Honey: a therapeutic agent for disorders of the skin

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Assistant Professor

Nazarbayev University School of Medicine

Seminar Outline

- Introduction
- Antimicrobial properties of honey in relation to skin disease
- Immunomodulatory properties of honey
- Anti-carcinogenic properties of honey
- Evidence for the efficacy of honey in the treatment of skin disease

Dermatology Department,
Ninewells Hospital, Dundee

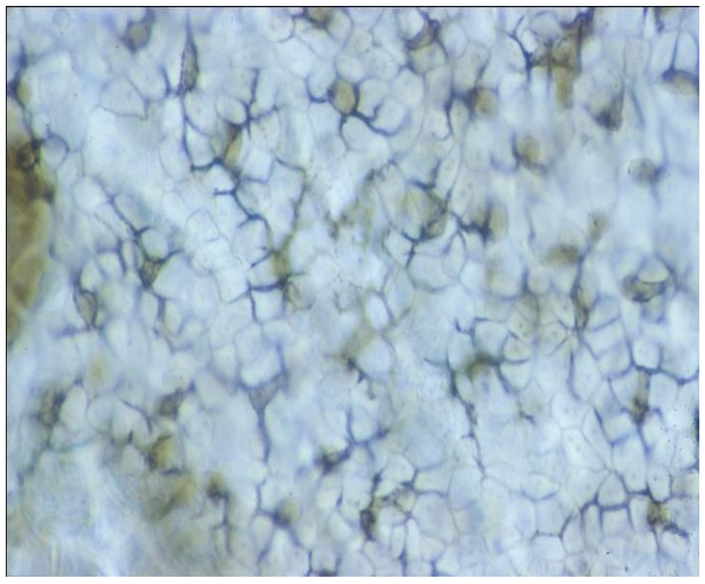
UNIVERSITY OF DUNDEE

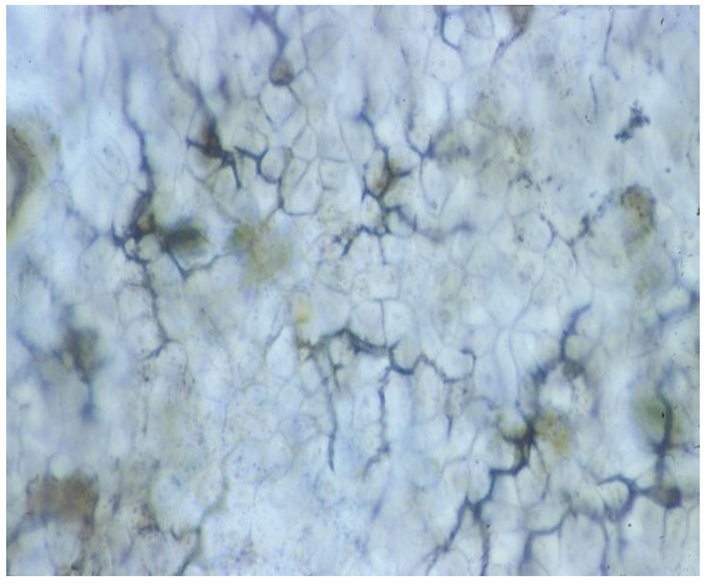
The effects of ultraviolet radiation on the immune system.

UV Induced Immune Suppression

Local Effects

- Reduces Langerhans cell numbers in the skin.
- Langerhans cells migrate from the skin to the regional lymph nodes.





- Suppresses a contact hypersensitivity response in the skin.
- Stimulates cytokine production in the skin.

Systemically

- Suppresses macrophage phagocytic activity.
- Suppresses natural killer cell activity.
- Increases dendritic cell numbers in draining lymph nodes.

Eczema

Folliculitis

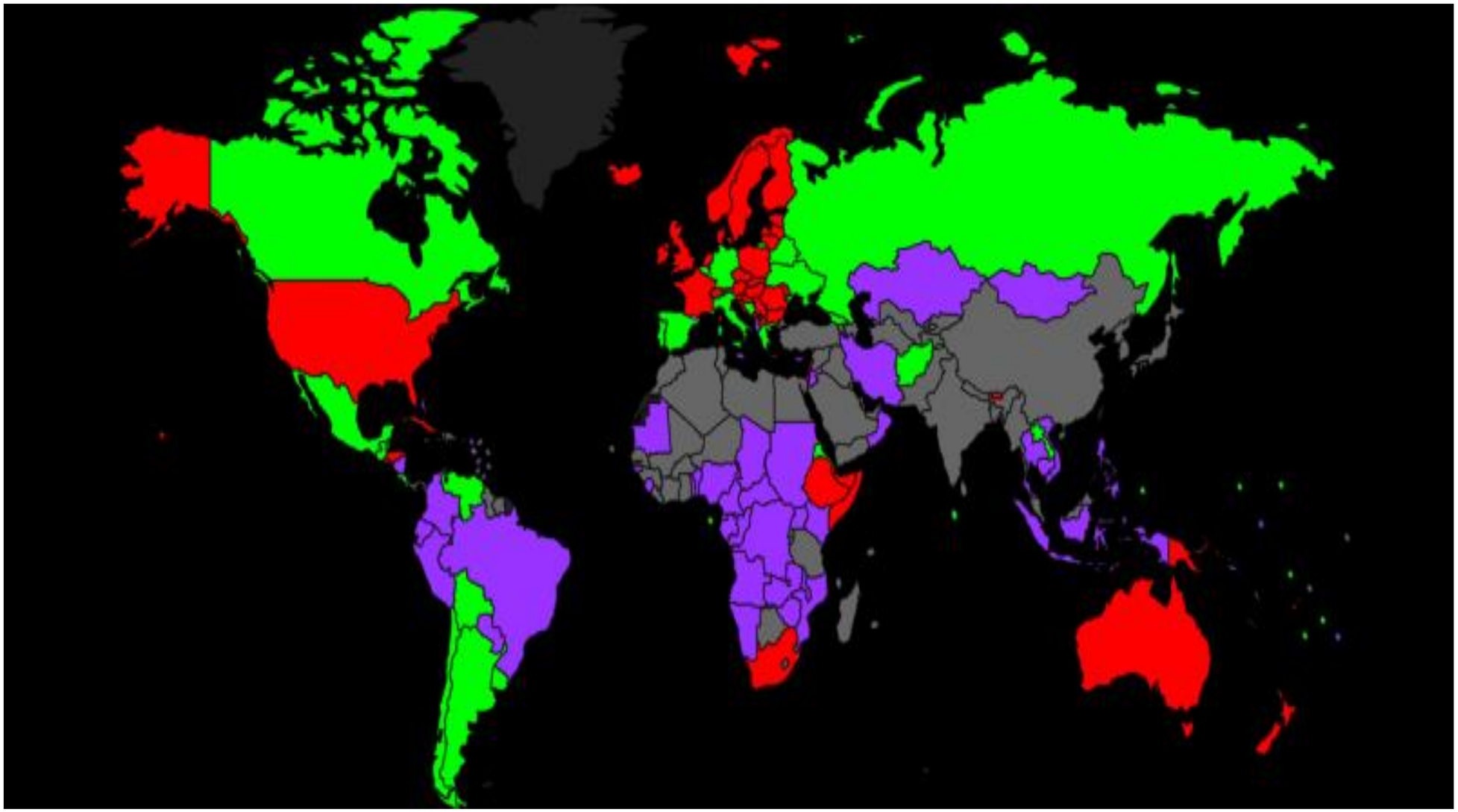
Psoriasis

Contact Dermatitis

Statistics and Problems in Dermatology

- **Eczema**- a chronic and distressing skin condition that affects up to 8% of the UK population and about 20% of children.
- **Psoriasis**- affects approximately 2% of the UK population.
- Treatments rely heavily on steroids- cause skin thinning.
- Ultraviolet radiation is associated with the development of skin cancer.
- **Wound Infections –** because of antibiotic resistance are becoming progressively more difficult to treat (Godebo et al, 2013, Annals of Clinical Microbiology and Antimicrobials, 12:17).
- The incidence of both **non-melanoma and melanoma skin cancers** has been increasing over the past decades.
- Currently between 2 and 3 million non melanoma skin cancers and 132, 000 melanoma skin cancers occur globally each year (WHO, 2015).
- Each year there are more new cases of skin cancer than the combined incidence of cancers of the breast, prostate, lung and colon (American Cancer Society, 2015).

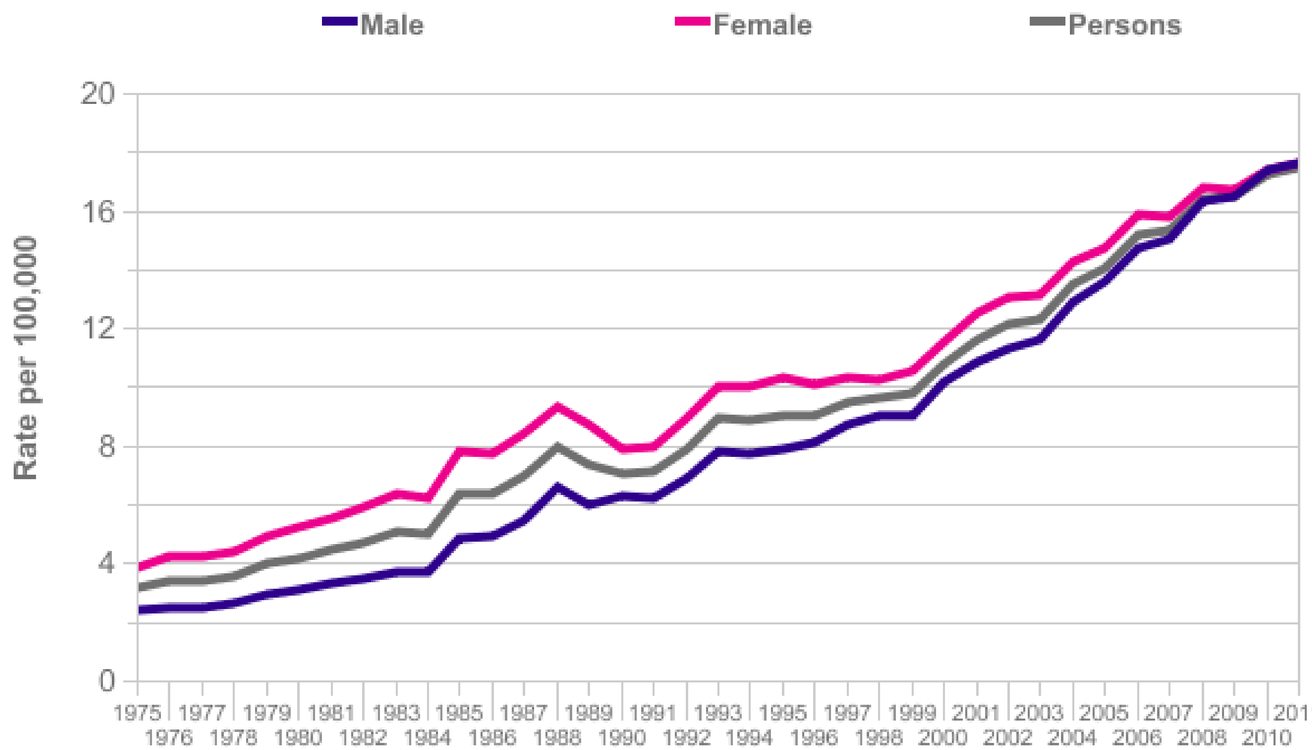
Skin Cancer World Statistics (WHO, 2011), Death rate per 100,000



