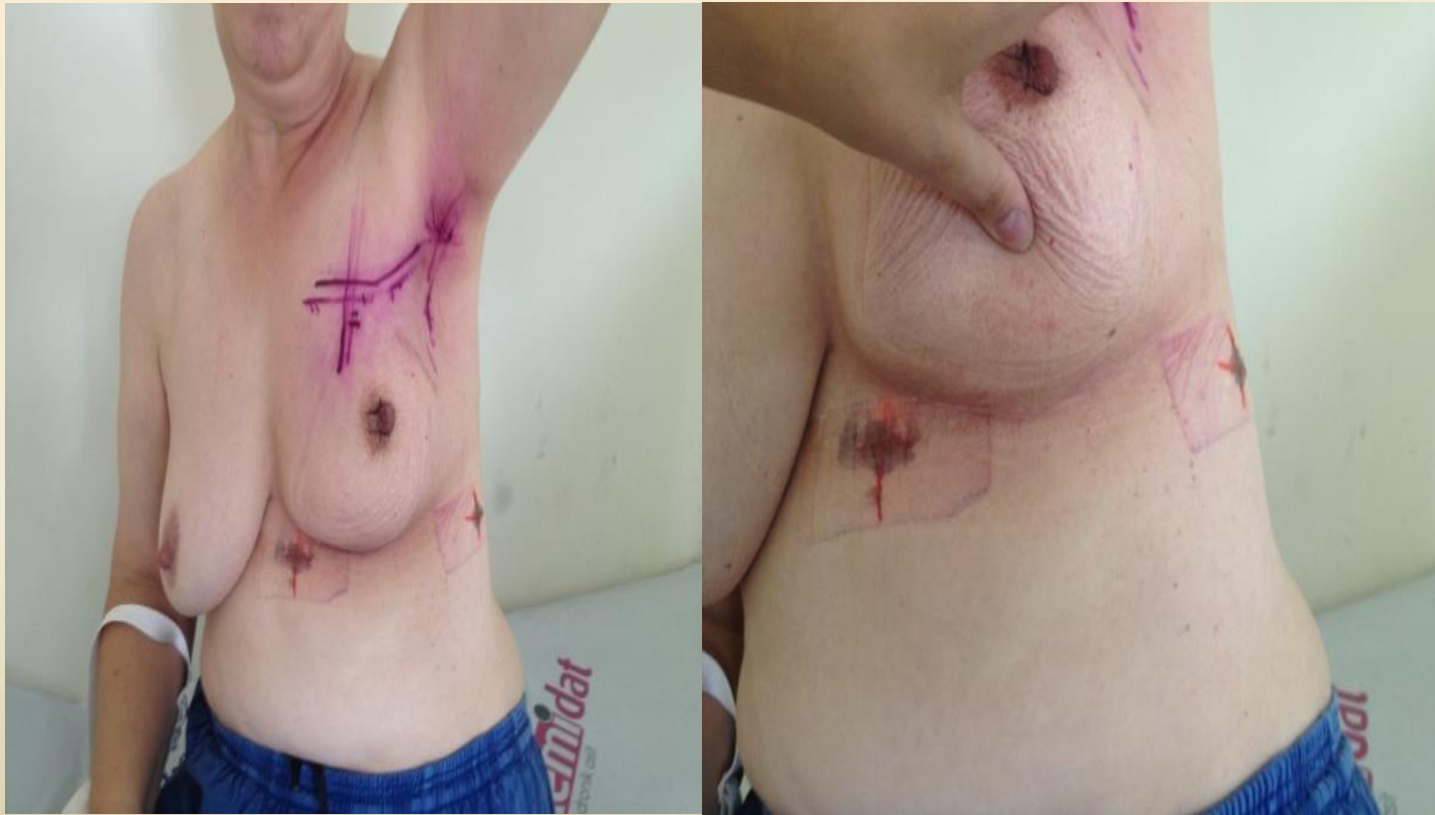
**6th week of Radiotherapy.. Patient #11
(Placebo Group)**



**6th week of Radiotherapy.. Patient #27
(Treated with DB Added Gel)**



**5th week of Radiotherapy.. Patient #29
(Treated with DB Added Gel)**



DB ADDED GEL / CONTROL (ULTRASOUND) GEL



Biol Trace Elem Res
DOI 10.1007/s12011-015-0533-y

Relation
and Bo
Boron

Fulya Koc¹
Selami Demirci

Biol Trace Elem Res
DOI 10.1007/s12011-015-0338-z

Boron an
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Selami Demirci¹
Elif Demirci⁴ • F



Biol Trace Elem Res
DOI 10.1007/s12011-013-9657-0

Boron Enhances Odontogenic and Osteogenic Differentiation of Human Tooth Germ Stem Cells (hTGSCs) In Vitro

Pakize Neslihan Taşlı • Ayşegül Doğan •
Selami Demirci • Fikrettin Şahin

Antibacterial and cytotoxic

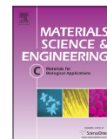
Selami DEMİRCİ¹, Mu

Materials Science and Engineering C 44 (2014) 246–253

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec



Boron containing poly-(lactide-co-glycolide) (PLGA) scaffolds for bone tissue engineering

