Papers+Articles

R-001 manuka honey research

2018.11.05

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Outline

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Introduction

Manuka Honey is increasingly in the news as both a luxury food and a medical product.

The following pages outline some of the varied research that has been undertaken by scientists in order to understand how Manuka Honey chemistry works. Manuka Honey has been studied by scientists in universities and private laboratories in different countries. These separate, independent tests, help to validate the research provided and underline Manuka as an important natural food.

Honey is an ancient luxury food, but has also been used by various cultures throughout centuries for wound dressing, and aliments such as indigestion.

Work initiated by Dr. Peter Molan, Professor at Waikato University, in New Zealand has focused on Manuka honey and how it functions in respect to anti-microbial, anti-inflamatory and anti-oxidant properties. Work includes the discovery that unique anti-bacterial activity by Manuka Honey could be reliably demonstrated. Following on from this, research and practical work has been completed by him and team using Manuka Honey in wound dressing design, as well as numerous topics of related research.

Dr. Molan developed a standard test to measure Non-Peroxide activity against bacteria. This enabled test laboratories in New Zealand to use a consistent system to provide certification for Manuka honey.

Further work In Germany led to the discovery that the active molecule in Manuka Honey is Methylglyoxal. This was completed by Thomas Henle, Elvira Mavric, Silvia Wittmann, and Gerold Barth from the Technische Universitt Dresden, Dresden, Germany in 2007.

Other work includes research by Stefan Bogdanov Federal Dairy Research Institute, Bee Department, Bern, Liebefeld, Switzerland, in 1997.

Evident now, is that all honey provides some level of anti-bacterial resistance due to high sugars and consequent osmotic potential, as well as due to it's natural acidity. However, what is shown from the included research is that Manuka honey provides a level of anti-bacterial and anti-microbial activity that is markedly higher than most other honey types. It also functions in a more robust fashion within the human body.

In the following pages, a set of Articles and Charts and are provided to outline the features of Manuka honey. Some of the relevant scientific papers are provided to give an insight into the detail of some of the research completed to date.

Anti-bacterial activity comes from a number of elements present in the natural production of Manuka Honey by honey bees themselves.

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Outline

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Presentation of Information

Scientists researching Manuka Honey - partial list only.

1 Dr Peter Molan, MBE, Associate Professor in Biochemistry at The University of Waikato, Manuka Honey, Hamilton, New Zealand, who has researched the ancient healing properties of honey since 1981.

2 Professor Thomas Henle + Research Team at the Technical University of Dresden, Germany.

3 Stefan Bogdanov Federal Dairy Research Institute, Bee Department, 3003 Bern, Liebefeld (Switzerland) March 10, 1997)

4 Professor Rose Cooper / Dr Rowena Jenkins
University of Wales Institute Cardiff.

5 Scientists from:
University of Ottawa's Department of Otolaryngology - Head and Neck Surgery.

6 Associate Professor Dee Carter
Sydney University's School of Molecular and Microbial Biosciences

7 Koichi Inoue,1 Shiho Murayama,1 Fumie Seshimo,1 Kazue Takeba,2 Yoshihiro Yoshimura1 and Hiroyuki Nakazawa1
1Department of Analytical Chemistry, Faculty of Pharmaceutical Sciences, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan
2Department of Food Hygiene and Nutrition, The Tokyo Metropolitan Research Laboratory of Public Health, 3-24-1 Hyakunin-cho,Tokyo 169-0073, Japan

8 Roderick J Weston

9 Prakash A, Medhi B, Avti PK,

10 Blair SE, Cokcetin NN, Harry EJ, Carter DA

11 Willix DJ, Harfoot CG

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Features vs. Papers

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Terms

The term Active is used by researchers to indicate that honey has an increased anti-bacterial activity which has been accurately measured in a laboratory to set standards, and then recorded.

The plus (+) sign used on ACTIVE honey means that the activity in the honey is likely to increase over time as the honey product sits on a shelf.

Nb. The term 'Active' has been discontinued in labelling as of 2015.

How information is presented

Information of Manuka Honey Research is presented in two ways, in the following pages:

1 Charts. These are simple grids that combine the known features of Manuka Honey with their relevant Research papers.

2 Papers and Articles. A selection of these are attached to provide more detail on what the topic of research is, who the scientific team responsible for the work are, and what their conclusions are. These have been published on the web in complete form if further information is required.

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Features vs. Papers

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R-001 manuka honey research

Features	Notes	Relevant Scientific Paper
Bacteria		
Methylglyoxal is the effective molecule in Manuka Honey that produces such effective antibacterial activity.	1	Mol. Nutr. Food Res. 2008, 52, 000 – 000 DOI 10.1002/mnfr.200700282 1 Research Article Identification and quantification of methylglyoxal as the dominant antibacterial constituent of Manuka (Leptospermum scoparium) honeys from New Zealand Elvira Mavric1, Silvia Wittmann1, Gerold Barth2 and Thomas Henle1 1Institute of Food Chemistry, Technische Universitt Dresden, Dresden, Germany 2Institute of Microbiology, Technische Universitt Dresden, Dresden, Germany
The nonperoxide antibacterial activity in honey was found to correlate significantly with the acid content of honey, but not with its pH.	2	"Stefan Bogdanov • Nature and Origin of the Antibacterial Substances in Honey Federal Dairy Research Institute, Bee Department, 3003 Bern, Liebefeld (Switzerland)
Anti-Inflamatory, Digestive, reduces inflammation in Inflamatory Bowel disease.	3	Molan PC. Re-Introducing honey in the management of wounds and ulcers - Theory and practice. Ostomy Wound Management. 2002;48(11):28-40.
	4	Prakash A, Medhi B, Avti PK, et al. Effect of different doses of Manuka honey in experimentally induced inflammatory bowel disease in rats. Phytother Res. 2008;22(11):1511-1519.
Destroys Multiple Bacteria	5	Blair SE, Cokcetin NN, Harry EJ, Carter DA. The unusual antibacterial activity of medical-grade Leptospermum honey: antibacterial spectrum, resistance and transcriptome analysis. Eur J Clin Microbiol Infect Dis. 2009;28(10):1199-1208.
	6	Cooper RA, Molan PC, Harding KG. The sensitivity to honey of Gram-positive cocci of clinical significance isolated from wounds. J Appl Microbiol. 2002;93(5):857-863.
	7	Willix DJ, Molan PC, Harfoot CG. A comparison of the sensitivity of wound-infecting species of bacteria to the antibacterial activity of Manuka honey and other honey. J Appl Microbiol. 1992;73(5):388-394.
Two medicinal honeys have different mechanisms of bactericidal activity.	8	http://www.researchgate.net/publication/50364545_Two_major_medicinal_honeys_have_different_mechanisms_of_bactericidal_activity
Methicillin-resistant S. aureus (MRSA) defeated by Manuka Honey	9	George NM, Cutting KF. Antibacterial Honey (MedihoneyTM): in-vitro activity against clinical isolates of MRSA, VRE and other multiresistant gram-negative organisms including Pseudmonas aruginosa. Wounds. 2007;19(9):231-236.
Honey and MRSA	10	Allen KL, Hutchinson G, Molan PC. The Potential for using honey to treat wounds infected with MRSA and VRE. First World Wound Healing Congress Melbourne Australia. 2000.
How honey kills bacteria	11	http://www.researchgate.net/publication/41943769_How_honey_kills_bacteria
Wound Sites		
Manuka Honey As Medicine	12	Manuka honey as a medicine. P. C. Molan, Honey Research Unit, University of Waikato, Hamilton, New Zealand http://bio.waikato.ac.nz/pdfs/honeyresearch/bioactives.pdf

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Features	Notes	Relevant Scientific Paper
Clears Infected wounds Hospitals use Manuka to treat burns, and chronic and infected wounds.	13	Cooper RA, Molan PC, Krishnamoorthy L, Harding K. Manuka Honey Used to Heal a Recalcitrant Surgical Wound. European Journal of Clinical Microbiology & Infectious Diseases. 2001;20(10):758-759.
	14	Gethin G, Cowman S. Manuka honey vs. hydrogel--a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. J Clin Nurs. 2009;18(3):466-4725. Natarajan S, Williamson D, Grey J, Harding K, Cooper R. Healing of an MRSA-colonized, hydroxyurea-induced leg ulcer with honey. J Dermatolog Treat. 2001;12(1):33-36.
	15	Visavadia B, Honeysett J, Danford M. Manuka honey dressing: An effective treatment for chronic wound infections. British Journal of Oral and Maxillofacial Surgery. 2008;46(1):55-56.
	16	Molan PC, Betts JA. Clinical usage of honey as a wound dressing: an update. Journal of Wound Care. 2004;13(9):353-356.
Healing skin wounds Reduces scarring of skin Burns and full thickness wounds	3	Molan PC. Re-Introducing honey in the management of wounds and ulcers - Theory and practice. Ostomy Wound Management. 2002;48(11):28-40.
Lowers the amount of inflamation causing molecules Prostaglandin	17	http://www.bee-hexagon.net/files/file/fileE/HealthHoney/Honey_NutritionJACN.pdf
Anti Microbial Anti Viral Anti parasitory Anti Inflamatory Anti Oxidant Anti Mutagenic Anti Tumour	17	http://www.bee-hexagon.net/files/file/fileE/HealthHoney/Honey_NutritionJACN.pdf After: American Journal of the College of Nutrition, 2008, 27: 677-689 Honey for Nutrition and Health: a Review Stefan Bogdanov, PhD, Tomislav Jurendic, Robert Sieber, PhD, Peter Gallmann, PhD1 Swiss Bee Research Centre, Agroscope Liebefeld-Posieux Research Station ALP, Berne, Switzerland
Wound Care	18	http://www.youtube.com/watch?v=wXVNn1qp5-Q
Wound Care	19	http://www.worldwidewounds.com/2001/november/Molan/honey-as-topical-agent.html
Digestion System		
May stimulate growth of desirable intestinal bacteria Lactobacillius and Bifidobacterium = good health.	20	Rosendale DI, Maddox IS, Miles MC, et al. High-throughput microbial bioassays to screen potential New Zealand functional food ingredients intended to manage the growth of probiotic and pathogenic gut bacteria. International Journal of Food Science & Technology. 2008;43(12):2257-2267.
Peptic Ulcers. Can erradicate Heliobacter pylori from the digestive system. Gastric ulcers, faster healing, recurrance is reduced.	21	Al Somal N, Coley KE, Molan PC, Hancock BM. Susceptibility of Helicobacter pylori to the antibacterial activity of Manuka honey. J Roy Soc Med. 1994;87:9-12.