High Low

Malignant Melanoma (C43): 1975-2011

European Age-Standardised Incidence Rates per 100,000 Population, by Sex, Great Britain



Please include the ciation provided in our Frequently Asked Quesitons when reproducing this chart: http://info.cancerresearchuk.org/cancerstats/faqs/#How

Prepared by Cancer Research UK

Original data sources:

1. Office for National Statistics. Cancer Statistics: Registrations Series MB1. http://www.statistics.gov.uk/statbase/Product.asp?vlnk=8843.
2. Welsh Cancer Intelligence and Surveillance Unit. http://www.wcisu.wales.nhs.uk.
3. Information Services Division Scotland. Cancer Information Programme. www.isdscotland.org/cancer.

CANCER RESEARCH UK

Skin Cancer Statistics, Kazakhstan

(Ministry of Health, Kazakhstan)

Type of Cancer	Incidence 2012	Incidence 2013
Total Cancers	31258	32097
Lip	174	195
Esophagus	1341	1232
Stomach	2686	2733
Rectal	1288	1375
Larynx	384	430
Lung	3541	3614
Skin	2978	3250
Breast	3924	3815
Cervix	1616	1622
Lymph	626	636

Curapel

A privately held healthcare company that is developing innovative and effective treatments for common and distressing skin conditions.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South West Nigeria

Indigenous people use the local plants for the treatment of a wide range of health conditions

Acalypha wilkesiana (Eela)

Azadirachta indica (Dongoyaro)

Bryophyllum pinnatum (Abamoda*)*

Centrosema pubescens (Ewa-ahun)

Queen Margaret University

Portobello honey 'kills bacteria'

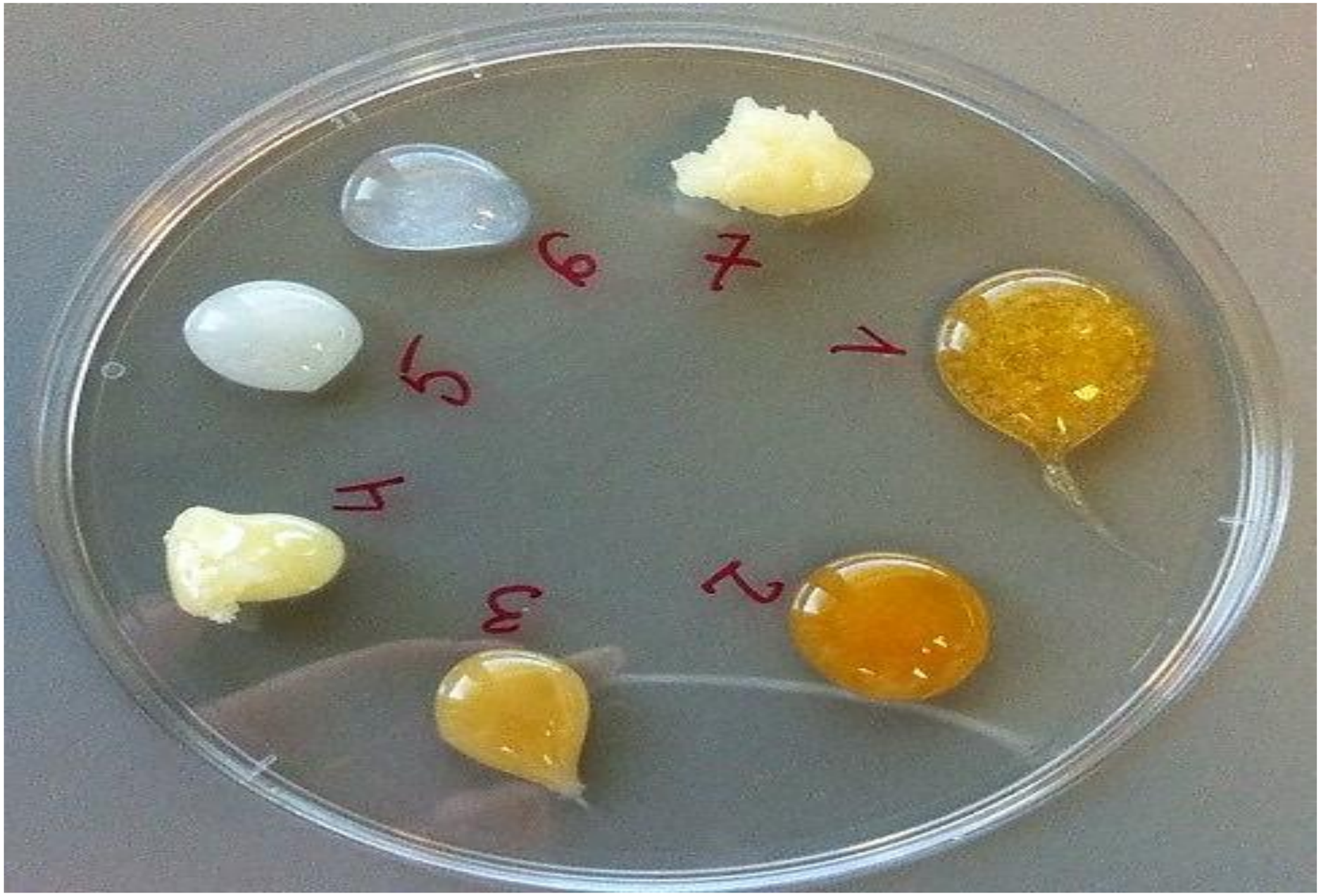
19 November 2012 | Edinburgh, Fife & East Scotland

Edinburgh scientists studying the properties of honey produced in Portobello have said it could be used to kill bacteria.

The medicinal value of honey to treat wounds is well known.

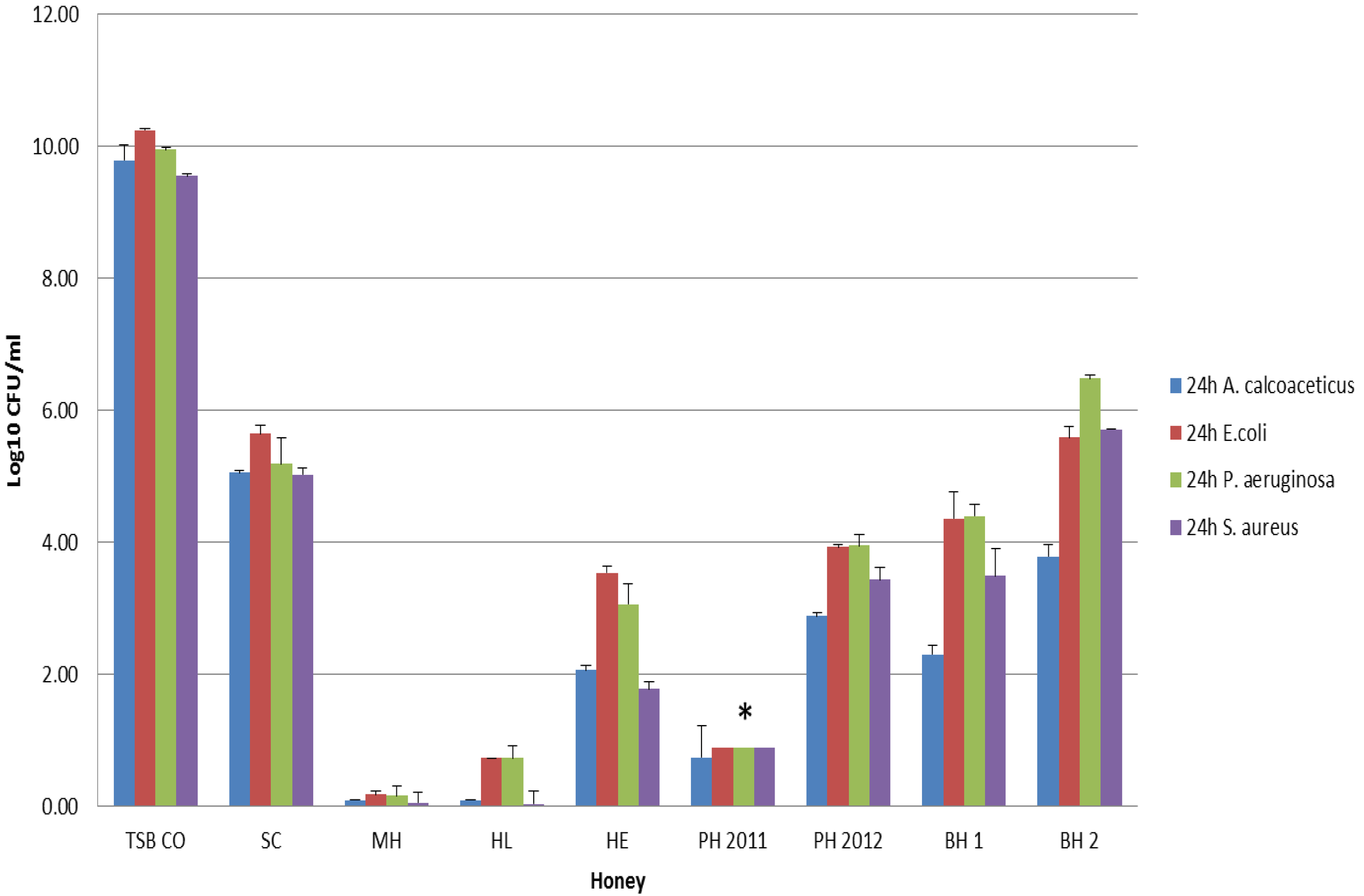
However, scientists at Queen Margaret University have found honey produced by bees in Portobello is as effective as

