EVIDENCED BASED APITHERAPY

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What does Evidenced Based Mean?

• There are over 100 different scales used in the literature to grade medical evidence on which strength of recommendations for treatments for particular conditions are based.
Types of Study Design

- **Randomized controlled trial (RCT):** Participants are assigned randomly to receive either an intervention being tested or placebo, often blinded as are the researchers.
- **Equivalence trial:** An RCT which compares two active agents and may not include a placebo arm.
- **Case series:** A description of a group of patients with a condition, treatment, or outcome. Case series are considered weak evidence of efficacy.
- **Cohort study:** A study which assembles a group of patients with certain baseline characteristics (e.g., use of a drug), and follows them forward in time for outcomes.
- **Meta-analysis:** A pooling of multiple trials to increase statistical power. Multiple difficulties may result if outcomes measures or therapies differ between studies, hindering direct comparison.
- **Review:** An author’s description of his or her opinion based on personal, nonsystematic review of the evidence.
- **Systematic review:** A review conducted according to prespecified criteria in an attempt to limit bias from the investigators and often include a meta-analysis of data from the included studies.
Different scales are used for grading the studies themselves
Jadad Quality of Study Score

- Was the study described as randomized (this includes words such as randomly, random, and randomization)? 0/1

- Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc.)? 0/1

- Was the study described as double blind? 0/1

- Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc.)? 0/1

- Was there a description of withdrawals and dropouts? 0/1

- Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or by date of birth, etc.). 0/−1

- Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection).
Different scales are used for grading

- Then the level of evidence for the treatment for a particular problem has to be considered.
Natural Standard

Level of Evidence

• **A (Strong scientific evidence)** Statistically signif. benefit from > 2 p.c. RCTs,
  • OR one properly conducted RCT + one p.c. meta-analysis,
  • OR mult. RCTs with a majority of the p.c. trials signif. positive + support from science, animal studies, or theory.

• **B (Good scientific evidence)** Stat. signif. benefit from 1–2 randomized trials,
  • OR benefit from > 1 p.c. meta-analysis,
  • OR benefit from > 1 cohort/case-control/nonrandomized trials + support from science, animal studies, or theory.

• **C (Unclear or conflicting scientific evidence)** Benefit from > 1 small RCT(s) without adequate size, power, stat. sig., or quality of design by objective criteria,
  • OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness,
  • OR evidence of benefit from > 1 cohort/case-control/nonrandomized trials + without supporting evidence in basic science, animal studies, or theory,
  • OR evidence of efficacy only from basic science, animal studies, or theory.
Natural Standard

Level of Evidence

• D (Fair negative scientific evidence) Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/nonrandomized trials, and evidence in basic science, animal studies, or theory suggesting a lack of benefit.

• F (Strong negative scientific evidence) Statistically sig. negative evidence (i.e., lack of evidence of benefit) from > 1 properly randomized adequately powered trial(s) of high-quality design.

• High study quality criteria are derived from validated instruments, including the 5- point scale developed by Jadad et al., in which a score below 4 is considered to indicate lesser quality methodologically (Jadad et al., 1996).

• Lack of evidence Unable to evaluate efficacy due to lack of adequate available human data.
US Preventative Services Task Force Level of Evidence

- **Level I**: Evidence obtained from at least one properly designed randomized controlled trial
- **Level II-1**: Evidence obtained from well designed controlled trials without randomization
- **Level II-2**: Evidence obtained from well designed cohort or case-control analytic studies, preferably from more than one center
- **Level II-3**: Evidence obtained from multiple time series with or without intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence
- **Level III**: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees
National Health Service
Level of Evidence

- **Level A**: Consistant Randomized Controlled Clinical trial, cohort study
- **Level B**: Consistant Retrospective Cohort, Exploratory Cohort Outcomes Research, case-controlled study or extrapolations form level A
- **Level C**: Case-series study or extrapolations from level B
- **Level D**: Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.
Different scales are used for grading

• Then the strength of a recommendation depends on the strength of patient oriented outcomes in which type of trial.
• Evidence from a consistent good quality patient oriented study is rated more highly than that from good quality study that is disease oriented or based on opinion, usual practice or consensus.
• Did the patient get better or?
• What about risk and how is it weighed in recommending a treatment?
History Of Honey Use

Hippocrates wrote “honey and pollen cause warmth, clean sores and ulcers, soften hard ulcers of the lips, heal carbuncles and running sores”. Galen, the great Roman physician, considered honey an all-purpose remedy, recommending it to treat many kinds of poisoning and intestinal ailments, in particular gangrenous stomatitis.
Honey for Wounds

Review Articles:


17 randomized controlled trials with 1965 participants showed significantly faster healing, less pain and eradication of infection when compared to any other dressing, most commonly sulfadiazine.