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Features	Notes	Relevant Scientific Paper
Reduces swelling pain in digestive infection.	3	Molan PC. Re-Introducing honey in the management of wounds and ulcers - Theory and practice. Ostomy Wound Management. 2002;48(11):28-40.
Inflammatory bowel disease is reduced.	22	Medhi B, Prakash A, Avti PK, et al. Effect of Manuka honey and sulfasalazine in combination to promote antioxidant defense system in experimentally induced ulcerative colitis model in rats. Indian J. Exp. Biol. 2008;46(8):583-590.
Oral Health		
Gum Disease, Plaque, Gingivitis	23	English HKP, Pack ARC, Molan PC. The effects of Manuka honey on plaque and gingivitis: a pilot study. J Int Acad Periodontol. 2004;6(2):63-67.
Periodontal disease	24	Molan PC. The potential of honey to promote oral wellness. Gen Dent. 2001;49(6):584-589.
Dental Caries	25	Badet, Quero. The in vitro effect of Manuka honeys on growth and adherence of oral bacteria. Anaerobe. 2011;17(1):19-22.
Lower Gut		
Haemorrhoids	26	Al-Waili NS, Saloom KS, Al-Waili TN, Al-Waili AN. The safety and efficacy of a mixture of honey, olive oil and beeswax for the management of hemorrhoids and anal fissure: A pilot study. TSW Holistic Health & Medicine. 2006;1:26-33.
	27	Dado S. Substance mixture for topical application comprising olive oil and honey. 2002. Available at: http://www.google.com/patents?hl=en&lr=&vid=USPAT6482442&id=g6AKAAAAEBAJ&oi=fnd&dq=U.S.+Pat.+No.+6,482,442&printsec=abstract#v=onepage&q&f=false. Accessed July 12, 2011.
Skin		
Antioxidants and Cancer.	28	http://www.cancer.gov/cancertopics/factsheet/prevention/antioxidants
Activates skin immune cells to induce fresh collagen production	29	Tonks A, Cooper RA, Price AJ, Molan PC, Jones KP. Stimulation of TNF-alpha release in monocytes by honey. Cytokine. 2001;14(4):240-242.
	30	Tonks AJ, Cooper RA, Tonks A, et al. Honey stimulates inflammatory cytokine production from monocytes. Cytokine. 2003;21(5):242-247.
Improved Skin Tone	31	http://www.bastyrcenter.org/content/view/422/
Anti-Fungal Infections	32	Khalil MI, Sulaiman SA, Boukraa L. Antioxidant properties of honey and its role in preventing health disorder. The Open Nutraceuticals Journal. 2010;3:6-16.
	33	Brady NF, Molan PC, Harfoot CG. The sensitivity of dermatophytes to the antimicrobial activity of Manuka honey and other honey. Pharm Pharmacol Comm. 1996;2(10):471-473.
Psoriasis	34	http://www.livestrong.com/article/29500-manuka-honey-good-psoriasis/
Acne Treatment	35	Leyden JJ. Antibiotic resistance in the topical treatment of acne vulgaris. Cutis. 2004;73(6 Suppl):6-10.
	36	Gormley JL, Majewski GP, Shah AR. Anti-acne composition - GRANT INDUSTRIES, INC. 2007. Available at: http://www.freepatentsonline.com/y2007/0207112.html. Accessed September 6, 2011.

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Can be used to incorporate other bio-active substances	37	Teslenko A, Hagen DE. Microemulsion. Available at: http://www.freepatentsonline.com/y2011/0159104.html.
Plant Antioxidant on skin may protect against UV induced UV induced skin damage.	38	Pinnell S. Cutaneous photodamage, oxidative stress, and topical antioxidant protection. Journal of the American Academy of Dermatology. 2003;48(1):1-19.
Cell Level		
Enhance healing Action	29	Tonks A, Cooper RA, Price AJ, Molan PC, Jones KP. Stimulation of TNF-alpha release in monocytes by honey. Cytokine. 2001;14(4):240-242.
	30	Tonks AJ, Cooper RA, Tonks A, et al. Honey stimulates inflammatory cytokine production from monocytes. Cytokine. 2003;21(5):242-247.
Osmotic Potential Draws moisture	39	http://www.vascularconsultancy.com/blog/2010/nov/honey-in-treating-leg-ulcers
Antioxidants Neutralises free radicals	40	http://www.rps.psu.edu/probing/antioxidants.html
Free Radicals damage collagen cells	41	Pinnell S. Cutaneous photodamage, oxidative stress, and topical antioxidant protection. Journal of the American Academy of Dermatology. 2003;48(1):1-19.
Antioxidants protect the body from free radicals.	42	http://www.cancer.gov/cancertopics/factsheet/prevention/antioxidants
Anti Viral	43	Simon A, Traynor K, Santos K, et al. Medical Honey for Wound Care—Still the "Latest Resort"? Evidence-Based Complementary and Alternative Medicine. 2009;6(2):165-173.
Free Radicals and Aging of Skin	44	http://www.rxskinclinic.com/pdf/freeradical.pdf
Stimulation of immune cells	46	http://www.ncbi.nlm.nih.gov/pubmed/17675558
Plant Claims		
Methyl Gloxal only in Manuka	47	TBA
Manuka Rich source of plant derived antioxidants Has flavenoids and Phenolic compounds	48	Inoue K, Murayama S, Seshimo F, et al. Identification of phenolic compound in Manuka honey as specific superoxide anion radical scavenger using electron spin resonance (ESR) and liquid chromatography with coulometric array detection. J. Sci. Food Agric. 2005;85(5):872-878.
	49	Alvarez-Suarez JM, Tulipani S, Romandini S, Vidal A, Battino M. Methodological Aspects about Determination of Phenolic Compounds and In Vitro Evaluation of Antioxidant Capacity in the Honey: A Review. Current Analytical Chemistry. 2009;5(4):293-302.
	50	Khalil MI, Sulaiman SA, Boukraa L. Antioxidant properties of honey and its role in preventing health disorder. The Open Nutraceuticals Journal. 2010;3:6-16.
Chemistry Claims		
Hydrogen Peroxide is in honey	51	http://www.prlog.org/10227103-the-hydrogen-peroxide-producing-capacity-of-honey.