Ayşegül Doğan^a, Selami Demirci^a, Yasin Bayir^b, Zekai Halici^c, Emre Karakus^d, Ali Aydın^e, Elif Cadirci^f, Abdulmecit Albayrak^c, Elif Demirci^g, Adem Karaman^h, Arif Kursat Ayanⁱ, Cemal Gundogdu^g, Fikrettin Şahin^{a,*}



Biol Trace Elem Res
DOI 10.1007/s12011-015-0253-3

Dose-dependent Effect of Boric Acid on Myogenic Differentiation of Human Adipose-derived Stem Cells (hADSCs)

Hüseyin Apdik • Ayşegül Doğan • Selami Demirci •
Safa Aydın • Fikrettin Şahin



Boron cont
tissue engi
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Abdulmecit Al

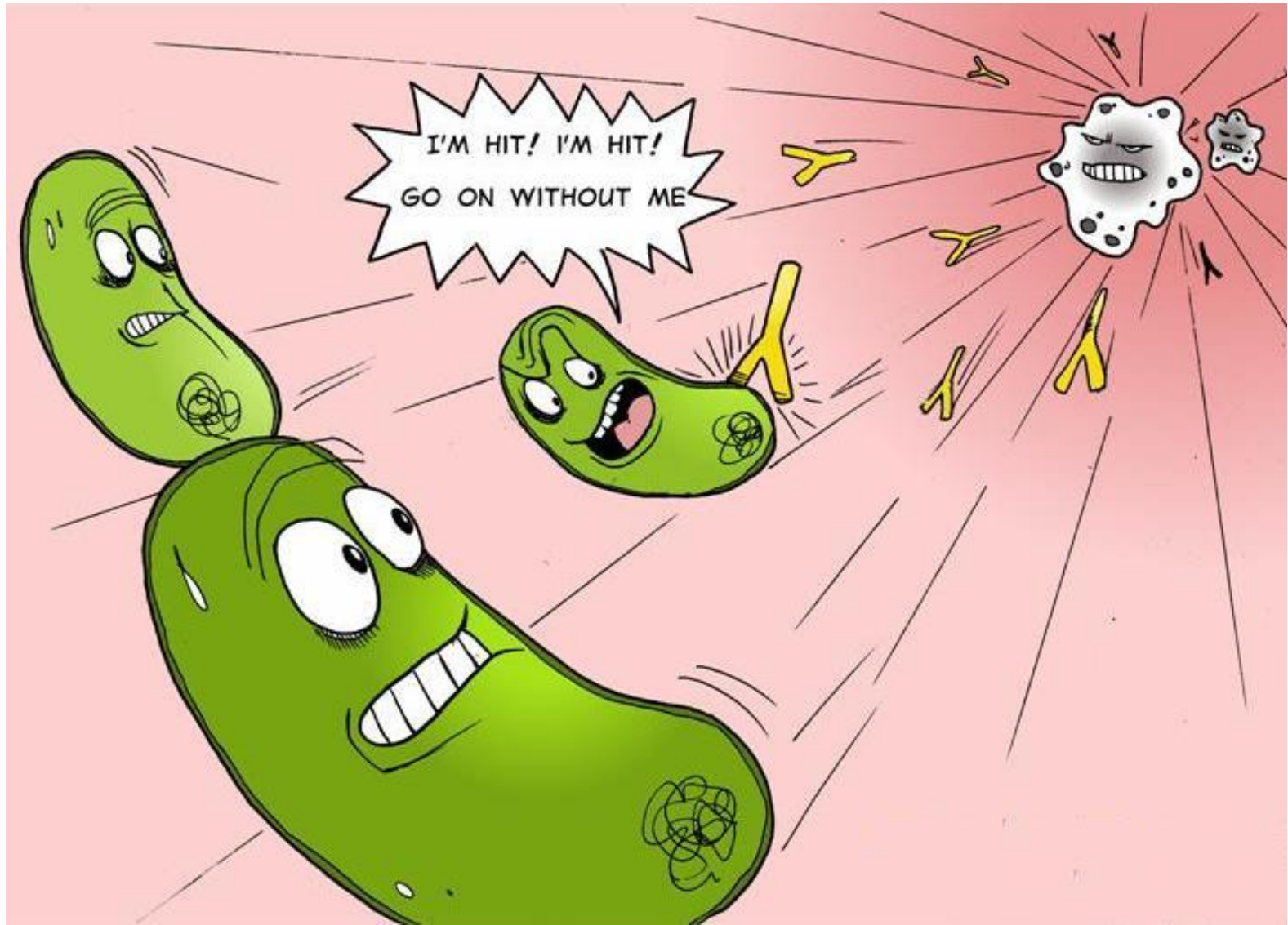


Boron increases the
long-term cryopres
Selami Demirci, Ayşegül
Department of Chemistry and Biochemistry

ARTICLES

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ANTIMICROBIAL PRODUCTS







Acknowledgements

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Alev Cumbul



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Esra Cıkler Dülger

Medipol University

Ertuğrul Kılıç
Burak Çağlayan



Bezmialem University

Erhan Ayşan





THANK YOU