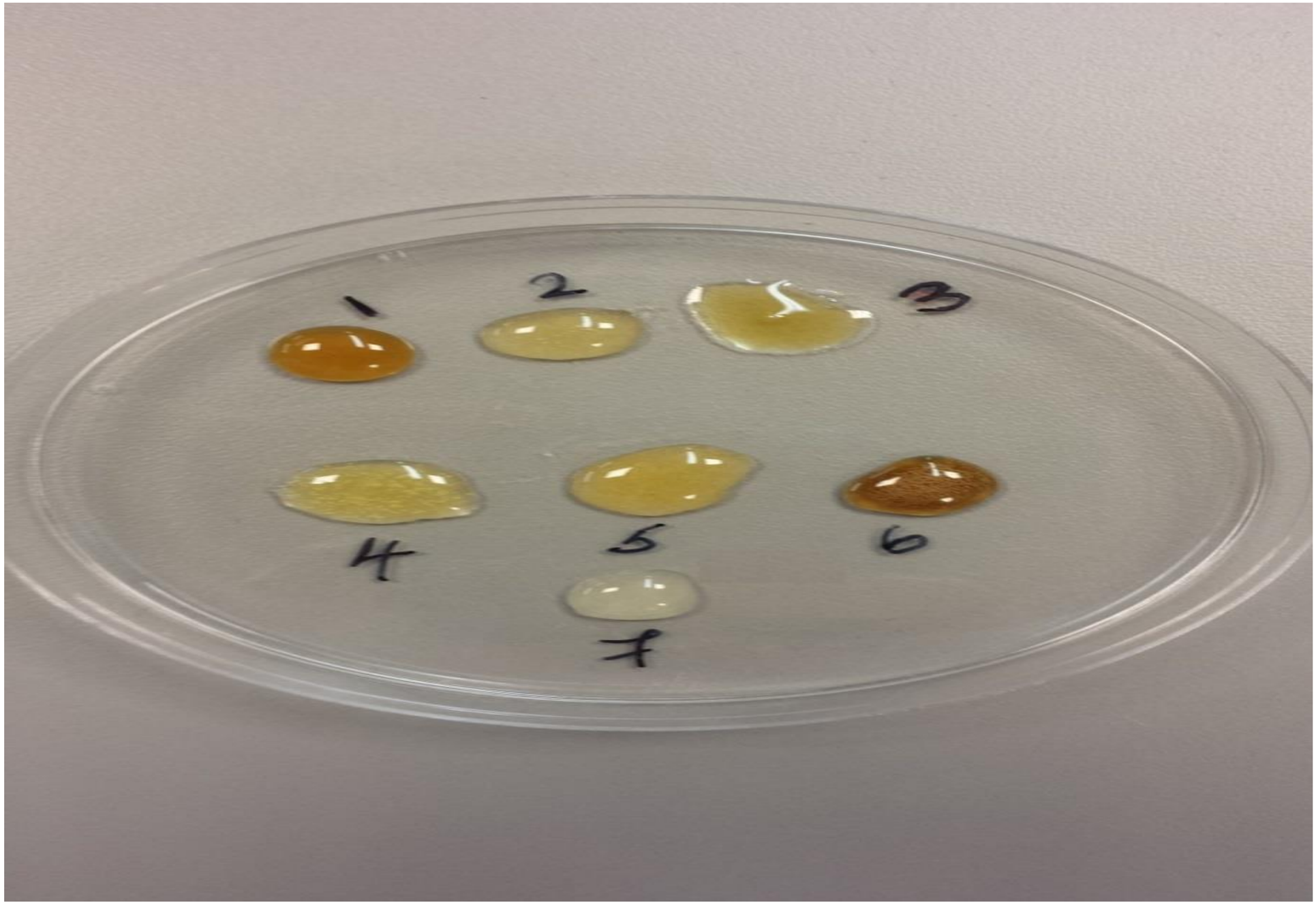
The hives involved in the study are in Portobello in Edinburgh



1. Heather; 2. Manuka; 3. Highland; 4. Blossom; 5 PH2011; 6 Sugar control; 7 Blossom.

Bacterial count after 24h incubation in TSB with 75% honey





1. Manuka; 2. Highland; 3. Chilean; 4.Colonsay;
5. Heather; 6. Buckwheat; 7. Capstone Valley

Sherlock et al. BMC Complementary and Alternative Medicine 2010, 10:47
http://www.biomedcentral.com/1472-6882/10/47

BMC
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RESEARCH ARTICLE Open Acces

Comparison of the antimicrobial activity of Ulmo honey from Chile and Manuka honey against methicillin-resistant Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa

Journal of Environmental Science and Health, Part B:
Pesticides, Food Contaminants, and Agricultural Wastes
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lesb20

Antibacterial activity of different natural honeys from Transylvania, Romania

Zainol et al. BMC Complementary and Alternative Medicine 2013, 13:129
http://www.biomedcentral.com/1472-6882/13/129

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RESEARCH ARTICLE Open Access

Antibacterial activity of selected Malaysian honey

Mohd Izwan Zainol[1*], Kamaruddin Mohd Yusoff[2] and Mohd Yasim Mohd Yusof[3]

Composition of Honey

- Approximately 80% sugars (40% fructose, 35% glucose and 5% sucrose) and 20% water.
- Also contains amino acids, vitamins, minerals, polyphenols and enzymes.
- pH ranges from about 3.2 to 4.5.
- Microbes
- Pollen
- Propolis

Antimicrobial Components in Honey

- High Sugar Concentration
- Low pH
- Hydrogen Peroxide (H_2O_2)
- Methyglyoxal (MGO)
- Anti-microbial peptides e.g. bee defensin-1
- Polyphenols

	Polyphenols (mg/L GAE)	Antioxidants (mM Fe^{2+}/L)	H_2O_2 (ug/ml)	pH	Sugar	Colour
Manuka	1282.47± 25.68*	4.56± 0.14*	3.35± 1.38x	3.00	78%	Amber
Highland	702.38± 15.15*	1.39± 0.06*	1.44± 0.03*	3.00	79%	Light Amber
Chilean	867.32± 28.43*	3.01± 0.15*	74.5± 11.6*	4.00	80%	Light Amber
Colonsay	1184.94± 22.68*	10.55± 0.11*	2.25± 0.29*	5.00	81%	Light Amber
Heather	824.86± 20.69*	2.23± 0.05*	35.63± 7.49*	5.00	77%	Light Amber
Buckwheat	2034.65± 53.90*	6.17± 0.10*	26.7± 3.34*	3.00	79%	Dark Amber
Capstone V.	240.75± 11.36*	0.69± 0.03*	244.87± 41.59*	5.00	81%	White

Effects of Honey on Microbial Pathogenicity

- Sub-inhibitory concentrations of Manuka honey have been shown to reduce the expression of α-toxin in Methicillin Resistant *Staphylococcus aureus* (MRSA) (Jenkins et al (2014) J Antimicrob Chemother, 69, 603-615).
- Expression of other virulence genes, quorum sensing genes and genes associated with cell division were also reduced.
- Sublethal concentrations of Manuka honey reduced siderophore production a virulence factor that scavenges iron for bacterial growth in clinical and non-clinical strains of *P. aeruginosa* (Kronda et al (2013) J Appl Microbiol, 115, 86-89).
- A honey flavonoid extract was also found to alter membrane integrity and branching processes associated with virulence in *Candida albicans* *(Canonico et al, 2014, Future Microbiol, 9, 445-456)*.
- Sub-inhibitory concentrations of Scottish Highland, Chilean and Manuka Honey reduced Toxic Shock Syndrome Toxin (TSST-1) production in a penicillin resistant strain of *Staphylococcus aureus* *(Okoro et al (2015), Food Science and Technology, 3(2), 29-36)* .

Honey Reversed Antibiotic Resistance

- Remarkably, *in vitro* research has also shown that honey can actually reverse antibiotic resistance, suggesting that honey used in combination with antibiotics may have additional therapeutic effects (Jenkins and Cooper (2012), J Antimicrob Chemother; 67: 1405–1407).
- A suggested mechanism is via honey-induced down-regulation of *mecR1* gene product, a transducer associated with antibiotic resistance in MRSA.
- Manuka honey worked synergistically with the antibiotic rifampicin to inhibit the growth of MRSA and clinical isolates of *S. aureus* *(Muller et al, 2013, PLoS One, e57679)*.

Traditional Uses of Honey

- Ancient Greeks and Egyptians used honey to treat skin wounds and burns (cited in Molan (1992), Bee World, 73 (1) 5-28).
- In Malaysian tradition, honey is used to treat furuncles, diabetic wounds and burns (Barakhbah (2007), Malays J Med Sci, 14 (1): 106).
- Persian traditional medicine documented honey as effective in the treatment of wounds, eczema and inflammation (Sepehr (2010) J Apiprod Apimed Sci; 2 (1); 43).
- In Ayruvedic medicine honey is used to treat cuts, wounds, eczema, dermatitis, burns, skin diseases and Fournier's gangrene (Deshpande and Kulkani (2010) J Apiprod Apimed Sci, 2 (1): 45).
- Quranic medicine- honey combined with cinnamon powder is used to treat eczema and ringworm (Marwat et al (2013) Pak J Pharm Sci (2013): 26(2): 307-314).
- Burkina Faso, Africa- indigenous people use honey as a skin cleansing agent and as a treatment for measles rash (Meda et al, 2004, 95, J Ethnopharmacol: 103-107).

