Role of Traditional Medicine in improving quality of life in Kostmann Syndrome

KAUH Case Report

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Objectives

Evaluation of *Nigella sativa* and Saudi Honey supplementation for improving immunity in a severe neutropenic patient.

Methodology:

Assessing hospital admission due to febrile illness, outpatient routine checkup monitoring adverse events after regimen of Honey and Nigella sativa.
Case report:
Fifteen years old Yamani male patient was diagnosed during the first few months of life as 
Kostmann Syndrome after being presented by frequent admission for recurrent bacterial infection 
started from first week of life. Persistent severe neutropenia with automated neutrophil count 
(ANC) range from $0.1 \text{ to } 0.2 \times 10^9/L$, with no blasts or dysplastic leukocytes were observed. Bone 
marrow aspiration confirmed the diagnosis.

Patient have positive consanguinity and family history for a similar condition, elder brother died of 
sepsis during the first year of life.

Frequent documented hospital admissions for infections 26 inpatient admissions between 2003 to 
2005 with positive blood and urine cultures.

Patient received courses of Filgrastim recombinant granulocyte colony-stimulating factor (G-CSF) with 
reported cataract after few months later. No HLA matched donor for HSCT.

Soad K. Aljaouni *, Hanadi M. Aljedani, Cataract associated with high-dose hematopoietic colony stimulating factor, 
Kostmann Syndrome

Congenital agranulocytosis associated with severe neutropenia due to **Maturation arrest of granulopoiesis at the** promyelocytic stage of differentiation

It was generally lethal before treatment with G-CSF was available, The mortality rate was 70% within the first year of life.
Kostmann paradigm shift

It was believed to be an autosomal recessive disorder, yet many suggested genes as ELA-2, the neutrophil elastase gene, and G-CSFR granulocyte colony-stimulating factor receptor, were normal in many survivors with the disease. So it is now a member of congenital neutropenic family.


Al Jaouni SK, Review Article: Severe Congenital Neutropenia (Kostmann Syndrome). The Egyption Journal of Medical Human Genetics 2010
Congenital neutropenia: an evolving definition

The definition encompasses a family of neutropenic disorders with different patterns as

**permanent** if present in all samples, **intermittent** if there are periods of spontaneous normalization, **cyclic** if episodes occur about every 21 days

Neutropenia is said to be **severe** when below 0.5 G/l and **Chronic** if it lasts more than 3 months, whether it is intermittent or permanent.
Genes with germline mutations associated with severe congenital neutropenia

Karl Welte et al., Nat Rev Dis Primers. 2017 Jun 8; 3: 17032. severe congenital neutropenias. Tübingen, Germany,
Management Plan for congenital Neutropenia

Initiation of G-CSF therapy in CN patient with 5 µg/kg/day

- Good response to G-CSF
  - Annual bone marrow examination
    - Monitoring for CSF3R mutations, cytogenetics and morphology
      - Mo abnormalities
        - Continue G-CSF
      - CSF3R mutations
        - Close observation
      - Abnormalities typical of AML or MDS
        - SCT within 3 months

- No response to G-CSF
  - Gradual increase to a maximum G-CSF dose of 50 µg/kg/day
    - No response to maximum G-CSF dose
      - SCT
Alternatives Therapy

- Filgrastim (recombinant G-CSF) was stopped due to cataract
- No matched donor
- The mother was advised to start traditional alternative Medicine from mid 2006
- *Nigella sativa* and Saudi Honey (Doaany) were a safe Combination for the mother to give on daily basis with close follow up and monitor adverse occurrences.

( Medication safety, patient compliance, doses & side effect)
# Patient Follow up

<table>
<thead>
<tr>
<th>Date</th>
<th>Automated Neutrophils</th>
<th>K/uL</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/03/17</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>30/11/15</td>
<td>0.3</td>
<td></td>
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<tr>
<td>13/09/15</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>26/10/14</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>20/04/14</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>15/09/12</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>08/10/11</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>20/04/11</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>27/10/10</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>20/03/10</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>16/06/07</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>14/04/07</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>17/02/07</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>
Patient was started on regular daily intake of _Nigella sativa_ and Saudi Honey from mid 2006.