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Features	Notes	Relevant Scientific Paper
Methyl Gloxal is anti bacterial	52	Methylglyoxal in Manuka Honey – Correlation with Antibacterial Properties J. Atrott* and T. Henle http://www.agriculturejournals.cz/publicFiles/07735.pdf
Most honeys Antibacterial	53	Honey as a topical antibacterial agent for treatment of infected wounds http://www.worldwidewounds.com/2001/november/Molan/honey-as-topical-agent.html
Peroxide activity of honey short lived in body	54	Allen KL, Molan PC, Reid GM. A Survey of the Antibacterial Activity of Some New Zealand Honeys. Journal of Pharmacy and Pharmacology. 1991;43(12):817-822
Can be Freeze Dried without losing antioxidant	55	Mousa MA. Honey preparations - Google Patents. Available at: http://www.google.com/patents?hl=en&lr=&vid=USPAT5980875&id=wyQZAAAAEBAJ&oi=fnd&dq=dehydrated+honey+formulations&printsec=abstract#v=onepage&q&f=false. Accessed July 7, 2011.
How Methylglyoxal discovered	56	http://www.youtube.com/watch?v=pE_NLIydWac
Why does Manuka honey produce Methylglyoxal	57	http://www.youtube.com/watch?v=GCjNuXhn97Q&feature=relmfu
Identification of Methylglyoxal	58	Mavric E, Wittmann S, Barth G, Henle T. Identification and quantification of methylglyoxal as the dominant antibacterial constituent of Manuka (Leptospermum scoparium)honeys from New Zealand. Mol. Nutr. Food Res. 2008;52(4):483-489.
Honeys in General		
Have been used historically for wounds Ancient texts outline use of honey.	59	http://www.youtube.com/watch?v=mk0OY4-MoJw
Manuka Honey Specifically		
Ecology of Manuka - Leptospermum Scoparium (Myrtaceae)	60	http://dx.doi.org/10.1080/0028825X.1984.10425282 http://www.tandfonline.com/doi/pdf/10.1080/0028825X.1984.10425282
Methylglyoxal 70X higher in Manuka	61	TBA
Can be freeze Dried	62	Mousa MA. Honey preparations - Google Patents. Available at: http://www.google.com/patents?hl=en&lr=&vid=USPAT5980875&id=wyQZAAAAEBAJ&oi=fnd&dq=dehydrated+honey+formulations&printsec=abstract#v=onepage&q&f=false. Accessed July 7, 2011.
Unique Antioxidant activity	63	Inoue K, Murayama S, Seshimo F, et al. Identification of phenolic compound in Manuka honey as specific superoxide anion radical scavenger using electron spin resonance (ESR) and liquid chromatography with coulometric array detection. J. Sci. Food Agric. 2005;85(5):872-878.
5% Manuka inhibits bacteria wheras non manuka honey no effect	64	Al Somal N, Coley KE, Molan PC, Hancock BM. Susceptibility of Helicobacter pylori to the antibacterial activity of Manuka honey. J Roy Soc Med. 1994;87:9-12.
May have unique antioxidant activiity	65	Inoue K, Murayama S, Seshimo F, et al. Identification of phenolic compound in Manuka honey as specific superoxide anion radical scavenger using electron spin resonance (ESR) and liquid chromatography with coulometric array detection. J. Sci. Food Agric. 2005;85(5):872-878.
Background Video Clips		
How Methylglyoxal was discovered	66	http://www.youtube.com/watch?v=pE_NLIydWac
Why does Manuka honey produce Methylglyoxal ?	67	http://www.youtube.com/watch?v=GCjNuXhn97Q&feature=relmfu

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Paper 1

Reduces swelling pain in digestive infection.

Mol. Nutr. Food Res. 2008, 52, 000 – 000 DOI 10.1002/mnfr.200700282 1
Research Article

- **Identification and quantification of methylglyoxal as the dominant antibacterial constituent of Manuka (Leptospermum scoparium) honeys from New Zealand**

Elvira Mavric1, Silvia Wittmann1, Gerold Barth2 and Thomas Henle1
1Institute of Food Chemistry, Technische Universitt Dresden, Dresden, Germany
2Institute of Microbiology, Technische Universitt Dresden, Dresden, Germany

The 1,2-dicarbonyl compounds 3-deoxyglucosulose (3-DG), glyoxal (GO), and methylglyoxal (MGO) were measured as the corresponding quinoxalines after derivatization with orthophenylendiamine using RP-HPLC and UV-detection in commercially available honey samples. Whereas for most of the samples values for 3-DG, MGO, and GO were comparable to previously published data, for six samples of New Zealand Manuka (Leptospermum scoparium) honey very high amounts of MGO were found, ranging from 38 to 761 mg/kg, which is up to 100-fold higher compared to conventional honeys. MGO was unambigously identified as the corresponding quinoxaline via photodiodearry detection as well as by means of mass spectroscopy. Antibacterial activity of honey and solutions of 1,2-dicarbonyl towards Escherichia coli (E. coli) and Staphylococcus aureus (S. aureus) were analyzed using an agar well diffusion assay. Minimum concentrations needed for inhibition of bacterial growth (minimum inhibitory concentration, MIC) of MGO were 1.1 mM for both types of bacteria.

MIC for GO was 6.9 mM (E. coli) or 4.3 mM (S. aureus), respectively. 3-DG showed no inhibition in concentrations up to 60 mM. Whereas most of the honey samples investigated showed no inhibition in dilutions of 80% (v/v with water) or below, the samples of Manuka honey exhibited antibacterial activity when diluted to 15–30%, which corresponded to MGO concentrations of 1.1–1.8 mM.

This clearly demonstrates that the pronounced antibacterial activity of New Zealand Manuka honey directly originates from MGO.

MGO UP TO 100X CONVENTIONAL HONIES

ANTI-BACTERIAL ACTIVITY DUE TO METHYLGLOXYL

Keywords: 1,2-Dicarbonyl compounds / 3-Deoxyglucosulose / Bacteria / Glyoxal / Methylglyoxal /
Received: July 22, 2007; revised: September 13, 2007; accepted: September 19, 2007

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Paper 2

Stefan Bogdanov

- **Nature and Origin of the Antibacterial Substances in Honey**

Federal Dairy Research Institute, Bee Department, 3003 Bern, Liebefeld (Switzerland)
(Received August 21, 1996; accepted March 10, 1997)
LWT - Food Science and Technology, Volume 30, Issue 7, November 1997, Pages 748–753
Original Research Article

Abstract
The nonperoxide antibacterial activity of honey and honey fractions was tested with Staphylococcus aureus and Micrococcus luteus bacterial species. Antibacterial activity correlated significantly with the honey acidity but did not correlate with honey pH.
There were small differences between the antibacterial activities of different honey types: rhododen dron, eucalyptus and orange honeys had a relatively low activity, whereas dandelion, honeydew and rape honeys had a relatively higher activity. These results suggest that a part of the antibacterial activity might be of plant origin. However, the antibacterial activity of sugar-adulterated honeys was the same as that of control honeydew honeys produced in the same apiary suggesting that the major part of the antibacterial activity of honeydew honey is of bee origin.

Ten different honeys were fractionated into four fractions using column chromatography or vacuum distillation: acidic; basic; nonvolatile, nonpolar; and volatile. The antibacterial activity of the different fractions tested was: acids > bases = nonpolar, nonvolatiles > volatiles. This order was the same using either Staph. aureus or Micrococcus luteus as test strains.

An exception was manuka honey from New Zealand where almost the entire activity was found in the acidic fraction.

Conclusions

NON-PEROXIDE ACTIVITY CORRELATES WITH ACID

The nonperoxide antibacterial activity in honey was found to correlate significantly with the acid content of honey, but not with its pH. There are differences in the activity of different unifloral honeys: rhododendron and eucalyptus honeys had the lowest activity, while honeydew and rape honeys had the highest activity. However due to the considerable variation of the antibacterial activity within honey types the differences were not statistically significant.

ACTiVITY OF BEE ORIGIN

From experiments with sugar-adulterated honey it can be concluded that the antibacterial activity of honeydew honeys was of bee origin. By fractionation into different substance classes the following relative distribution of nonperoxide antibacterial activity was found: acids > bases = nonpolar, nonvolatiles > volatiles. This order was the same using Staph. aureus and Micrococcus luteus as test strains.

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Paper 3

Roderick J Weston

- **The contribution of catalase and other natural products to the antibacterial activity of honey: a review**

Food Chemistry, Volume 71, Issue 2, November 2000, Pages 235–239
Original Research Article

Abstract
Several natural products are collected or manufactured by bees to construct their hive and produce honey. These include beeswax, flower volatiles, nectar, pollen, propolis and honey itself. Some of the components of these materials possess antibacterial properties and are discussed briefly to ascertain their contribution to the antibacterial activity of honey.

New Zealand's manuka honey is known to possess a high level of "non-peroxide" antibacterial activity and research to identify the origin of this activity is briefly reviewed. Finally a hypothesis is advanced to explain the Activity possibly due to phenomenon of "non-peroxide" antibacterial activity in honey.

CONCLUSION:
The author concludes that this activity should be residual non-peroxide interpreted as residual hydrogen peroxide activity, which is probably due to the absence of plant-derived Activity catalase from honey, an idea first suggested by Dustman in 1971.

[Dustman, J. H. (1971). Über die Katalaseaktivität in Bienenhonig aus der Tracht der Heidekrautgewächse (Ericaceae). Zeitschrift für Lebensmittel-Untersuchung und Forschung, 145, 292–295]

Paper 4

Julie Irish, Shona Blair, and Dee A. Carter*

- **The Antibacterial Activity of Honey Derived from Australian Flora**

Author information Article notes Copyright and License information
This article has been cited by other articles in PMC.

Abstract:
Chronic wound infections and antibiotic resistance are driving interest in antimicrobial treatments that have generally been considered complementary, including antimicrobially active honey. Australia has unique native flora and produces honey with a wide range of different physicochemical properties. In this study we surveyed 477 honey samples, derived from native and exotic plants from various regions of Australia, for their antibacterial activity using an established screening protocol. A level of activity considered potentially therapeutically useful was found in 274 (57%) of the honey samples, with exceptional activity seen in samples derived from marri (Corymbia calophylla), jarrah (Eucalyptus marginata) and jellybush (Leptospermum polygalifolium). In most cases the antibacterial activity was attributable to hydrogen peroxide produced by the bee-derived enzyme glucose oxidase. Non-hydrogen peroxide activity was detected in 80 (16.8%) samples, and was most consistently

ANTI BACTERIAL ACTIVITY
ATTRIBUTED TO HYDROGEN

PEROXIDE

Paper 4

seen in honey produced from Leptospermum spp. Testing over time found the hydrogen peroxide-

The Antibacterial Activity of Honey Derived from Australian Flora

dependent activity in honey decreased, in some cases by 100%, and this activity was more stable at 4°C than at 25°C. In contrast, the non-hydrogen peroxide activity of Leptospermum honey samples increased, and this was greatest in samples stored at 25°C. The stability of non-peroxide activity from other honeys was more variable, suggesting this activity may have a different cause. We conclude that many Australian honeys have clinical potential, and that further studies into the composition and stability of their active constituents are warranted.