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Article in Press

Honey: A realistic antimicrobial for disorders of the skin

Pauline McLoone, Mary Warnock, Lorna Fyfe

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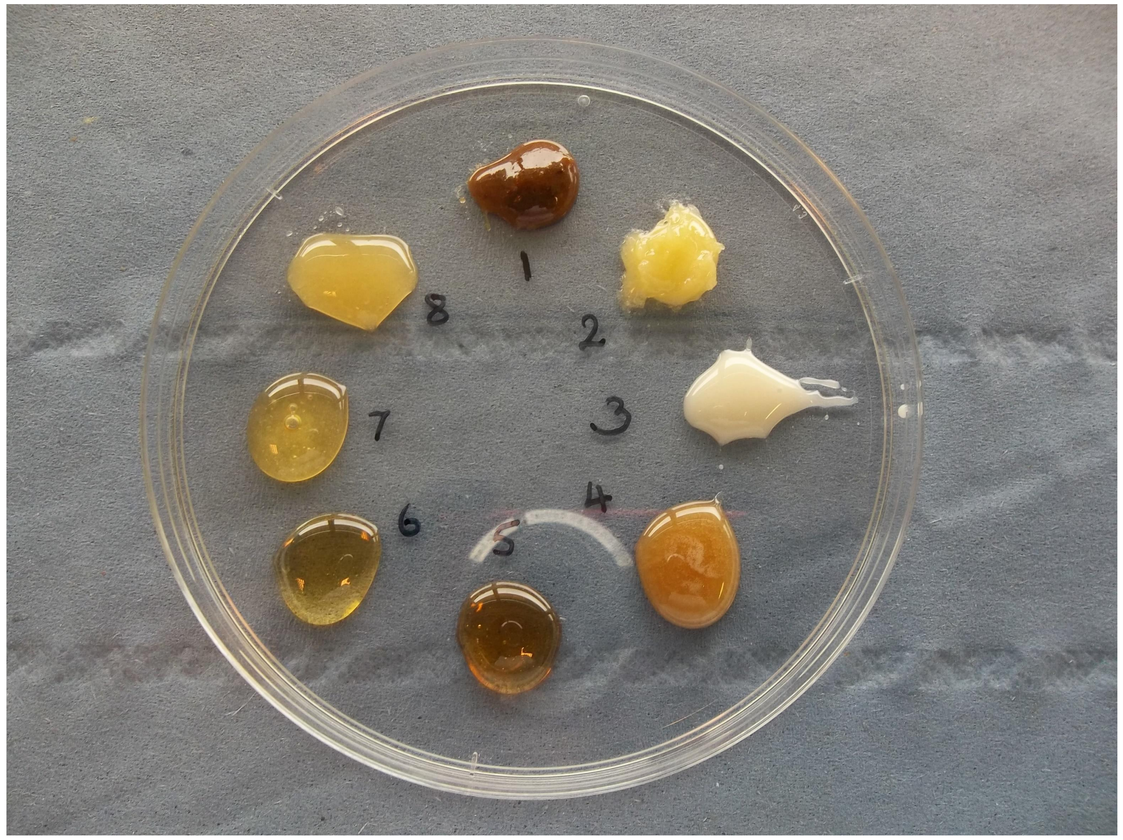
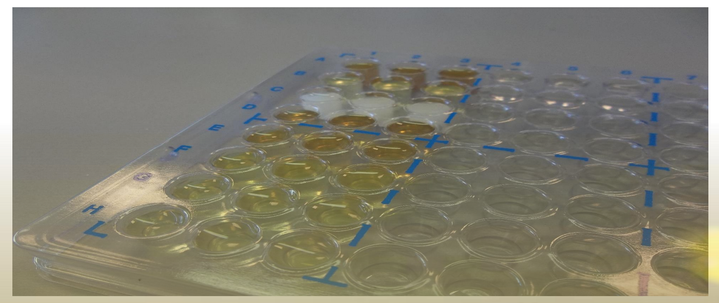
Publication stage: In Press Corrected Proof

Honeys of different types inhibit the growth of a range of dermatologically important microbes, including;

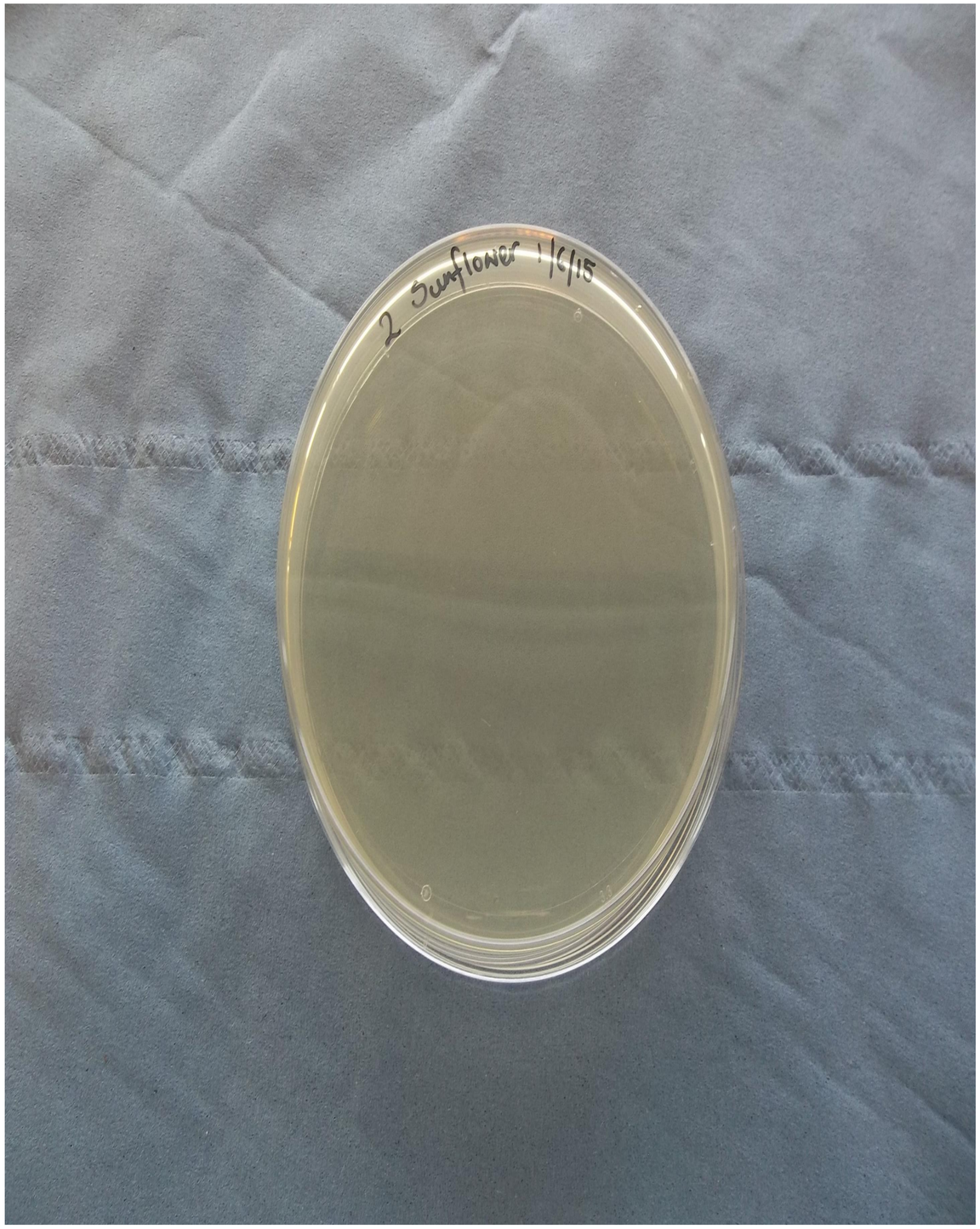
- *Pseudomonas aeruginosa;*
- *Staphylococcus aureus;*
- *Escherichia coli;*
- Candida albicans;
- Dermatophytes
- Varicella Zoster Virus