He showed dramatic improvement as no single admission for febrile infection from mid 2007 till 2017.

Family reports marked improvement in patient quality of life with better _regular school attendance_ after subsidence of infections.

Patient was monitored regularly in Hematology clinic.
<table>
<thead>
<tr>
<th>Test Name</th>
<th>Result</th>
<th>Unit</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Blood Count &amp; Differential (CBC &amp; D)</td>
<td>L 3.6</td>
<td>K/uL</td>
<td>4.5 - 13.5</td>
</tr>
<tr>
<td>White Blood Cell Count (WBC)</td>
<td>L 10.7</td>
<td>d/L</td>
<td>12.0 - 15.0</td>
</tr>
<tr>
<td>Red Blood Cell Count (RBC)</td>
<td>4.28</td>
<td>M/uL</td>
<td>4.00 - 5.40</td>
</tr>
<tr>
<td>Hemoglobin (Hb)</td>
<td>L 32.1</td>
<td>%</td>
<td>35 - 49</td>
</tr>
<tr>
<td>Hematocrit (HCT)</td>
<td>L 74.9</td>
<td>FL</td>
<td>80 - 94</td>
</tr>
<tr>
<td>Mean Cell Volume (MCV)</td>
<td>L 25.0</td>
<td>pg</td>
<td>32 - 36</td>
</tr>
<tr>
<td>CH (Mean Cell Hemooglobin)</td>
<td>33.5</td>
<td>%</td>
<td>32 - 36</td>
</tr>
<tr>
<td>Platelets (PLT)</td>
<td>3568</td>
<td>K/uL</td>
<td>150 - 450</td>
</tr>
<tr>
<td>Automated Basophils (%)</td>
<td>0.5</td>
<td>%</td>
<td>0 - 2</td>
</tr>
<tr>
<td>Automated Neutrophils K/uL</td>
<td>L 0.7</td>
<td>K/uL</td>
<td>1 - 0.8</td>
</tr>
<tr>
<td>Automated Lymphocytes K/uL</td>
<td>2.3</td>
<td>K/uL</td>
<td>1.5 - 6.8</td>
</tr>
<tr>
<td>Automated Monocytes K/uL</td>
<td>0.4</td>
<td>K/uL</td>
<td></td>
</tr>
<tr>
<td>Automated Eosinophils K/uL</td>
<td>L 0.1</td>
<td>K/uL</td>
<td>0.2 - 0.8</td>
</tr>
<tr>
<td>Automated Basophils K/uL</td>
<td>0.0</td>
<td>K/uL</td>
<td></td>
</tr>
<tr>
<td>DYe</td>
<td>13.7</td>
<td>%</td>
<td>11.5 - 14.5</td>
</tr>
<tr>
<td>PV</td>
<td>11.8</td>
<td>FL</td>
<td>0 - 100</td>
</tr>
<tr>
<td>Automated Neutrophils (%)</td>
<td>L 20.9</td>
<td>%</td>
<td>35 - 65</td>
</tr>
<tr>
<td>Automated Lymphocytes (%)</td>
<td>H 65.2</td>
<td>%</td>
<td>10 - 15</td>
</tr>
<tr>
<td>Automated Monocytes (%)</td>
<td>10.1</td>
<td>%</td>
<td>2 - 11</td>
</tr>
<tr>
<td>Automated Eosinophils (%)</td>
<td>3.3</td>
<td>%</td>
<td>1 - 4</td>
</tr>
<tr>
<td>and Film Comment</td>
<td>Stained slide</td>
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</tr>
</tbody>
</table>
Follow up in last visit CBC showed: white cell count of $6 \times 10^9/L$ with absolute neutrophil count (ANC): $0.2 \times 10^9/L$, 13% monocytes, and 76% lymphocytes.

Severe neutropenia yet monocytes and lymphocytes were slightly increased.
Possible interpretations

• Evidence based approach
• Critical appraisal for evidence and regimes done for similar cases to find most favorable protocol for adjuvant therapy.
• No claim that this is a complete cure
• Yet it is a powerful supplementation that needs further investigations.
Absolute Phagocyte Count APC

The number of phagocytes (neutrophils and monocytes-macrophages) in a cubic millimeter of blood. The APC is the sum of the neutrophils ("segs" and "bands"), monocytes, and macrophages.