Conclusion:
This study has provided a broad overview of the antibacterial activity of Australian honey and shown that many honeys have potential for therapeutic use as antibacterial agents. Jarrah and marri honeys have exceptional levels of hydrogen peroxide-dependent activity, and non-peroxide activity in Australian Leptospermum honeys is comparable to that found in New Zealand manuka honey. These findings indicate that there is an opportunity for Australian apiarists to share in the lucrative medicinal honey market. However, the factors affecting antibacterial activity in honey are complex, numerous, and not solely dependent on the floral source. This prevents generic statements being made regarding the activity of honey derived from a given floral source, and indicates the need to test individual batches of honey for their level of antibacterial activity before they are designated as therapeutic products.

Paper 5

Alvarez-Suarez JM, Tulipani S, Romandini S, Vidal A, Battino M.

- **Methodological Aspects about Determination of Phenolic Compounds and In Vitro Evaluation of Antioxidant Capacity in the Honey: A Review.**

Current Analytical Chemistry. 2009;5(4):293-302.

Methodological Aspects about Determination of Phenolic Compounds and In Vitro Evaluation of Antioxidant Capacity in the Honey: A Review Jose M. Alvarez-Suarez1, Sara Tulipani1, Stefania Romandini1, Alexis Vidal2 and Maurizio Battino1,*

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ABSTRACT: The antioxidant activity of honey varies greatly depending on the honey's floral source. There is little knowledge about the profiles of antioxidant substances in honey from different floral sources. The variation in these profiles might be responsible for the widely varying ability of honey to protect against oxidative reactions. Honey is rich in polyphenol compounds, which act as natural antioxidants, and are becoming increasingly popular because of their potential role in contributing to human health. These compounds can also be used as indicators in studies about the floral and geographical origin of the honey. Therefore, we overviewed the current analytical methods for measuring polyphenols and antioxidant capacity in honey. The analytical procedure to determine individual phenolic compounds involves their extraction from the sample, analytical separation and quantification. The analytical separation techniques widely employed are gas chromatography, high-pressure liquid chromatography and capillary electrophoresis. The techniques to evaluate the antioxidant capacity are based on colorimetric assays such as DPPH, FRAP, TEAC (ABTS) and

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microplate fluorescence reader like ORAC assay.
Keywords: Phenolic compounds, Honey, Antioxidant capacity, TEAC, FRAP, DPPH, ORAC.
Rolnoue K, Murayama S, Seshimo F, et al.

- **Identification of phenolic compound in Manuka honey as specific superoxide anion radical scavenger using electron spin resonance (ESR) and liquid chromatography with coulometric array detection**. J. Sci. Food Agric. 2005;85(5):872-878.

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Yoshihiro Yoshimura1 and Hiroyuki Nakazawa1
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Abstract:
Apitherapy has become the focus of attention as a form of folk and preventive medicine for treating certain conditions and diseases as well as promoting overall health and well-being. In apitherapy, honey is the therapeutic agent used for dressing surgical wounds, burns or skin ulcers, as well as for dyspepsia, peptic ulcer, etc., because of its antioxidant activity. Therefore, it is important to determine the antioxidants in honey by analytical techniques.

In the present study, the antioxidant activities of honeys from different floral sources were investigated by electron spin resonance (1,1-diphenyl-2-picrylhydrazyl (DPPH) and H2O2/NaOH/DMSO scavenging systems), liquid chromatography with coulometric array detection (LC-ED), and liquid chromatography with electrospray mass spectrometry (LC-MS). The antioxidant activities of some unifloral honeys (acacia, Chinese milk vetch, buckwheat and manuka) were evaluated using the radical scavenging systems. It was shown that DPPH radical scavenging activity was significantly different among the honeys, with buckwheat and manuka honeys having significantly higher scavenging activity than acacia honey. In addition, only manuka honey had specific scavenging activity for superoxide anion radicals. The compound responsible for this activity in manuka honey was identified by LC-ED and LC-MS. Careful examination of the LC-ED chromatographic patterns of manuka and other honey samples revealed a distinct peak in the chromatogram of manuka honey to be methylsyringate (MSYR). The radical scavenging activity of MSYR was specific for superoxide anion radicals, similar to the case of manuka honey.

MANUKA ANTIOXIDANT ACTIVITY

1. INTRODUCTION
Honey has been used as a food since the earliest times. It is the natural substance produced by honeybees, Apis mellifera, from the nectar of blossoms or from exudates of trees and plants to produce nectar honeys or honeydews, respectively.
It is also used as a food preservative, preventing deteriorative oxidation reactions in foods, such as lipid oxidation in meat and the enzymatic browning of fruits and vegetables [1-5]. Antioxidants specifically retard deterioration, rancidity or discoloration due to oxidation caused by light, heat and some metals. Nevertheless, the composition of honey and its antioxidant activity vary greatly depending on the floral source and external factors such as the season and environment [6]. Honey contains at least 181 substances and is considered as part of traditional medicine [7]. It is a

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supersaturated solution of sugars, mainly composed of fructose (38%) and glucose (31%), contain ing also minerals, proteins, free amino acids, enzymes and vitamins [8, 9]. A wide range of minor constituents are also present in honey, many of which are known to have antioxidant properties. These include phenolic acids and flavonoids [10-12], certain enzymes (glucose oxidase, catalase) [13], and amino acids [14, 15].

Honey shows great potential in serving as an antioxidant in an emulsion system. It has been incorporated into meat matrices to inhibit lipid oxidation as well as to prevent browning reactions in fruits and vegetables [4, 5, 16, 17]. Polyphenols, including flavonoids and phenolic acids, are *Address correspondence to this author at the Department of Biochemistry,

Biology & Genetics, Faculty of Medicine, Università Politecnica delle Marche, Via Ranieri 65, 60100 Ancona, Italy; Tel: +39 071 2204646; Fax: +39 071 2204398; E-mail: m.a.battino@univpm.it found in honey, and these compounds act as free radical scavengers, peroxy radical scavengers, and as metal chelators [18, 19]. The antioxidant capacity of a number of honeys has been determined and found to be significantly correlated to the phenolic content [20].

Many authors have studied the phenolic and flavonoid contents of honey to determine if a correlation exists with floral origins [10, 11, 21, 22], and also to determine the presence of antimicrobial activity [23]. The analysis of their phenolic compounds, including flavonoids, has been suggested and this method tends to be used to study their floral and geographical origins [24]. Before this, researchers tried to use the analysis of amino acids to complement pollen analysis in the determination of the floral origins of honey [15, 25, 26]. Even so, the analysis of phenolic compounds has been regarded as a very promising way of studying the floral and geographical origins of honey [21, 24, 27-30]. In these studies,the flavanone hesperetin was used as a marker for citrus honey, the flavonol kaemp ferol for rosemary honey and quercetin for sunflower honey [31, 32]. Some phenolic acids, such as ellagic acid in heather honey, have also been used as floral markers, and the hydroxycinnamates (caffeic, pcoumaric and ferulic acids) in chestnut honey [33].

Lots of methods for determining the antioxidative activity in honey have been used, e.g., determina tion of active oxygen species (viz. the superoxide anion, peroxyl and hydroxyl radicals), their radical scavenging ability [6, 20, 34- 36], enzymatic or non-enzymatic measurements of lipid peroxidation inhibition [4, 17, 35], the 1,1-diphenyl-2 picrylhydrazyl (DPPH) antioxidant content [17, 37], the ferric reducing/antioxidant power assay (FRAP) [38, 39], and 294 Current Analytical Chemistry, 2009, Vol. 5, No. 4 Alvarez-Suarez et al. the TEAC (Trolox equivalent antioxidant capacity) assay [40]. This review examines the available procedures and technical analytical methods for the analysis of polyphenolic compounds as well as the radical scavenging activity in the honey.

CONCLUSIONS:

The quality of honey depends on its chemical composition and floral origin. The composition of active components in plants depends on various factors, particularly on plant bio, chemotype and climatic conditions. Consequently, it can be reasonably expected that honey properties from different locations should be different. Therefore, the polyphenolic content of honey is strongly affected by the floral, geographical origin and climatic characteristics of the site. Furthermore, it has a very important antioxidant capacity that is provided by polyphenols such as flavonoids and phenolic acids that produce beneficial effects in human health. For these reasons, the identification and quantification of the polyphenols of honey are of nutritional and commercial interest.