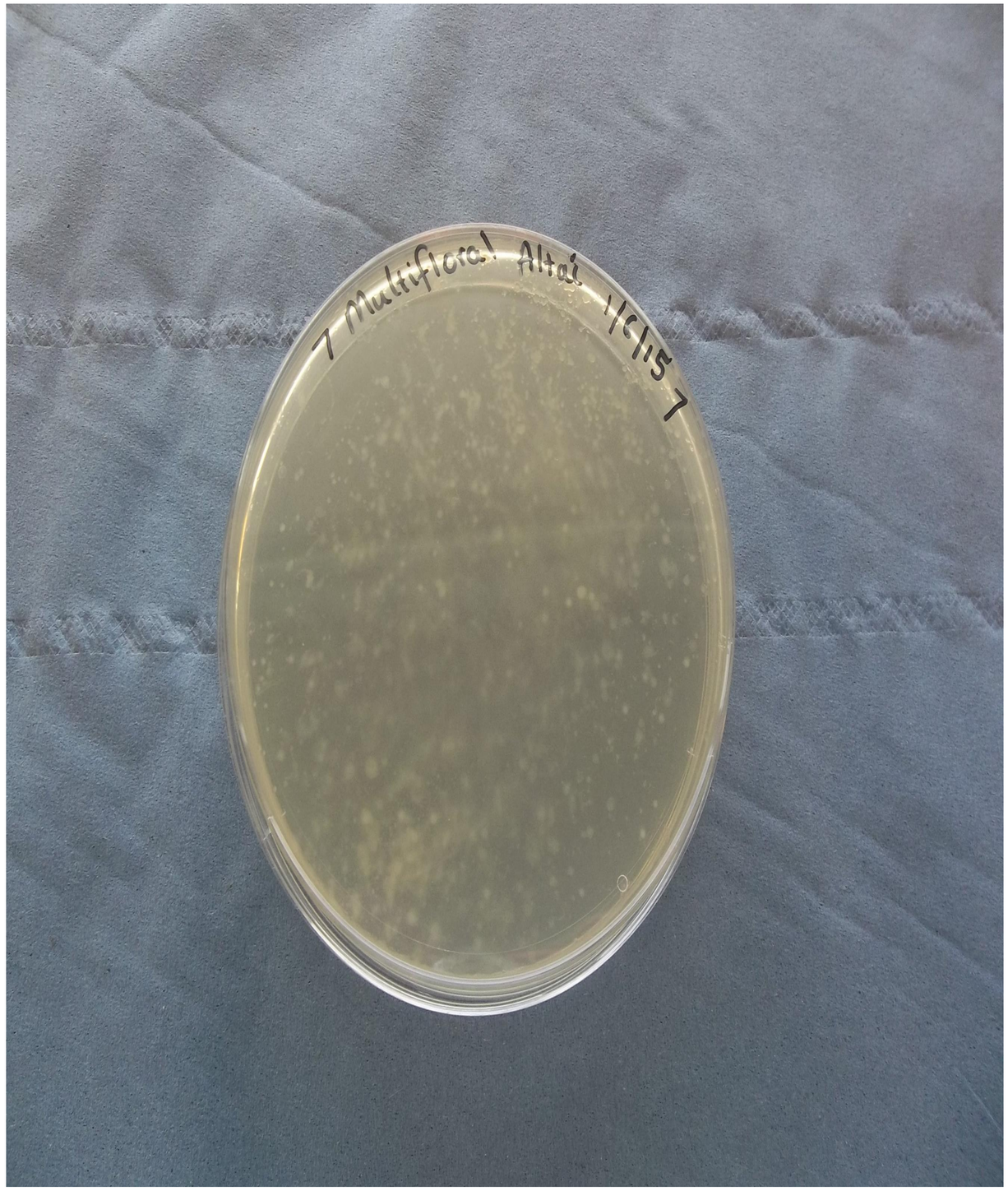
Honeys from Kazakhstan





Honey Sterility



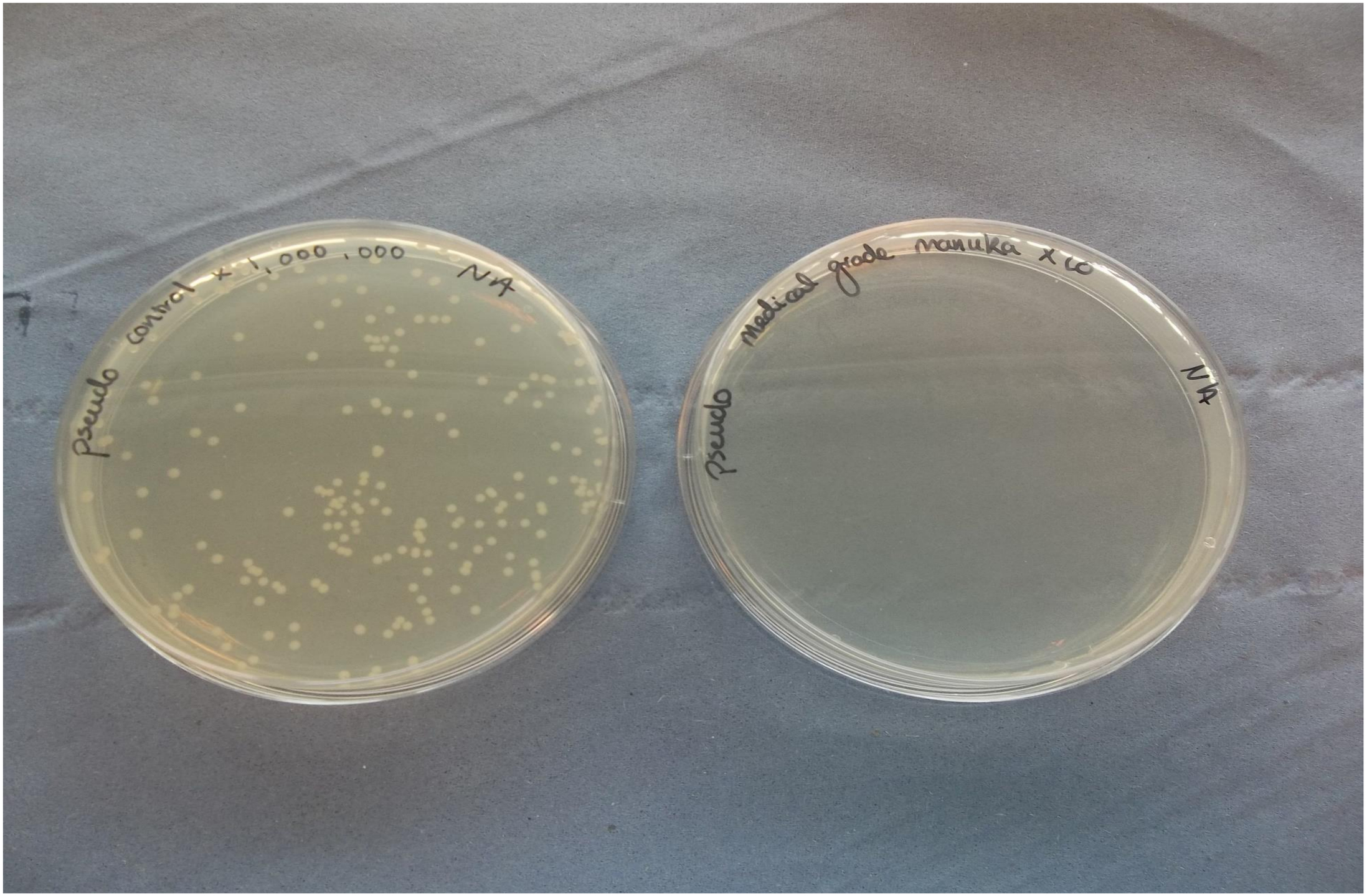


Broth Dilution Assay

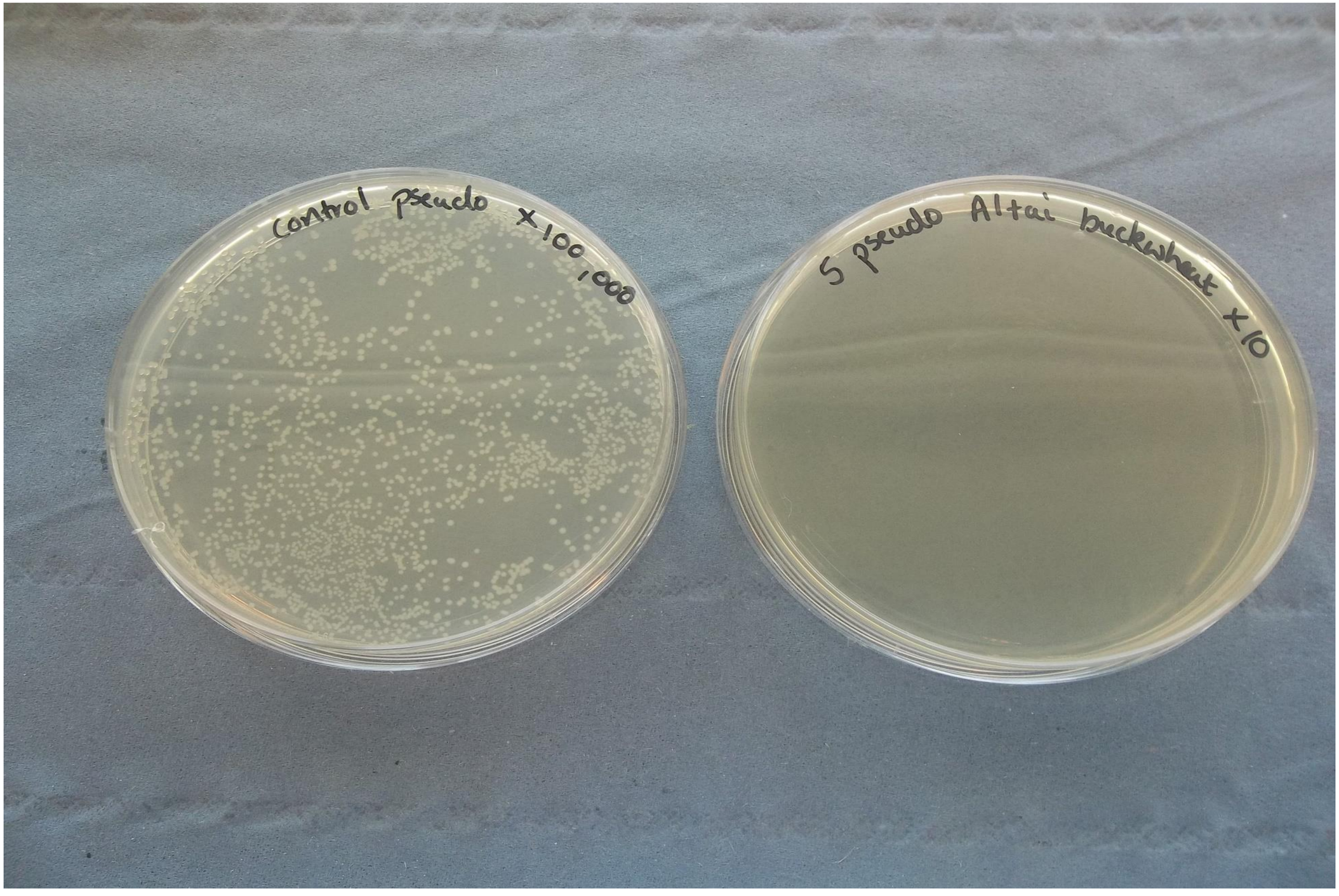
- Prepared 75% of each honey in Tryptone Soya Broth (TSB)
- Positive control 100% TSB
- Samples inoculated with 100µl of an overnight starting culture of *Pseudomona aeruginosa* or *Staphylococcus aureus*.
- Inoculated broths incubated for 24 hrs at 37^{o}C.
- Broths then sampled and serially diluted.
- 100 µl of each sample taken and spread onto Tryptone Soya Agar and incubated in 37^{o} C incubator overnight.
- Plates with 30-300 cfu were counted.

Honey, I shrunk the microbes!

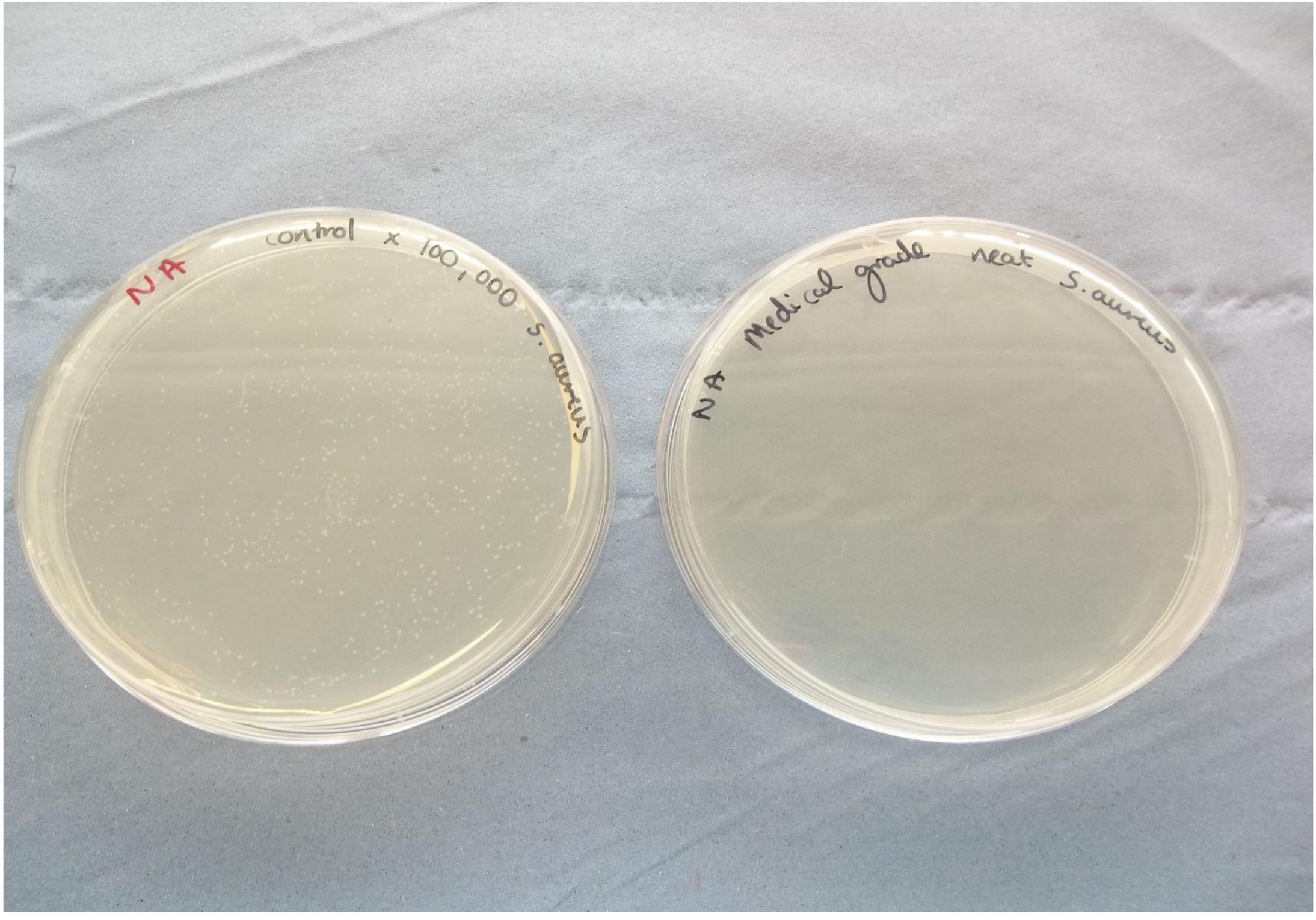
Manuka Honey Kills *Pseudomonas aeruginosa*