Utility of automated counting to determine absolute neutrophil counts and absolute phagocyte counts for pediatric cancer treatment protocols.


Author information

1Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA. nobuko.hijiya@stjude.org
Immune Modulation of Honey

King Saud University
Saudi Journal of Biological Sciences
www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Antimicrobial activities of Saudi honey against Pseudomonas aeruginosa

Alaa A.M. Al-Nahari a, Saad B. Almasaudi a, El Sayed M. Abd El-Ghany b, Elie Barbour c,d, Soad K. Al Jaouni e, Steve Harakeh f,*

Parasitic and immune modulation of flight activity in honey bees tracked with optical counters.

Alaux C1, Crauser D2, Pioz M2, Saulnier C2, Le Conte Y2.

Author information
1 INRA, Institut National de la Recherche Agronomique, UR 406 Abeilles et Environnement, Domaine Saint-Paul, CS 40509, 84914 Avignon, France cedric.alaux@avignon.inra.fr.
2 INRA, Institut National de la Recherche Agronomique, UR 406 Abeilles et Environnement, Domaine Saint-Paul, CS 40509, 84914 Avignon, France.
Original Article

Antimicrobial effect of different types of honey on Staphylococcus aureus

Saad B. Almasaudi a, Alaa A.M. Al-Nahari a, El Sayed M. Abd El-Ghany b, Elie Barbour c,d, Saad M. Al Muhayawi c, Soad Al-Jaouni f, Esam Azhar g, Mohamad Qari f, Yousef A. Qari h, Steve Harakeh g,*

PubMed.gov
US National Library of Medicine
National Institutes of Health

Format: Abstract


Immune system stimulation by the native gut microbiota of honey bees.
Kwong WK1, Mancenido AL2, Moran NA2.

Author information
1 Department of Integrative Biology, University of Texas at Austin, Austin, TX, USA.
2 Department of Ecology and Evolutionary Biology, Yale University, New Haven, CT, USA.
Research Article

Effects of Honey on Oral Mucositis among Pediatric Cancer Patients Undergoing Chemo/Radiotherapy Treatment at King Abdulaziz University Hospital in Jeddah, Kingdom of Saudi Arabia

Soad K. Al Jaouni, 1,2 Mohammad S. Al Muhayawi, 1 Abear Hussein, 1
Iman Elfiki, 1 Rajaa Al-Raddadi, 3 Saad M. Al Muhayawi, 4 Saad Almasaud, 5,6
Mohammad Amjad Kamal, 2,6,7,8 and Steve Harakeh 2,9

Investigation of gut microbial communities associated with indigenous honey bee (Apis mellifera jemenitica) from two different eco-regions of Saudi Arabia

Khalid Ali Khan a, Mohammad Javed Ansari a,*, Ahmad Al-Ghamdi a, Adgaba Nuru a, Steve Harakeh b, c, Javaid Iqbal a
Molecular biology of CN

"Neutrophils from patients are shown to have dramatically increased levels of 2 cytosolic protein tyrosine phosphatases that contain src-homology 2 (SH2): SHP-1 and SHP-2. One hypothesis is that overexpression of these proteins, which are involved in cytokine receptor signaling, plays a role in altering intracellular signal transduction processes.

• "A selective decrease of B-cell lymphoma-2 (Bcl-2) expression in myeloid cells and an increase in apoptosis in bone marrow progenitor cells have been observed." [3]

• Honey immunomodulation effect is reported as anti-apoptotic agent Nature 2004

( Cytokine receptors take sugar)
Seeds of Nigella sativa therapeutic properties that have been attributed to the seeds/oil include,

- Anti-inflammatory,
- Analgesic,
- Antipyretic,
- Antimicrobial,
- Antineoplastic activity,
- Nephroprotective
- Hepatoprotective properties.