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Nowadays, there is a group of analytic procedures that can be used in the analysis of chemical composition and biological properties of honeys. The techniques employed in the study of the poliphenolic composition of honey has been carried out with great success, thanks to the application of the solid-phase extraction with following identification by means of GC, HPLC and CE, mainly combined with diode array detection and mass spectrometry, which have demonstrated a high grade of effectiveness, mainly HPLC in the case of flavonoids and GC in the case of phenolic acid.

A large diversity of analytical methods for determination of antioxidant capacity in honey is available as reported here.These assays differ from each other in terms of reaction mechanisms, oxidant species, reaction conditions, and in the form that results are expressed: the electron transfer assays (ABTS, FRAP, DPPH) measure the reducing ability of the substrate (antioxidant) and hydrogen transfer assays (ORAC) measure the hydrogen donating ability of the substrate. It is clear that hydrogen atom donation is essential in the radical chain reaction stage of lipid peroxidation; therefore hydrogen transfer assays are relevant to the measurement of chainbreaking antioxidant capacity. Lastly, it may be necessary to use a variety of methods and a variety of conditions in order to correctly describe the in vitro antioxidant capacity of honey. Therefore, it is worthwhile to select methods that are validated, standardized and widely reported. Misunderstanding what these methods are actually measuring has led to misrepresentation and misinterpretation of data, which has complicated the measurement of antioxidant capacity in vitro.

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Khalil MI, Sulaiman SA, Boukraa L.

- **Antioxidant properties of honey and its role in preventing health disorder.**

The Open Nutraceuticals Journal. 2010;3:6-16.

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Abstract: Honey is being used since long time both in medical and domestic needs, but only recently its antioxidant property has come to limelight. With increasing demand for antioxidant supply in the food, honey is becoming popular as a source of antioxidant since it is rich in phenolic acids and flavonoids and other antioxidants including glucose oxidase, catalase, ascorbic acid, carotenoid derivatives, organic acids, amino acids and proteins. The antioxidants have several preventative effects against different diseases like cancer, cardiovascular diseases, inflammatory disorders, neurological degeneration, wound healing, infectious diseases and aging, which led to search for foods rich in antioxidants. Various studies on antioxidant properties of honey have been done. The present article is a short review on the antioxidant properties of honey and its role against health disorder.
Keywords: Honey, Antioxidant, Phytochemicals, Health disorder.

INTRODUCTION

Mum always said, “Eat your fruits and vegetables, they’ll help you grow big and strong.” Although dietary recommendations have changed over the years, this is one bit of advice even Father Time can’t ignore. According to recent studies, antioxidant substances available in various natural sources and foods may actually represent a modern-day “fountain of youth.”

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Evidence suggests that vitamins C and E, and beta-carotene, a precursor to vitamin A, may reduce the risk of some forms of cancer, heart disease, strokes, and cataracts and may slow the aging process [1].

Honey is a remarkably complex natural liquid that is reported to contain at least 181 substances [2]. The composition of honey is rather variable and primarily depends on the floral source; however, certain external factors also play a role, such as seasonal and environmental factors and processing. Honey is a supersaturated solution of sugars, of which fructose (38%) and glucose (31%) are the main contributors.
A wide range of minor constituents is also present in honey, many of which are known to have antioxidant properties. These include phenolic acids and flavonoids [3, 4], certain enzymes (glucose oxidase, catalase) [2], ascorbic acid [2], carotenoid-like substances [5], organic acids [6], Maillard reaction products [2], and amino acids and proteins [7]. The antioxidant activity of phenolic compounds might significantly contribute to the human health benefits of plant foods [8, 9] and beverages such as red wine and tea [9-11].

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There is much information regarding the health benefits of honey but a little information is available about the antioxidant properties of honey and its role against different types of diseases. The objective of this review is to summarize antioxidant properties of honey and its role against health disorder like cancer, cardiovascular diseases, inflammatory disorders, neurological degenera tion, infectious diseases and aging.

COMPOSITIONAL PROPERTIES OF HONEY
Phytochemicals are one wide class of nutraceuticals found in plants which are extensively re searched by scientists for their health-promoting potential. Honey has a wide range of phytochemi cals including polyphenols which act as antioxidants. Polyphenols and phenolic acids found in the honey vary according to the geographical and climaticconditions. Some of them were reported as a specific marker for the botanical origin of the honey. Considerable differences in both composition and content of phenolic compounds have been found in different unifloral honeys [12]. Terpenes, benzyl alcohol, 3, 5-dimethoxy-4-hydroxybenzoic acid (syringic acid), methyl 3, 5-dimethoxy-4-hydroxybenzoate (methyl syringate), 3, 4, 5-trimethoxybenzoic acid, 2-hydroxy-3-phenylpropionic acid, 2-hydroxybenzoic acid and 1, 4-dihydroxybenzene are some of the phytochemicals ascribed for the antimicrobial activity of honey [13].

The color of the honey collected by the bees varies according to the floral source and its mineral content, which usually ranges from water white to dark amber. Flavor of the honey depends upon the color, generally the darker the honey the stronger the flavor and quality. It has been reported more than 300 unique varieties of honey depending upon the floral sources from United States alone. Honey mainly composed of sugars and water which accounts roughly 79.6% and 17.2%, respectively. Major sugars of honey are levulose and dextrose which constitutes 38.19% and 31.28% correspondingly, remaining is the sucrose 1.3% and maltose 7.3%.

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Honey minor constituents include acids (0.57%), protein (0.266%), nitrogen (0.043%), amino acids (0.1%), a little amount of minerals (0.17%), and a number of other minute quantities of components like pigments, flavor and aroma substances, phenolics compounds, colloids, sugar alcohols and vitamins which all together accounts for the 2.1% of whole honey composition [14].

FREE RADICAL AND ANTIOXIDANTS

Although oxygen is vital to life, scientists are also finding that this essential element may contribute to human aging and illness. When oxygen is metabolized, cells form byproducts called "free radicals." Free radicals travel through the cell, disrupting the structure of other molecules and resulting in cellular damage. Such damage is believed to contribute to aging and various health problems. Antioxidants protect key cell components from damage by neutralizing the free radicals. Antioxidants that occur naturally in the body or are consumed through the diet may block damage to cells. However, over time, damaged cells can accumulate and lead to age-related diseases, research ers say [15].

In an effort to combat free-radical activity, scientists are studying the effects of increasing individu als' antioxidant levels through the diet and dietary supplements. Honey appears to act as an antioxidant in more ways than one. In the body, honey can take up free radicals and contribute to better health. When used in foods, the compounds produced when honey is heated can prevent rancidity in some products, particularly meats [16].

ANTIOXIDANT PROPERTIES OF HONEY

Although free radicals of oxygen are a natural byproduct of metabolism within the organism, they cause cellular damage and breakdown the structure of DNA. Exactly these processes cause premature aging. Antioxidants bind these dangerous molecules, preventing their harmful effects [17].

Unlike synthetic compounds, honey represents a natural product that does not carry side effects which can be harmful to health. Among the compounds found in honey; vitamin C, phenol compounds, catalase, peroxides, glucose oxydase enzymes have antioxidant properties. Honey also contains flavonoids and carotinoids. High levels of these indicators ensure a high level of antioxidants in honey. Antioxidant properties of honey act as an antidepressant during high emotional, physical and intellectual stress [17].

Various polyphenols are reported in honey. Some of the polyphenols of honey like Caffeic acid, Caffeic acid phenyl ester, Chrysin, Galangin, Quercetin, Acacetin, Kaempferol, Pinocembrin, Pinobanksin and Apigenin have evolved as promising pharmacological agents in treatment of cancer[17].

"Gram for gram, antioxidants in buckwheat honey equal those of fruits and vegetables," said Dr. May Berenbaum, head of the University of Illinois' entomology department. "It packs the antioxidant power of Vitamin C in a tomato." Researchers at the University of Illinois-Champaign/Urbana have identified the antioxidant values of 14 unifloral honeys. The antioxidative components of honey were compared to anascorbic acid standard. The water-soluble antioxidant content of the honey samples varied more than 20-fold, from a high value of 4.32×10-3 eq for Illinois buckwheat honey to a low value of 21.3×10-5 eq for California button sage honey [15].

Research showed a correlation between color and antioxidant capacity, with the darker honeys

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providing the highest levels of antioxidants. With antioxidant levels reaching 4.32×10-3 meq., honey rivals those levels found in tomatoes (2.83×10-3 meq) and sweet corn (1.36×10-3 meq). Although honey by itself may not serve as a major source of dietary antioxidants, it demonstrates the potential for honey to play a role in providing antioxidants in a highly palatable form.

Due to honey's pleasing taste, it may be more readily consumed by individuals reluctant to ingest plant-derived antioxidants. Certainly, compared to sucrose, which has no antioxidant value, honey can be a flavorful, supplementary source of antioxidants [17].