43 studies- 17 RCT not blinded. The one study with a Jadad of 5 was for infections of the conjunctiva was negative, the study with a 4 was equivical.

The rest of the RCT’s with Jadad’s of 1 or 2 were mostly significantly positive and the comparative studies showed faster healing of wounds and burns with honey. The conclusion was that “the quality of the studies relating to honey is generally poor but there is an overwhelming body of evidence to support the efficacy of honey.
Honey and Wounds

Jull AB, Rodgers A, Walker N, Honey as a topical treatment for Wounds, Cochrane Database System Rev. 2008 Oct 8(4)

19 trials were indentified with mixed types of lesions, acute and chronic, burns, lacerations. The poor quality of the reports means caution about the results. Conclusion was that in mild to moderate thickness burns compared to conventional dressings honey may shorten healing time. In venous leg ulcers honey does not help and in other wounds there is insufficient evidence to make a conclusion.


Healing time with honey 100 days control group 140 days. There were other differences but they were not statistically different overall. The results do trend but further research is indicated.
Honey and Wounds

Majtan, J. et al, Effect of Honey and Its Major Royal Jelly Protein 1 on Cytokine and MMP-9 mRNA Transcripts in Human Keratinocytes, Exp Dermatology, 2009 Oct 21

Honey activates keratinocytes and up-regulates expression of certain cytokines (TNF-a, IL-1b and TGF-b) and MMP-9. Degradation of type IV collagen is facilitated.

Antibacterial Activity of 13 Honeys Against E. Coli and Pseudomonas Aeruginosa, J of Medicinal Food, 3/2005, Vol. 8, No. 1: 100-103

13 different honeys were tested at 4 different concentrations against E. coli and P. aeruginosa. All honeys were inhibitory down to 5% some down to 2.5% and none at 1%.


102 patients with ulcers and wounds which had not healed after a month of conventional treatment (antibiotics, debridement, saline or povidone-iodine dressing) were treated with daily honey dressing changes. Within two weeks the wounds were clean and odorless and within three weeks were discharged from the hospital.
Honey and Radiation induced Mucositis


- Single blind RCT of 40 patients. 20 rinsed with 20 ml saline before and after radiation therapy and 20 swallowed 20 ml honey 15 min before, 15 min after and 6 hours after. Patients were evaluated weekly. There was a significant reduction of mucositis in the honey treated group with p=0.000


- 40 patients in RCT. 20 patients had topical honey applied to mucosal tissue, prior to therapy 20 patients had none. Evaluated weekly for mucositis and colonization of candida and aerobic cultures taken.
Honey and Radiation induced Mucositis

• In the treatment group 7 patients developed grade 3 or 4 mucositis and in the other 13 did. (P< 0.05).
• Candida colonization 15% in treatment group 60% in control (p=0.003).
• Positive cultures for pathogenic aerobic bacteria 15% in honey group 65% (p=0.007).
• Conclusion: Honey is effective in reducing post radiation mucositis.
Honey and Cough

- Axelsson, Inge, Honey, not dextromethorphan, was better than no treatment for nocturnal cough in children with upper respiratory infections. Archives of Disease in Childhood -- Education & Practice Edition; Jun2009, Vol. 94 Issue 3, p11

- RCT in 108 children with cough due to URI receive one dose of Buckwheat Honey, one dose of flavored Dextromethorphan or no treatment. Results reveal Honey better than Dextromethorphan for nocturnal cough frequency in children.
POLLEN- General Uses

- Increase energy & endurance
- Help with weight loss or gain depending on need
- Multivitamin (especially in pregnancy)
- Allergies and Asthma
- Anemia
- Improves overall immunity
- Aids in health conditions such as: Crohn’s disease, seizures, cancer, radiation treatments, hepatitis, prostate diseases, ulcers and more
- Antibiotic
Pollen and BPH

Buck, A.C., R. Cox, R.W.M. Rees, L. Ebeling, and A. John, Treatment of Outflow Tract Obstruction Due to Benign Prostatic Hyperplasia with the Pollen Extract, Cernilton British Journal of Urology. 1990. 66

In a double blinded placebo 60 men with outflow obstruction due to BPH were given pollen extract or placebo for 6 months. At that time 60% of the treated men vs 30 % of control men were improved or symptom free. 57% of the pollen group vs 30% of controls reported improved bladder emptying.