Biological activity of the seeds due to **Thymoquinone (TQ)** major component of the essential oil.
Nigella sativa antioxidant


Nigella sativa fixed and essential oil improves antioxidant status through modulation of antioxidant enzymes and immunity.

Sultan MT¹, Butt MS², Karim R¹, Ahmad N³, Ahmad RS², Ahmad W².

Author information
1 Faculty of Food Science & Technology, University of Putra Malaysia, Serdang, Selangor, Malaysia.
2 National Institute of Food Science and Technology, University of Agriculture, Faisalabad, Pakistan.


Effect of thymoquinone on cytosolic pH and Na+/H+ exchanger activity in mouse dendritic cells.

Yang W¹, Bhandaru M, Pasham V, Bobbala D, Zelenak C, Jilani K, Rotte A, Lang F.

Author information
1 Department of Physiology, University of Tübingen, Tübingen, Germany.
Nigella sativa immunomodulation

*Nigella sativa: effect on human lymphocytes and polymorphonuclear leukocyte phagocytic activity.*

Haq A, Abdullatif M, Lobo PJ, Khabar KS, Sheth KV, al-Sedairy ST.

*Author information*

1. Department of Biological and Medical Research, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.


**Thymoquinone, the active ingredient of Nigella sativa seeds, enhances survival and activity of antigen-specific CD8-positive T cells in vitro.**

Salem ML, Alenzi FQ, Attia WY.


**Nigella sativa seed extract: 1. Enhancement of sheep macrophage immune functions in vitro.**

Elmowalid G, Amar AM, Ahmad AA.

*Author information*

1. Department of Bacteriology, Immunology and Mycology, Faculty of Veterinary Medicine, Zagazig University, Zagazig, Sharkia Governorate, Egypt. gelmowalid@yahoo.com
Nigella sativa as detoxifier


Nigella sativa (black cumin seed) as a biological detoxifier in diet contaminated with aflatoxin B1.
Rasouli-Hig AA¹, Bagherzadeh-Kasmani E¹, Mehri M¹, Karimi-Torshizi MA².

Author information
1  Department of Animal Science, College of Agriculture, University of Zabol, Zabol, Iran.
2  Department of Poultry Science, Faculty of Agriculture, Tarbiat Modares University, Tehran, Iran.

Nigella sativa Antineoplastic activity


Effects of thymoquinone in the expression of mucin 4 in pancreatic cancer cells: implications for the development of novel cancer therapies.
Torres MP¹, Ponnusamy MP, Chakraborty S, Smith LM, Das S, Arafat HA, Batra SK.

Author information
1  Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, Omaha, NE 68198-5870, USA.
Nigella sativa Antimetastic activity

Therapeutic implications of *Nigella sativa* against cancer metastasis

Muhammad Sheraz Arshad Malik¹, Soad K Al Jaouni², Steve M Harakeh³ and Muhammad Faraz Arshad Malik⁴*

¹Department of Computer Sciences, National Textile University, Pakistan
²Department of Pediatric Hematology/Oncology, Prophetic Medicine Application, King Abdulaziz University Hospital (KAUH), Faculty of Medicine, King Abdulaziz University (KAU), Jeddah, Kingdom of Saudi Arabia (KSA)
³Special Infectious Agents Unit, King Fahd Medical Research Center, Yousef Abdullatif Jameel Chair of Prophetic Medicine Application, KAU, KSA
⁴Department of Biosciences, COMSATS-Institute of Information Technology, Islamabad, Pakistan
• *Nigella sativa* and honey may not affect the automated neutrophil count but may improve the immune system and the quality of life in congenital neutropenia (Kostmann syndrome).

• The mortality was reduced in this case and no adverse outcomes come.

• *Nigella sativa* and honey have an Evidence-Based role in immune modulation.

• Natural Products research is vital to improve health science in Academic tertiary care Medical center.

• More research is needed to find the relation between synergistic effect of Honey with *Nigella sativa* supplementation in immune modulation therapy.
Thank you for working together in Research in Health Science to improve the quality of life of your patients.

With Compliments

Prof. Soad Khalil Al Jaouni,

MD. FRCPC

President of Saudi Society of Hematology

saljaouni@kau.edu.sa