BOTANICAL ORIGIN AND ANTIOXIDANT ACTIVITIES OF HONEY

Honey has been found to contain significant antioxidant compounds including glucose oxidase, catalase, ascorbic acid, flavonoids, phenolic acids, carotenoid derivatives, organic acids, Maillard reaction products, amino acids and proteins [18-26]. The antioxidative activity of honey polyphenols can be measured in vitro by comparing the oxygen radical absorbance capacity (ORAC) with the total phenolics concentration (Table 1). There is a significant correlation between the antioxidant activity, the phenolic content of honey and the inhibition of the in vitro lipoprotein oxidation of human serum [27]. Furthermore, in a lipid peroxidation model system buckwheat honey showed a similar antioxidant activity as 1 mM -tocopherol [25]. The influence of honey ingestion on the antioxidative capacity of plasma was tested in two studies [28, 29]. In the first one, the trial persons were given

maize syrup or buckwheat honeys with a different antioxidant capacity in a dose of 1.5 g/kg body weight. In comparison to the sugar control, honey caused an increase of both the antioxidant and the reducing serum capacity.

In the second study humans received a diet supplemented with a daily honey serving of 1.2 g/kg body weight. Honey increased the body antioxidant agents: blood vitamin C concentration by 47%, b-carotene by 3%, uric acid by 12%, and glutathione reductase by 7% [29]. It should be borne in mind that the antioxidant activity depends on the botanical origin of honey and varies to a great extent in honeys from different botanical sources [30-32].

ANTIOXIDANT IN HONEY ADDS HEALTH

Departments of Nutrition and Internal Medicine at the University of California and National Honey Board, showed that free radicals and reactive oxygen species (ROS) have been implicated in contributing to the processes of aging and disease [34]. Humans protect themselves from these damaging compounds, in part, by absorbing antioxidants from high-antioxidant foods. This report describes the effects of consuming 1.5 g/kg body weight of corn syrup or buckwheat honey on the antioxidant and reducing capacities of plasma in healthy human adults. The corn syrup treatment contained 0.21 (0.06 mg of phenolic antioxidants per gram, and the two buckwheat honey treatments contained 0.79 (0.02 and 1.71 (0.21 mg of phenolic antioxidants per gram. Following consumption of the two honey treatments, plasma total-phenolic content increased ($P<0.05$) as did plasma antioxidant and reducing capacities ($P<0.05$). These data support the concept that phenolic antioxidants from processed honey are bioavailable, and that they increase antioxidant activity of plasma. It can be speculated that these compounds may augment defenses against oxidative stress and that they might be able to protect humans from oxidative stress.

Given that the average sweetener intake by humans is estimated to be in excess of 70 kg per year,

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the substitution of honey in some foods for traditional sweeteners could result in an enhanced antioxidant defense system in healthy adults [34].
Beretta et al. demonstrated the protective activity of a honey of multifloral origin, standardized for total antioxidant power and analytically profiled (HPLC-MS) in antioxidants, in a cultured endothelial cell line (EA.hy926) subjected to oxidative stress. Cumene hydroperoxide (CuOOH) was used as free radical promoter. Native honey (1% w/v pH 7.4, 10(6) cells) showed strong quenching activity against lipophilic cumoxyl and cumoperoxyl radicals, with significant suppression/prevention of cell damage, complete inhibition of cell membrane oxidation, of intracellular ROS production and recovery of intracellular GSH. Experiments with endothelial cells fortified with the isolated fraction from native honey enriched in antioxidants, exposed to peroxyl radicals from 1,1-diphenyl-2-picryl hydrazyl (AAPH, 10 mM) and to hydrogen peroxide (H2O2, 50-100 microM), indicated that phenolic acids and flavonoids were the main causes of the protective effect. They suggested that, through the synergistic action of its antioxidants, honey by reducing and removing ROS, may lower the risks and effects of acute and chronic free radical induced pathologies in vivo [35].

ROLE OF ANTIOXIDANT IN PREVENTING CANCER

Chemoprevention utilizes appropriate pharmacological agents [3, 4] or of dietary agents, consumed in diverse forms like macronutrients, micronutrients, or nonnutritive phytochemicals.
Various polyphenols, which have antioxidant properties, are reported in honey. Some of the polyphenols of honey like Caffeic acid, Caffeic acid phenyl ester, Chrysin, Galangin, Quercetin Acacetin, Kaempferol, Pinocembrin, Pinobanksin and Apigenin have evolved as promising pharmacological agents in treatment of cancer [15].

Mok-Ryeon Ahn et al. showed that acacetin, apigenin, artepillin C, caffeic acid phenethyl ester, chrysin, p-coumaric acid, galangin, kaempferol, pinocembrin, and quercetin have antioxidant activity. These components were evaluated for their antioxidant activities by 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical-scavenging and ferric reducing/ antioxidant power (FRAP) assays. Furthermore, the effects of these components were tested on in vitro models of angiogenesis, tube formation and growth of human umbilical vein endothelial cells (HUVECs). Caffeic acid phenethyl ester, and quercetin, possessed strong inhibitory effects on tube formation and on endothelial cell prolie and, coincidentally, showed strong antioxidant activity. Artepillin C, galangin, and kaempferol also possessed strong antiangiogenic and antioxidant activities to a slightly less degree. In contrast, acacetin, apigenin, and pinocembrin possessed a considerable degree of antiangiogenic activities, although they showed very low antioxidant activities. These results demonstrated that artepillin C, caffeic acid phenethyl ester, galangin, kaempferol, and quercetin might represent a new class of dietary-derived antioxidative compounds with antiangiogenic activities. These components may have the potential to be developed into pharmaceutical drugs for the treatment of angiogenesis-depen dent human diseases such as tumors [36]. Caffeic acid has been reported as a carcinogen in initial studies, but the same caffeic acid along with combination of other antioxidant has been shown to suppress colon tumors in rats. Natarajan et al. demonstrated that Caffeic acid phenyl ester (CAPE) is known to have antimitogenic, anticarcinogenic, antiinflammatory and immunomodulatory properties [37]. CAPE's antiinflammatory and anticancer property has also been shown to protect skin cells when exposed to ultra-violet radiation and UVB radiation [38]. Weng et al. showed that the growth inhibitory effect of chrysin in C6 glioma cells was either though activating p38- MAPK which leads to the accumulation of p21Waf1/Cip1 protein or mediating the inhibition of proteasome activity [39]. In another study by Woo et al. it has been elucidated that chrysin induces apoptosis in association

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with the activation of caspase-3 and Akt signal pathway, that plays a crucial role in chrysin-induced apoptosis in U937 cells [40]. Galangin expressed antiproliferative effect on HL-60 cells on dose dependent manner and also induced DNA fragmentation without loss of membrane integrity [41].

Quercetin also inhibited the HL-60 cell proliferation inassociation with the inhibition of cytosolic Protein Kinase C (PKC) and membrane Tyrosine Protein Kinase (TPK) invitro [42]. It has been reported that quercetin in low concentration promoted cell proliferation of A-549 cells, whereas in higher concentration it inhibited cell proliferation and survival [43]. Further quercetin exerted antiproliferative effect against glioma and breast cancer cells [44-46].

Acacetin, another important flavanoid inhibited the proliferation of A549 cells, induced apoptosis and blocked the cell cycle progression at G1 phase. It also improved the expression of p53 and Fas ligands [47]. In another study, it has been shown to inhibit HepG2 cell proliferation and provoke apoptosis by enhancing the p53 and Fas ligands as in the case of A549 cells [48]. Kaempferol induced apoptosis in H460 cells which was accompanied by significant DNA condensation and increasing ATP levels. It also changed the expression of Caspase 3 and Apoptosis Inducing Factor (AIF) levels [49]. Bestwick et al. reported recently that kaempferol growth inhibitory effect on HL-60 leukemia cells is due to heterogeneous response mainly dominated by cell cycle alternation although some degree of cytotoxicity results from apoptotic as well as nonapoptotic process [50].

Pinocembrin induced loss of mitochondrial membrane potential (MMP) with subsequent release of cytochrome c and processing of caspase-9 and -3 in colon cancer cell line HCT 116 [51]. Apigenin exerted antiproliferative effect against colon, breast, cervical, neuroblastoma and liver cancer cell lines [52-56].

ANTIOXIDANT AND CARDIOVASCULAR DISEASES

CONCLUSION:

It is clear that the antioxidants properties of honey are due to the presence of some antioxidant compounds such as Vitamin C, monophenolics, flavonoids, and polyphenolics.

Although there is a wide spectrum of antioxidant types, Caffeic acid, Caffeic acid phenyl ester, Chrysin, Galangin, Quercetin, Acacetin, Kaempferol, Pinocembrin, Pinobanksin and Apigenin predominate in many honeys. These antioxidant compounds have a promising pharmacological agent for preventing cancer, cardiovascular diseases, inflammatory disorders, neurological degeneration, wound healing, infectious diseases and aging as well as it can be used as food preservatives.

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Learn more: http://www.naturalnews.com/027170_honey_Manuka_bacteria.html#ixzz28Uvi7T9S

- **Scientists Document How Manuka Honey Fights Superbugs**

Monday, October 05, 2009 by: S. L. Baker, features writer

(NaturalNews) When infections caused by antibiotic-resistant bacteria, also known as superbugs, are in the mainstream news there's usually a sense of panic connected to the story. After all, this type of infection is spreading and can be life-threatening. For example, methicillin-resistant *Staphylococcus aureus* (MRSA) is a strain of staph that's become resistant to broad-spectrum antibiotics. MRSA can

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cause everything from swollen, painful boils to pneumonia, bloodstream infections and surgical wound infections that are lethal. And standard Western medicine has mostly run out of antibiotics to treat these potentially deadly health woes.