Rugendorff, E.W., W. Weidner, L. Ebling, and A.C. Buck Results of Treatment with Pollen Extract (Cernilton) in Chronic Prostatitis and Prostatodynia British Journal of Urology. 1993.71

90 patients had prostatitis for more than 1 yr. were given pollen extract for 6 months. In patients without strictures the prostate returned to normal size in some men, 36% cured of symptoms and 42% improved.

RCT and a Case series- poor design and no statistics and not the same disease.
Athletic Performance Enhancement

- Evidence: No changes in objective measures of athletic performance were reported in a group of athletes taking bee pollen for 75 days. Athletic performance was evaluated in this double-blind, placebo controlled study of 46 normal healthy adults (ages 20–42 years). All subjects ingested similar capsules, one of which contained granulated brown sugar, the other 400 mg bee pollen. (Chandler & Hawkins, 1985).

- The effects of a six-week course of pollen extract administration were investigated on a variety of physiological parameters in a group \( (N = 20) \) of adolescent swimmers. The number of training days missed due to upper respiratory tract infections was less in the pollen treatment group (4 days) than in the placebo group (27 days). (Maughan & Evans, 1982).

- **Summary**: well-designed clinical trials are required before recommendations can be made in this field.
Cancer Treatment Side-Effects

- Evidence: Bee pollen was effective in reducing adverse effects of cancer treatment in a double-blind, placebo controlled study of 25 women with inoperable uterine cancer. The stresses and adverse effects of radiation, such as anorexia, nausea, alopecia, inflammation, and sleeplessness were less in the bee pollen group. Leukocyte concentrations were also higher. (Murray, 1991).

- Summary: In a preliminary study, bee pollen was found to reduce some adverse effects of cancer treatment. Well-designed clinical trials are required before recommendations can be made in this field.
Pollen and other issues as evaluated in a Systematic Review by the Natural Standard Research Collaboration

**Memory**

- Evidence (combination study): No significant effects on memory, as determined by Wechsler Memory Scale scores, were noted in a three month, double-blind, placebo controlled, cross-over study of 100 elderly Danish volunteers taking NaO Li Su (a Chinese remedy which contains bee pollen as well as... (Iversen et al., 1997).

**Multiple Sclerosis**

- Evidence (combination study): Apitherapy (including bee venom, bee pollen, and honey) improved symptoms in 92 patients with multiple sclerosis (MS). Three 20-day courses of bee venom 4.5 mg daily was administered over one year. Honey 30 g twice daily (orally) was administered with bee pollen 10 g daily for six months. Clinical improvement was seen in 100% of patients and 72.8% of disabled patients were able to return to work (Krivopalov-Moscvin, 1997). In this study the criteria used to determine clinical improvement and improvement type were not cited and no control group was mentioned.

- **Summary**: Well-designed clinical trials are required before recommendations can be made in this field.
Pollen- Protection from Radiation

• In 1978, 84 female patients getting radiation for gynecological cancer were having side effects such as lack of energy, nausea, emesis, diarrhea, anorexia, headache, etc.

• After taking the pollen preparation (with RJ + honey)
  – Fatigue: none 30.5%, “light” 66.7%, still severe 2.8%
  – Anorexia: none 38.9%, “light” 41.6%, moderate 8.3%
  – Nausea: none 44.4%, minimal 50%

Therapeutic Effects of Melbrosin in Irradiation Diseases, Osmanagic, I, Mavric, N., from Univ. of Vienna, 1978
Pollen- Reproductive and Sexual Function

- In a study of 120 girls between 15 and 20 years of age with symptoms of pre-menstrual syndrome more than 90% had resolution of all symptoms within two months. In the control group less than 5% improved.
- The Treatment with Melbrosin of Dysmenorrhea in Adolescence, Pokrajcic, L. Osmanagic, I.
Propolis and Anti-Viral Activity

- During the winter 1976, the Dr Osmanagic in Sarajevo decided to supply a some of the nurses at the hospital with propolis. At the end of winter, he did list the number of persons having contracted flu. Surprisingly, he noticed that only 7% of nurses given propolis were infected by flu compared to the 63% of nurses not supplied with propolis. The similar results have been observed by the Dr Ceplak in 1978 in Yugoslavia.
Propolis and chronic vaginitis

- Imhof, M. Lipovac, M. Kurz, Ch. Barta, J. Verhoeven, H.C. Huber, J.C. Propolis solution for the treatment of chronic vaginitis

54 women with recurrent vaginal infections applied a 5% aqueous propolis solution as a vaginal douche daily for 7 days. Vaginal smears done at baseline and 14 days. Follow up was done by telephone at 6 mos. Result: Vaginal smear was improved at 14 days in 76%. 86% felt better. 61% were satisfied with no further treatment.