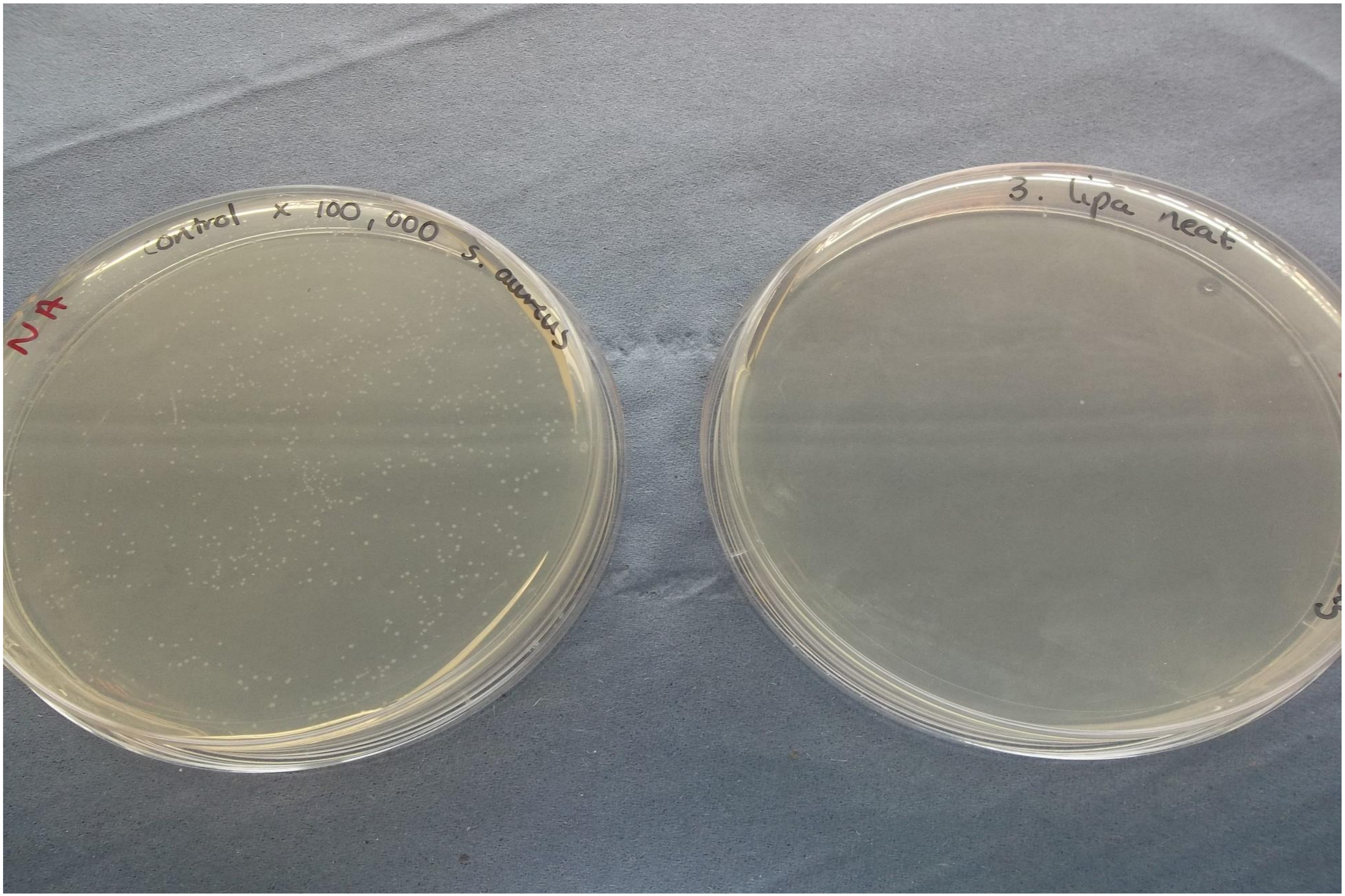
Honeys from Kazakhstan kill *Pseudomonas aeruginosa*



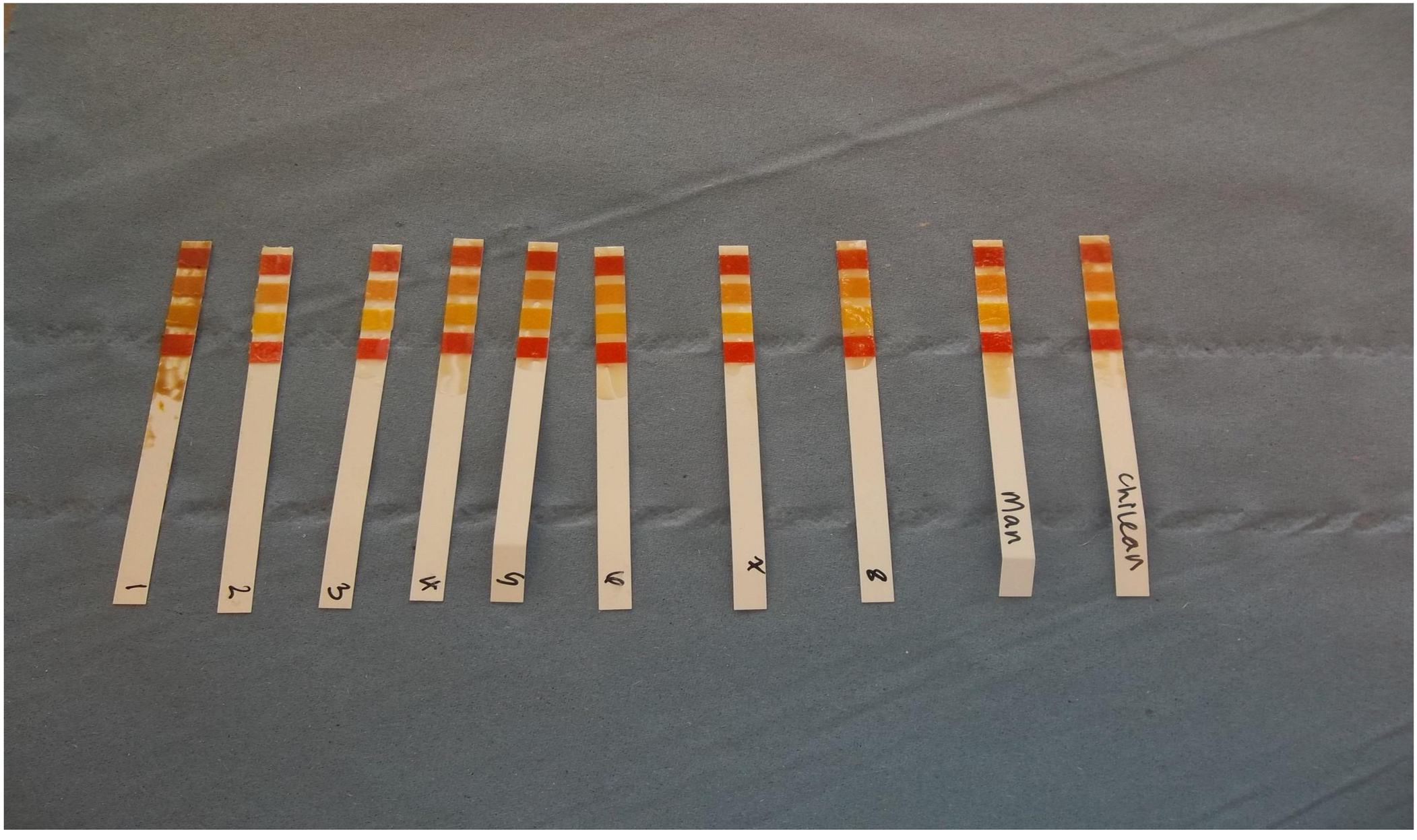
Manuka Honey Kills *Staphylococcus aureus*