However, a natural way to beat an enormous array of health-threatening germs has been around for thousands of years -- honey. And now scientists are zeroing in on just how a specific type known as manuka honey

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(http://www.naturalnews.com/023670_honey_antibiotics_Manuka_honey.html), **Honey made from the flowers of the New Zealand manuka bush, is able to stop superbugs in their tracks while standard antibiotic therapy is useless.**

Breakthrough research into the honey's remarkable disease-fighting abilities was announced this week (September 7 through 10) at the Society for General Microbiology's international meeting held at Heriot-Watt University in Edinburgh, Scotland. Dr Rowena Jenkins and her investigative team from the University of Wales Institute-Cardiff in the United Kingdom presented results of their study showing that manuka honey appears to wipe out superbugs by destroying key bacterial proteins. "Manuka and other honeys have been known to have wound healing and anti-bacterial properties for some time," Dr Jenkins said in a statement to the media. "But the way in which they act is still not known. If we can discover exactly how manuka honey inhibits MRSA it could be used more frequently as a first-line treatment for infections with bacteria that are resistant to many currently available antibiotics."

Dr. Jenkins and colleagues are closing in on that important discovery. For their latest research, MRSA was grown in their laboratory and treated with and without manuka honey for four hours. As a control, the experiment was repeated using a honey sugar syrup to document whether any anti-superbug effects seen were due to the sugar content in honey alone. Next, the cells of the bacteria were broken open so cell proteins could be isolated and separated on a system that documented and displayed each protein individually.

The results showed manuka honey's anti-bacterial properties were not due to the sugars in the honey. When MRSA infected cells were treated with the entire manuka honey, instead of just the honey sugar syrup, they appeared to lose many proteins. One in particular, dubbed FabI, was totally missing.

This is a critical finding because FabI is a protein necessary for the superbug's fatty acid biosynthe sis, a process which supplies the bacteria with precursors they need to grow, thrive and continue infecting cells. So the scientists believe manuka honey is effective in killing MRSA because it wrecks the superbug's ability to keep proteins it needs to thrive.

This latest research follows another manuka honey study published in Otolaryngology, the official journal of the American Academy of Otolaryngology-Head and Neck Surgery, last July. Scientists from the University of Ottawa's Department of Otolaryngology tested both manuka honey and sidr honey, which comes from the sidr tree in Yemen and has been used for its infection-stopping ability for countless centuries, on Pseudomonas aeruginosa (PA) and Staphylococcus aureus (SA) -- includ ing the MRSA type.

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The researchers worked with the infections growing in biofilms -- thin, slimy layers formed by bacteria that are especially resistant to antibiotics. But the PA and SA bacteria were no match for the manuka and sidr honey. In their conclusion, the scientists wrote: "Honey, which is a natural, nontoxic, and inexpensive product, is effective in killing SA and PA bacterial biofilms. This intriguing observation may have important clinical implications and could lead to a new approach for treating refractory CRS chronic rhinosinusitis (CRS)."

For more information:
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NHS Choices
http://www.nhs.uk/news/2011/04April/Pages/manuka-honey-mrsa-superbug-bacteria.aspx

- **Anti-Microbial "The researchers also say that honey has been shown to exhibit "broad-spectrum" Broad Spectrum antimicrobial activity, being able to act upon more than 80 species of pathogen.**

How is it meant to work?

The researchers point out that honey is a complex and variable product, so searching for "specific inhibitors" (the molecular compounds that might have an effect on bacteria) has not been easy. They think that several factors may together be implicated in its antimicrobial activity, including its high sugar content, low water content, low acidity, the presence of hydrogen peroxide and the presence of phytochemicals.

Manuka honey is thought to be particularly potent because it has high levels of a compound called dihydroxy acetone, which is present in the nectar of manuka flowers. This chemical produces methylglyoxal, a compound thought to have antibacterial and cell-killing properties.

Professor Rose Cooper from the University of Wales Institute Cardiff, who was one of the researchers, explained that the findings with Streptococci and Pseudomonas "suggest that manuka honey can hamper the attachment of bacteria to tissues", an essential step in the initiation of acute infections.

Inhibiting attachment also blocks the formation of biofilms, which can protect bacteria from antibiotics and allow them to cause persistent infections, she explained. "Other work in our lab has shown that honey can make MRSA more sensitive to antibiotics such as oxacillin – effectively reversing antibiotic resistance. This indicates that existing antibiotics may be more effective against drug-resistant infections if used in combination with manuka honey."

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Paper 11

http://www.sciencedaily.com/releases/2011/04/110412201713.htm ScienceDaily (Apr. 13, 2011)

- **Honey Can Reverse Antibiotic Resistance, Study Suggests**

— Manuka honey could be an efficient way to clear chronically infected wounds and could even help reverse bacterial resistance to antibiotics, according to research presented at the Society for General Microbiology's Spring Conference in Harrogate.

Professor Rose Cooper from the University of Wales Institute Cardiff is looking at how manuka honey interacts with three types of bacteria that commonly infest wounds: Pseudomonas aeruginosa, Group A Streptococci and Meticillin-resistant Staphylococcus aureus (MRSA). Her group has found that honey can interfere with the growth of these bacteria in a variety of ways and suggests that honey is an attractive option for the treatment of drug-resistant wound infections.

Honey has long been acknowledged for its antimicrobial properties. Traditional remedies containing honey were used in the topical treatment of wounds by diverse ancient civilisations. Manuka honey is derived from nectar collected by honey bees foraging on the manuka tree in New Zealand and is included in modern licensed wound-care products around the world. However, the antimicrobial properties of honey have not been fully exploited by modern medicine as its mechanisms of action are not yet known.
Professor Cooper's group is helping to solve this problem by investigating at a molecular level the ways in which manuka honey inhibits wound-infecting bacteria. "Our findings with streptococci and pseudomonads suggest that manuka honey can hamper the attachment of bacteria to tissues which is an essential step in the initiation of acute infections. Inhibiting attachment also blocks the formation of biofilms, which can protect bacteria from antibiotics and allow them to cause persistent infections," explained Professor Cooper. "Other work in our lab has shown that honey can make MRSA more sensitive to antibiotics such as oxacillin -- effectively reversing antibiotic resistance. This indicates that existing antibiotics may be more effective against drug-resistant infections if used in combination with manuka honey."

This research may increase the clinical use of manuka honey as doctors are faced with the threat of diminishingly effective antimicrobial options. "We need innovative and effective ways of controlling wound infections that are unlikely to contribute to increased antimicrobial resistance. We have already demonstrated that manuka honey is not likely to select for honey-resistant bacteria," said Professor Cooper. At present, most antimicrobial interventions for patients are with systemic antibiotics. "The use of a topical agent to eradicate bacteria from wounds is potentially cheaper and may well improve antibiotic therapy in the future. This will help reduce the transmission of antibiotic-resistant bacteria from colonised wounds to susceptible patients."

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Paper 12

http://manukahoney.com/resources/research/different-honeys.html

- **University Research Confirms Honey as a Healer**

Bees gather nectar from flowers. Back in the hive to help preserve the honey they add an enzyme, glucose oxidase, to the nectar when they are processing it into honey.

When honey comes into contact with body moisture the glucose oxidase enzyme slowly releases the antiseptic hydrogen peroxide. This is released at sufficient levels to be effective against bacteria but not tissue damaging.

In the research laboratory a catalase was added to honey samples to remove the hydrogen peroxide and then the honeys were tested to see if there was still any antibacterial activity.
Some manuka honey samples were found to still have significant antibacterial activity - a non-peroxide antibacterial activity.
This special non-peroxide antibacterial activity is called UMF (Unique Manuka Factor).
Click here to find out more about this important discovery and why the UMF property gives the honey enhanced healing qualities.
But the hydrogen peroxide antibacterial activity in honey can vary widely according to:

1 Honey floral type. Some floral nectars produce a catalase which destroys the glucose oxidase enzyme.

2 How the honey has been handled, especially during processing. The glucose oxidase enzyme is easily destroyed by heat, fluid and sunlight.

3 The hydrogen peroxide can be broken down by a catalase enzyme present in body tissue and serum, so reducing the antibacterial potency when used on a wound or infection.

Paper 13

http://manukahoney.com/resources/research/secondagent.html

- **A Second Natural Antibacterial Agent**

Dr Peter Molan and his research team at the Honey Research Unit at New Zealand's Waikato University found in some specific strains of manuka honey a second natural more powerful and more stable antibacterial property called UMF.
UMF is additional to the hydrogen peroxide activity and gives the honey a wider range of uses and effectiveness.

In laboratory tests the UMF property has been found to be effective against a wide range of bacteria including:

- helicobacter pylori - this bacteria causes most stomach ulcers,
- staphylococcus aureus and escherichia coli - the most common cause of infected wounds and MRSA,
- streptococcus pyogenes - causes sore throats.

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Paper 13

The hydrogen peroxide antibacterial property of other honeys (including ordinary manuka honey) is not effective against helicobacter pylori.

The UMF antibacterial property is very stable. It is resistant to heat and more resistant to being broken down by the catalase effect of body fluids than is the hydrogen peroxide activity.