- Eman Abdelhafiz A. Abdelal1, Ahmed T. Abdelhafez Egyptian Bee Honey and Propolis for Recurrent Intractable Childhood Candidal Vulvovaginitis
  2nd International Conference on the Medicinal use of Honey

62 females ages 2 to 6 had external vulvovaginal lavage with honey and an EtOH extraction of propolis BiD and qD sitting in bath for 10 min. These were compared to 70 girls getting antimycotic therapy. Results: Use of Prop+honey associated with better symptom control 83% to 50%, better candida cure 74% to 35%, and less recurrences 13% to 49%. No side effects reported.
Propolis and Warts

- Propolis as an Alternative Treatment for Cutaneous Warts International Journal of Dermatology Volume 48, Number 11, November 2009, pp. 1246-1249(4)

- In a single-blind, randomized, 3-months trial, 135 patients with different types of warts received oral Propolis, Echinacea, or placebo. In patients with plain and common warts treated with Propolis, cure was achieved in 75% and 73% of patients, respectively. These results were significantly better than those associated with Echinacea treatment or placebo.
Propolis and preventing Otitis Media

• Effectiveness of a Propolis and Zinc Solution in Preventing Acute Otitis Media in Children with a History of Recurrent Acute Otitis Media, Int J Immunopathol Pharmacol, 2010 Apr-Jun;23(2):567-75

• 122 children aged 1-5 years with a documented history of rAOM, who were prospectively, blindly, randomized 1:1 to receive the propolis and zinc suspension plus elimination of environmental risk factors or elimination of environmental risk factors only.

• In the 3-month treatment period AOM was diagnosed in 31 (50.8%) children given the propolis and zinc suspension and in 43 (70.5%) controls. The mean number of episodes of AOM per child/month was 0.23 +/- 0.26 in the propolis and zinc group and 0.34 +/- 0.29 in controls.

• Summary:
Children with a history of rAOM can significantly reduce the risk of new AOM episodes and AOM-related antibiotic courses, with no problem of safety or tolerability.
Propolis and Psoriasis

• Fatma A. Abd Raboo, Ahmed G Hegazi, Faten K. Abd El Hady, Nahla E. Ramzy, Dalia M. Shaaban and Doha Y. Khader

Apitherapy in Treatment of Psoriasis: A New Therapeutic Modality
Department of Dermatology & Venereology, Tanta University and
Department of Microbiology, National Research Center

• 42 patients were included in this study. They were divided into: group I (n=12): received intradermal bee venom, group IIA (n=9): received topical propolis ointment, group IIB (n=9): received oral propolis and group III (n=12): received intradermal bee venom and oral and topical propolis. Response to treatment was assessed by calculating PASI score and measuring serum interleukin-1 (IL-1) before and after treatment.

A significant reduction in both PASI score and serum level of IL-1 was observed in all groups of patients except group IIA which showed non-significant reduction in IL-1 level.

• Summary: Propolis and bee venom are safe and effective in treatment of psoriasis, with minimal tolerable side effects, when used either separately or in combination. However, combination of both can give better clinical and laboratory results.
Royal Jelly is reported to:

- Stimulate better memory and mental function
- Increase sexual vitality and rejuvenation
- Increase vigor and physical strength
- Regulate and balance hormonal activity and increase fertility
- Normalize blood pressure
- Improve skin smoothness and elasticity
- Regenerate bone tissue
- Promote building of soft tissues and muscles
- Enhance wound healing
- Decrease arthritic symptoms
- Protect the liver
- Decrease depression and calm anxiety
- Stimulate the immune system to fight infections and tumors
- Lower cholesterol and blood lipid levels
- Stimulate production of red blood cells
- Prevent hair loss
- Help in some CNS disorders including Parkinson’s Disease
Royal Jelly and Serum Lipids


- Meta-analysis was used for the evaluation of human trials. It was found that RJ significantly decreased serum and liver total lipids and cholesterol levels in rats and rabbits and also retarded the formation of atheromas in the aorta of rabbits fed a hyperlipemic diet.