Honeys from Kazakhstan kill *Staphylococcus aureus*



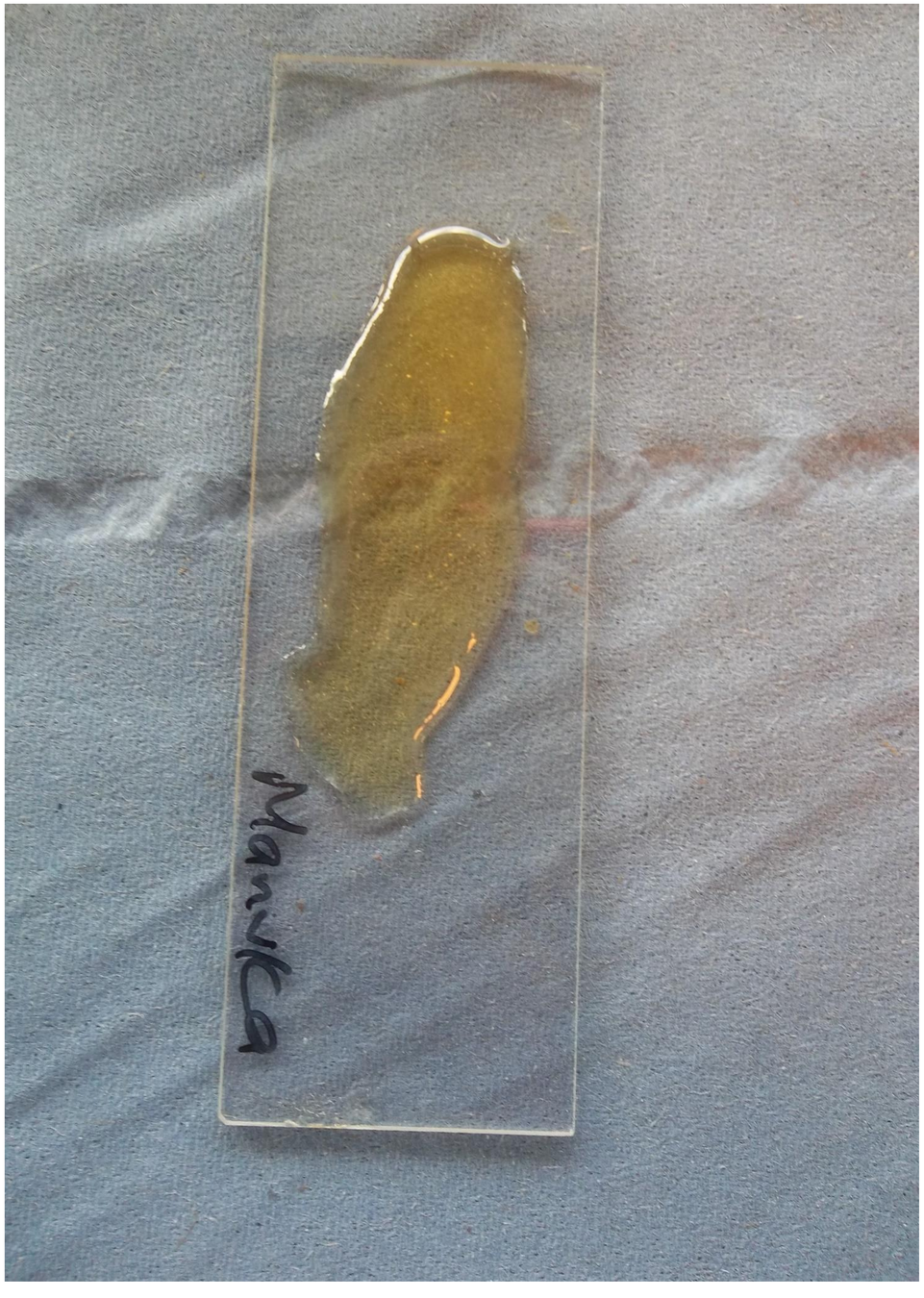
pH of Honey Samples



Sugar Content and pH of Honey

Honey	% Sugar ± SD	pH
1.Buckwheat + Perga	81 ± 0.006	4
2.Sunflower	81 ± 1	4
3.Lipa	81.7 ± 0.6	4
4.Buckwheat Akmola	76 ± 0.3	4
5.Buckwheat Altai	79.7 ± 0.3	4
6.Ginseng Altai	79.3 ± 0.3	4
7.Multifloral Altai	81.2 ± 0.3	4
8.Different Grasses Altai	82 ± 0	4

Hydrogen Peroxide Activity of Kazakhstan Honeys



Honey	Hydrogen Peroxide Activity
1. Buckwheat + Perga	0
2. Sunflower	++ active
3. Lipa	++ active
4. Buckwheat Akmola	++++ v.v. active
5. Buckwheat Altai	++++ v.v. active
6. Ginseng Honey	++++ v.v. active
7. Multifloral	+++ v. active
8. Different Grasses	+
9. Manuka Honey	0
10. Chilean Honey	++

The antimicrobial properties and composition of honeys from Kazakhstan and Russia

Pauline McLoone[1], Shirley Coyle[2] & Lorna Fyfe[2]
[1] School of Medicine, Nazarbayev University [2] Biological Sciences, Queen Margaret University,

Introduction

Antimicrobial drug resistance is considered a global crisis[1]. Wound infections, for example, are becoming progressively more difficult to treat because of infection with antibiotic resistant microbes such as *Pseudononas aeruginosa* and *Staphylococcus aureus*[2]. The discovery of new antimicrobial compounds is urgently required. Honey has been shown to have antimicrobial activity against a range of microbes and Manuka honey from New Zealand is currently used clinically in the treatment of wound infections[3]. A multitude of honeys are produced around the world and some may have superior antimicrobial activity that are yet to be discovered. The development of local honeys into medical grade honeys suitable for clinical use may have economic advantages for the country concerned.

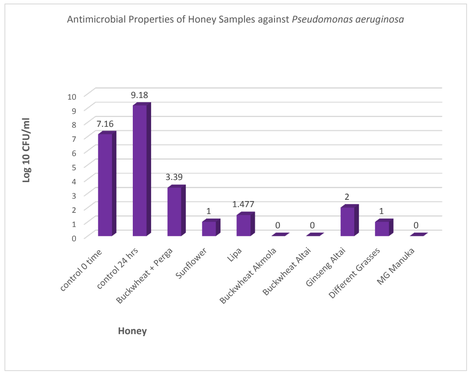
The antimicrobial properties of honey have been attributed to factors such as high sugar content, acidity, hydrogen peroxide and polyphenol content.

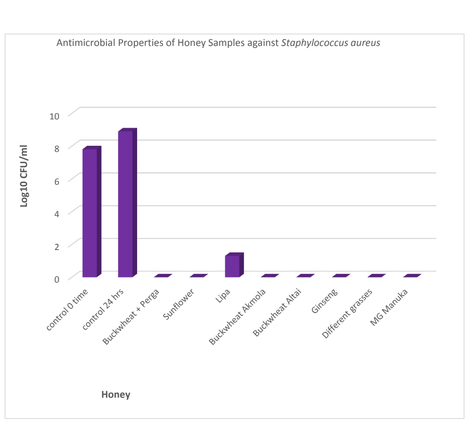
The aim of this study was to investigate the antimicrobial activity and composition of honeys from Kazakhstan and Russia.

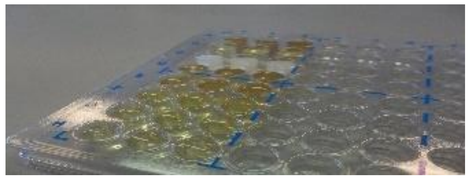
Materials and Methods

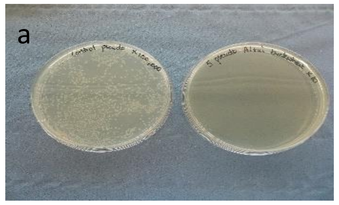
The antimicrobial activity of the honeys was tested against *P. aeruginosa* and *S. aureus.* Bacteria were cultured in 75% honey and bacterial counts were made after 24 hours. Broth medium was used as a positive control. Sugar content, pH and hydrogen peroxide activity were also determined.

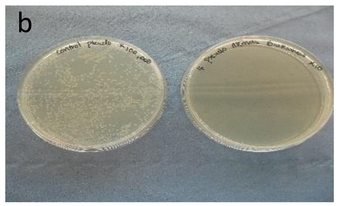
Results

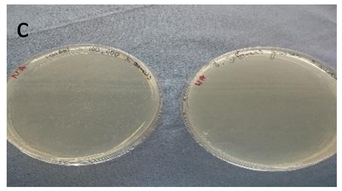












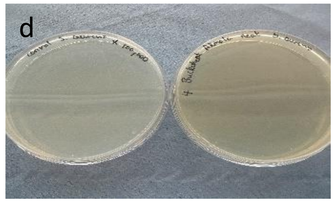


Figure 1. **a** *P. aeruginosa control* (left) *P. aeruginosa* grown in Buckwheat honey from Altai mountains (right). **b.** *P. aeruginosa* control (left) P.aeruginosa grown in Buckwheat honey from Akmola region Kazakhstan (right). **c&d** *S.aureus* control (left) *S.aureus* grown in honey from different grasses from Altai mountains and Buckwheat honey from Akmola region, Kazakhstan (right)

Colour of Honey

Figure 2. 1. Buckwheat + Perga honey (Altai mountains); 2. Sunflower honey (Ust-Kamenogorsk, Kazakhstan); 3. Lipa honey (Altai mountains, Russia) 4. Buckwheat honey (Akmola region, Kazakhstan); 5. Buckwheat honey (Altai mountains); 6. Ginseng honey (Altai mountains); 7. Multifloral honey (Altai mountains); 8. Different grasses (Altai mountains)

Figure 3. Hydrogen peroxide activity of honey samples

Sugar Content and pH

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Hydrogen Peroxide activity

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7. Multifloral	+++ v. active
8. Different Grasses	+
9. Manuka Honey	0
10. Chilean Honey	++

Conclusions

These preliminary findings suggest that honeys from Kazakhstan and Russia have potent antimicrobial activity against *P. aeruginosa* and *S. aureus.* The findings may be attributed to the high sugar content, low pH and hydrogen peroxide activity of the honeys. Further investigations are warranted..

References
1. World Health Organisation (2014). Antimicrobial drug resistance: global report on surveillance.
2. Collier M (2004). Recognition and management of wound infections. World Wide Wounds.
3. Irish J, Blair S, Carter DA (2011), 6:e18229


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TURKMENISTAN
CHINA
JAPAN
NORTH KOREA
SOUTH KOREA
SYRIA
IRAQ
IRAN
AFGHANISTAN
PAKISTAN
INDIA
MOROCCO
ALGERIA
LIBYA
EGYPT
SAUDI ARABIA
OMAN
MALI
NIGER
CHAD
SUDAN
ERITREA
YEMEN
GUINEA
BURKINA FASO
NIGERIA
CENTRAL AFRICAN REPUBLIC
ETHIOPIA
SOMALIA
CAMEROON
UGANDA
KENYA
GABON
CONGO
DEMOCRATIC REPUBLIC OF THE CONGO
TANZANIA
ANGOLA
ZAMBIA
NAMIBIA
BOTSWANA
SOUTH AFRICA
MADAGASCAR
VENEZUELA
GUYANA
SURINAME
COLOMBIA
PERU
BRAZIL
BOLIVIA
PARAGUAY
ARGENTINA
URUGUAY
MYANMAR (BURMA)
LAOS
THAILAND
CAMBODIA
VIETNAM
INDONESIA
AUSTRALIA
NEW ZEALAND

Research Collaborations

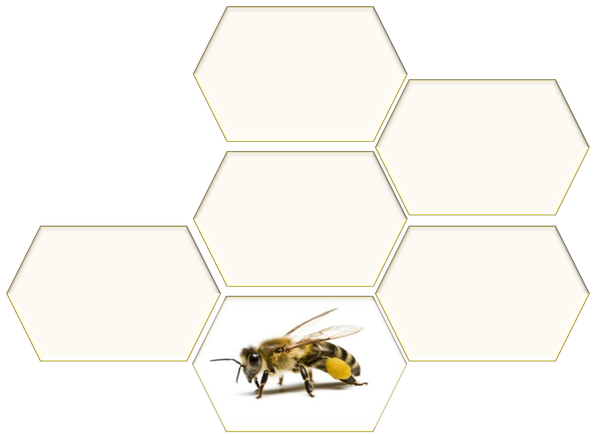
Professor Afolabi Oluwadun- *Staphylococcus aureus, Candida albicans*

Hyacinth Effedua- *Malassezia* yeasts

Raheem Ademola- Inhibitory effects of various honey on dermatophytes.

Seun Ejilude (PhD student) - *Mycobacterium tuberculosis*

14 Nigerian Honeys will also be tested

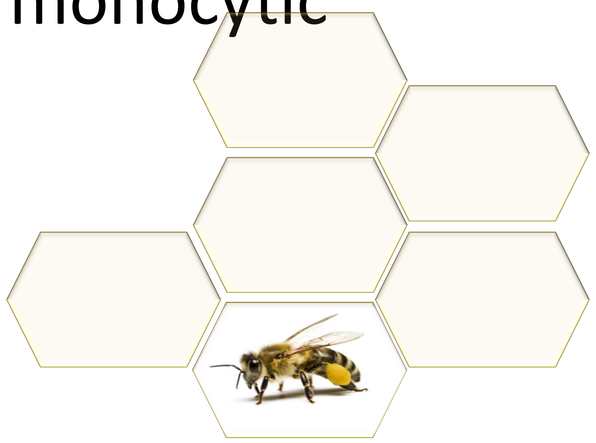


Immunomodulatory Properties of Honey (Immune Cells)

- Australian Jelly Bush Honey and New Zealand Manuka and Pasture honey stimulated increased production of the cytokines TNF-α, IL-1β and IL-6 by MM6 cells (a monocytic cell line) and human blood monocytes (Tonks et al, 2003, Cytokine, 21 (5): 242-247).
- A 5.8 kDa component in Manuka honey stimulated TNF-α cytokine production by MM6 cells, murine bone marrow derived macrophages and human monocytes (Tonks et al, 2007, Journal of Leukocyte Biology, 82 (5) 1147-1155).
- New Zealand Kanuka, Manuka and Clover honeys stimulated TNF-α production by the differentiated monocytic cell lines (THP-1) and U937 (Gannabathula et al (2012), Immunopharmacology and Immunotoxicology 34(4): 598-607).
- Thyme honey (France) stimulated PGE_2, COX-2 and TNF-α protein production and also induced NFκB and AP-1 activation in RAW 264.7 murine macrophages (Raynaud et al, 2013, International Immunopharmacology 17, 874-879).

Anti-inflammatory Properties of Honey (Immune Cells).

- Six different types of commercial honey, Clover honey (USA), Capilino honey (Australia), Langanese (Germany), Al-shafa swat and sidder (Pakistan) inhibited bovine thrombin induced respiratory burst in human neutrophils and rodent peritoneal macrophages (Ahmad et al, 2009, Phytotherapy Research, 23, 801-808).
- Raw Manuka honey containing high levels of Methylglyoxal (MGO) had contradictory effects on TNF-α production by neutrophils. Both the MGO250^{TM} and MGO400^{TM} Manuka honey samples induced inhibition of TNF-α production by neutrophils when measured at honey concentrations of 400µg/ml. Honey concentrations of 100µg/ml MGO250^{TM} stimulated TNF-α production by neutrophils (Chepulis and Francis (2012), Journal of Complementary and Integrative Medicine, 9: 10.1515/1553-3840.1646).
- Manuka and Pasture honey reduced ROI production in a monocytic cell line (Tonks et al, 2001, Cytokine, 14 (4), 240-242).



Immunomodulatory properties of Honey (Skin Cells).

- Acacia honey obtained from Slovakia stimulated TNF-α, TGF-β and IL-1β and MMP-9 mRNA expression by human primary keratinocytes (Majtan et al, 2009, Experimental Dermatology, 19(8), e73-e79).
- Honey component major royal jelly protein-1 significantly stimulated TNF-α mRNA by human primary keratinocytes (Majtan et al, 2009).
- Acacia and buckwheat honey upregulated IL-4 and IL-8 production in human dermal fibroblasts (Ranzato et al, 2013, Burns and Trauma, 1 (1): 32-38).
- Aqueous extract of fir honeydew honey from Slovakia inhibited TNF-α induced MMP-9 protein and mRNA production in human primary keratinocytes (Majtan et al, 2013, Archives of Dermatological Research , 305 (7): 619-627).

Topical Application of Honey

Acute Wounds

↑ NF-κβ & AP-1 activation

↑ TNF-α, IL-1β, IL-6, TGF-β, MMP-9, COX-2, PGE_2

↑ Macrophage activation

↑ Production of wound healing growth factors and infiltration of neutrophils

↑ Stimulation of re-epithelialisation and angiogenesis

↑ Microbial Clearance

Chronic Wounds

↓ ROIs, MMP-9, TNF-α

↓ Production of inflammatory mediators

↓ Degradation of matrix and cell growth promoting agents

↑ Antioxidant-free radical quenching activity

↓ Inflammation

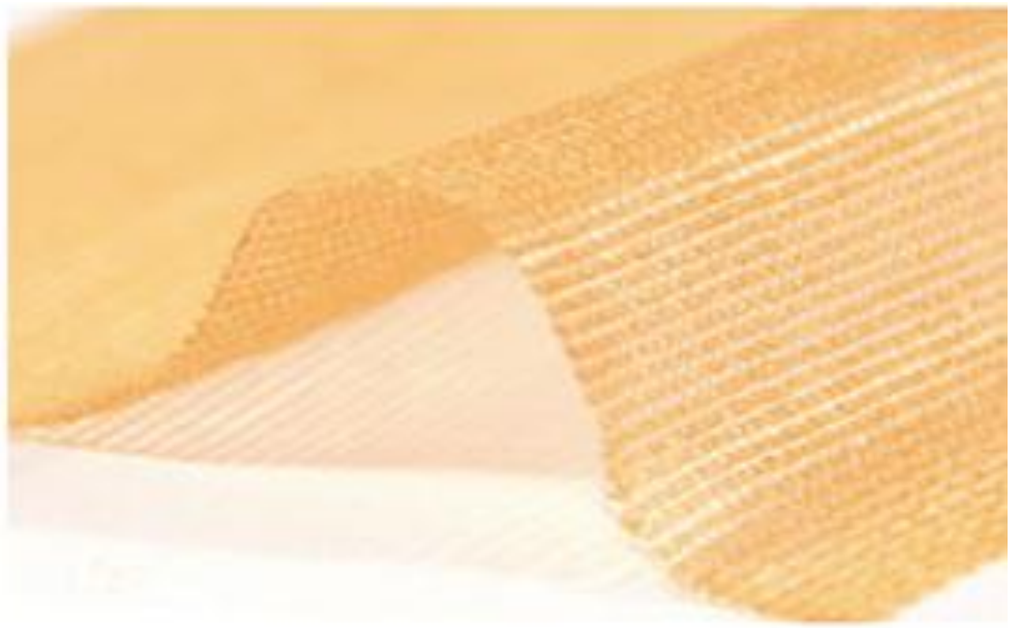
ENHANCED WOUND HEALING

Anti-Carcinogenic Properties of Honey

- Manuka honey inhibited the proliferation and induced apoptosis in a murine melanoma cell line B16.F1 *in vitro* (Fernandez-Cabezudo (2013), PLoS one, 8: e55993).
- Acacia honey inhibited proliferation of murine and human melanoma cells by introducing cell cycle arrest at $G_0/G1$ (Pichichero et al, 2013, Int J Oncol, 2010; 37:973-981).
- *In vivo* a murine melanoma tumour model treated with intravenous manuka honey displayed a significant reduction in tumour growth (Fernandez-Cabezudo, 2013).
- Tualang honey from Malaysia was shown to protect murine keratinocytes (PAM-212) cells from the immunomodulatory and photocarcinogenic effects of UVB radiation (Ahmad et al, 2012 Photochem Photobiol).

Manuka Honey Range includes:

- Activon Tulle - knitted viscose mesh impregnated with 100% medical grade Manuka honey



- Actilite – for use on low to moderate exuding wounds containing 99% Manuka honey and 1% Manuka oil, ideal for epithelialising wounds.

- Activon Tube 25g – 100% medical grade Manuka honey with no additives

- Algivon – alginate dressing impregnated with 100% medical grade Manuka honey. The alginate fibres enable a sustained slower release of honey


Revamil
Balm
15 gr
Revamil
Balm

Wounds

- A recent Cochrane based review concluded that there is quality evidence that honey heals partial thickness burn wounds more quickly than conventional treatments.
- Also, quality evidence that honey heals infected post-operative wounds more effectively than gauze or antiseptics.
- It was concluded that other studies comparing honey with conventional methods in wound healing were of insufficient quality to form any definitive conclusions.

Jull et al, 2015, Cochrane Database of Systematic Reviews DOI:10.1002/14651858.CD005083.pub4

HONEY

(Applied topically to wounds)

Antimicrobial effects

- Inhibition of growth of wound infecting microbes.
- Reduced pathogenicity of infecting microbes.

Immunomodulation

- Upregulation of tissue repair promoting cytokines by skin cells.
- Downregulation of mediators of chronic inflammation.

Tissue Repair

- Enhanced expression of cell growth promoting and adhesion molecules.
- Faster re-epithelialisation rates and promotion of angiogenesis.

ENHANCED WOUND HEALING

Efficacy of Honey in the treatment of other skin conditions

- Al-Waili (2001) reported a remarkable improvement of symptoms in patients with seborrheic dermatitis (n=30) following topical application of diluted crude honey (Al-Waili (2001) Eur J Med Res, 6, 306-308).
- A honey mixture containing natural honey olive oil and beeswax markedly improved the symptoms of patients with atopic dermatitis (n=21) and psoriasis (n=18) (Al-Waili, 2003, Complement Ther Med, 11, 226-234).
- The same honey mixture was found to cure the symptoms of the fungal skin infection pityriasis versicolor in 79% (n=14) of patients and tinea cruris in 71% (n=14) of patients (Al-Waili, 2004, Complement Ther Med, 12, 45-47).
- Prophylactic treatment with Manuka honey reduced the incidence of >grade 2 dermatitis in patients undergoing radiation therapy for breast cancer (Naidoo et al (2011), Eur J Cancer, 47, 1, S367).

Future Studies

Investigate the antimicrobial, immunomodulatory and skin healing properties of honeys from Kazakhstan.

Innovative research is required to exploit the properties of honey for clinical use.

Thanks

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Thank you for listening!