- **Meta-analysis of the controlled human trials of RJ to reduce hyperlipidemia showed a significant reduction in total serum lipids and cholesterol levels and normalization of HDL and LDL** as determined from decrease in beta/alpha lipoproteins. The best available evidence suggests that RJ at approximately 50 to 100 mg per day, decreased total serum cholesterol levels by about 14%, and total serum lipids by about 10% in the group of patients studied.
Royal Jelly and Lipids


- Fifteen volunteers were divided into an RJ intake group (n=7) and a control group (n=8). The RJ group took 6 g per day for 4 wk. Their serum total cholesterol (TC) and serum low-density lipoprotein (LDL) decreased significantly compared with those of the control group (p<0.05). There were no significant differences in serum high-density lipoprotein (HDL) or triglyceride concentrations.
Royal Jelly and Sugar Metabolism


• Twenty volunteers underwent the standardized oral glucose tolerance test (OGTT) and afterwards a second OGTT after ingestion of 20 g of royal jelly. Serum glucose levels after 2 hours and the area under the curve for glucose were significantly lower (P = .041) after royal jelly administration.
BVT History

• Alexander the Great in ancient Greece was treated with bee stings for hip pain
• Charlemagne “8th” Century conqueror was cured of gout by bee stings
• In old Saxony and Bavaria bee stings were a recognized remedy for gout
• In 1858, C. W. Wolf of Berlin wrote his book, *The Poison of the Honey Bee considered as a Therapeutic Agent*
An Austrian physician, Phillipp Terc in the late 1800’s, treated thousands of arthritic patients for more than 40 years.

<table>
<thead>
<tr>
<th>Ailment</th>
<th>Number of Cases</th>
<th>Cured</th>
<th>Improved</th>
<th>Unimproved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid heart affections</td>
<td>48</td>
<td>36</td>
<td>7</td>
<td>5</td>
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<tr>
<td>Muscular rheumatism</td>
<td>253</td>
<td>212</td>
<td>41</td>
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<tr>
<td>Chronic arthritis</td>
<td>186</td>
<td>151</td>
<td>35</td>
<td>0</td>
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<tr>
<td>Arthritis deformans</td>
<td>17</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
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In 1912, Rudolf Tertsch, Terc’s son, published 660 of his father’s cases showing these results:

- Perfectly cured .......... 544 82%
- Improved .................. 99  (Very advanced cases, some inter-
- Unimproved ............... 17  rupted treatments, others gave it up.)
Safety of BVT

- 9 patients with progressive forms of MS were placed on a one year immunization schedule. During that time four experienced worsening of their symptoms and withdrew, three had subjective amelioration of symptoms and two showed objective improvement.
- They concluded that BVT was safe
Safety of BVT


- 26 patients with relapsing remitting or secondary progressive MS were divided into two groups and for 24 weeks were stung up to 20 times three times a week into their upper thigh! 1 patient in a group refused to cross over because he was doing so well. No positive effect of the BVT was noted on MRI or functionally or on a wellness scale. They did however confirm that bee sting therapy “was well tolerated and there were no serious adverse events.” They also showed that BVT doesn’t work for MS on a systemic basis.
Bee venom acupuncture

• A systematic review was done in 2007 out of the universities of Exeter and Plymouth in England led by MS Lee. The literature from all over the world in all major languages was searched for RCTs of BVA for musculoskeletal pain with either placebo or comparator interventions.

• 11 RCTs met the inclusion criteria and a meta-analysis was done with an n=112. Pain was found to be significantly lower with BVA+classic acupuncture vs saline H2O injection+ acupuncture P less than 0.001. However they felt the total number of RCT’s included and the total sample size were too small to draw definitive conclusions.
BVT for RA

1989, Kim, C.M., Bee Venom Therapy for Arthritis, *Rhumatologie* 41(3), pp.67-72

In 27 RA patients reported a decrease on VAS from 8.5 to 2.0 with increased mobility
BVT for RA


• BVT vs NS 2 times a week for 8 wks. In 22 patients. After 2 mos. the BVT group had significant p< 0.01 decreases in tender joint count, swollen joint count, morning stiffness, ESR, CRP, and pain on VAS.
BVT for OA

In 80 patients VAS decrease from 6.3 to 0.7

70 patients, 11 excellent, 31 good and 16 improved
BVT for PHN

- 2001, Kochan, A. Successful Treatment of Post-Herpetic Neuralgia with the Venom of Apis Mellifera, presented at the Third International meeting of the Varicella-Zooster Research Foundation meeting San Diego, CA.

- 14 patients with duration of pain greater than 6 months were treated over the area of pain and/or scarring twice a week. Average VAS decreased from 7.8 to 2.1 p< 0.01 within four treatments. Pain was significantly decreased and sleep improved after the first treatment. Allodynia was resolved by the end of treatment. 24 month follow-up showed no increase in pain. The same response to BVT was seen in treatment of more acute shingles pain.
HAND SPREAD BEFORE BVT