Studies are showing UMF Manuka Honey with high levels of UMF could be very effective in:

- digestive care by helping relieve stomach ulcer symptoms and gastritis
- wound care by assisting the natural healing of skin ulcers, diabetic ulcers, wounds, burns, boils, cracked skin, pressure sores, MRSA, eczema, dermatitis
- relieving sore throats
- oral hygiene as it inhibits acid production and helps prevent cavities developing in teeth.

The UMF antibacterial property is a phytochemical property meaning it is a floral derived property coming from the nectar of some manuka flowers. For this reason it is in only some specific strains of manuka honey. The hydrogen peroxide antibacterial property is from the enzyme glucose oxidase which the bees have added to the honey.

Honey with high levels of UMF is identified by the name UMF and its level clearly displayed on the front label. The higher the UMF rating the greater the antibacterial strength of the honey. A high UMF activity ensures best results.

The glucose oxidase enzyme which produces hydrogen peroxide needs oxygen, but the phytochemical UMF does not.
So it could remain active even when smothered by wound dressings or in wound cavities.

Paper 14

Waikato Honey Research Unit

- **Antibacterial Activity of Different Honeys**

The following are some of the results observed in laboratory studies, in vitro results, when comparing the antibacterial activity of honeys against particular bacteria.
(Source: Manuka Honey as a Medicine by PC Molan, 2001. Honey Research Unit Website).

Other Honey is honey which has antibacterial activity due to hydrogen peroxide.

http://manukahoney.com/resources/research/secondagent.html

Non-Peroxide Activity

All types of honey have the ability to produce hydrogen peroxide which accounts for a portion of its healing qualities. Manuka honey from New Zealand is superior over other types of honey because, in addition to its ability to produce hydrogen peroxide, it also has a non-peroxide activity which researchers believe has a synergistic action in providing optimal healing benefits.

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Paper 14

When researchers began to recognize Manuka honey's additional healing components, they started measuring the non-peroxide activity comparing it to a solution with the same percentage of phenol. For example, Manuka honey with the non-peroxide activity of 15 has the same antibacterial potency as a solution that is 15% phenol.

Activity of honey increases

Very often the number used on labelling represents the non-peroxide activity of Manuka honey is followed by a plus with time in a jar sign (+). This is because the antibacterial potency of Manuka honey has a tendency to naturally increase over time. For example, Manuka honey that is labeled as a 10+ had a non-peroxide activity of 10 at the time it was tested but it could be higher depending on how long after testing the honey is used. It could have potentially increased to a 15+.

UMP

Manuka-honey.blogspot.co.nz
There have been some trademarks that have evolved over the course of time that precede the number that measures the non-peroxide activity of Manuka honey (i.e. UMF). These acronyms are less important than the actual number itself.

Paper 15

www.apicare.co.nz

- **Manuka Honey as a Medicine**

Manuka as a Medicine

The usage of honey as a medicine is referred to in the most ancient written records, it being prescribed by the physicians of many ancient races of people for a wide variety of ailments (Ransome 1937). It has continued to be used in folk medicine ever since, but in recent times there has been a renaissance of the use of honey in the medical profession: an editorial in the Journal of the Royal Society of Medicine (Zumla and Lulat 1989) Manuka underutilized discussing this expressed the opinion "The therapeutic potential of uncontaminated, pure honey is grossly as Medicine underutilized.

Medicine may be increasingly high-tech, but the latest wonder treatment which is being offered to patients is - honey.

Manuka and RSA reduction. Last week, it was announced that bandages soaked in manuka honey are to be given to mouth cancer patients at the Christie Hospital in Manchester to reduce their chances of contracting the MRSA superbug and to lessen wound inflammation following surgery.

This is just the latest study investigating this particular type of honey's healing powers. It is used routinely at the Manchester Royal Infirmary for dressing wounds, and other research has found it can fight gum disease, ease digestive problems and soothe sore throats.

What's special about active manuka honey?
For the past 28 years honey researchers at the University of Waikato have been investigating what many local New Zealanders have accepted as common wisdom: our local manuka honey is a superior treatment for wound infections. Manuka honey is gathered in New Zealand from the manuka bush, Leptospermum scoaparium, which grows uncultivated throughout the country.

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Paper 16

www.hill-laboratories.co.nz

- **Non-Peroxide Activity (NPA)**

Non-Peroxide Activity (NPA) is an indicator of the activity in Manuka honey and Hill Laboratories uses a chemical analysis method and GC-MS instrumentation to give reliable, accurate results every time. This is one we have developed specifically to meet the needs of the honey industry in New Zealand.

Methylglyoxal

MGO indicates Activity

Methylglyoxal(MGO®) is an indicator of the activity in Manuka honey. Methylglyoxal is a very popular test for those honey producers focusing on the production of Manuka honey.

Paper 17

http://www.bpsc.org.nz/

- **Bee Products Standards Council**

Proposed standard for measuring the non peroxide activity of honey

Purpose

This proposal sets out to define a core standard for the measurement of the non peroxide activity of honey.

Standard. The non peroxide antimicrobial activity of honey is measured by assessing the effect of the honey on the pathogen Staphylococcus aureus (ATCC 9144) after the peroxide activity of the honey has been is totally removed. This is initially measured using the 'well diffusion method for inhibitory substances' as described in the Microbiology Standard Methods Manual for the New Zealand Dairy Industry (1982). The scale of measurement used to measure the effect is referred to as 'the phenol standard' and the activity of the honey is expressed as the equivalent phenol concentration (% w/v).

Paper 18

www.sciencedirect.com

- **Abstract**

Some conclusions, which exist in the literature about the nature of non-peroxide antibacterial activity in manuka honey, have been revisited. The stability of non-peroxide antibacterial activity in manuka honey at basic pH was investigated. At pH 11 antibacterial activity was immediately and irreversibly destroyed. This antibacterial activity indicates that it is not possible to carry out chromatography of honey solutions at elevated pH with the intent to isolate the active fraction. The effect of 10-fold excess of catalase upon the antibacterial assay was examined. No statistical difference in the outcome was observed between the normal amount of catalase and the 10-fold excess. This indicates that non-peroxide antibacterial activity in manuka honey is not likely to be due to residual hydrogen peroxide.

High PH destroys

Paper 19

www.manukahealth.co.nz

- **The in vitro effect of Manuka honeys on growth and adherence of oral bacteria**

Abstract

Honey has been used since ancient times and more recently, for the healing of wounds and against infectious diseases. The aim of our study was to investigate the effect of two manuka honeys showing different potencies of their antibacterial activity, on potentially pathogenic oral bacteria. The antimicrobial activity was examined by determining the MIC and MBC using the macro dilution broth technique. The effect on the adherence was tested on growing cells of Streptococcus mutans

Healing of wounds

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Paper 19

on a glass surface and on a multi-species biofilm grown on saliva-coated hydroxyapatite discs.

High Activity more effective

As expected, the antibacterial activity of manuka Image (with higher potency of antibacterial activity) was the most important. The two tested honeys weakly inhibited the adherence of S.mutans cells to a glass surface at sub-MIC concentration.

Manuka Image showed a total inhibition of multi-species biofilm at the concentration of 200 µg/ml manuka Image inhibited biofilm formation weakly at the concentration of 200 µg/ml but firmly at the concentration of 500 µg/ml.

Manuka may reduce

Our findings suggest that manuka honeys might be able to reduce oral pathogens within dental plaque. Two honeys appear to be able to control dental biofilm deposit.
For more information: http://www.sciencedirect.com/science/article/pii/S1075996410001897

Paper 20

After: American Journal of the College of Nutrition, 2008, 27: 677-689

- **Honey for Nutrition and Health: a Review**

Stefan Bogdanov, PhD, Tomislav Jurendic, Robert Sieber, PhD, Peter Gallmann, PhD1
Swiss Bee Research Centre, Agroscope Liebefeld-Posieux Research Station ALP, Berne, Switzerland
Key words: honey, nutrition, composition, glycemic index
Due to the variation of botanical origin honey differs in appearance, sensory perception and composition. The main nutritional and health relevant components are carbohydrates, mainly fructose and glucose but also about 25 different oligosaccharides. Although honey is a high carbohydrate food, its glycemic index varies within a wide range from 32 to 85, depending on the botanical source. It contains small amounts of proteins, enzymes, amino acids, minerals, trace elements, vitamins, aroma compounds and polyphenols. The review covers the c omposition, the nutritional contribution of its components, its physiological and nutritional effects. It shows that honey has a variety of positive nutritional and health effects, if consumed at higher doses of 50 to 80 g per intake.

Paper 21

- **Peter Gallmann, PhD, Swiss Bee Research Centre,**

Agroscope Liebefeld-Posieux Research Station ALP, CH-3003 Bern, Switzerland
Abbreviations: CHO = carbohydrate, GI = glycemic index, GL = glycemic load, ORAC = oxygen radical absorbance capacity; PGE = prostaglandin E; PGF = prostaglandin F, RDI = recommended daily intake
Key teaching points:
• About 95% of the honey dry matter is composed of carbohydrates, mainly fructose and glucose. 5-10 % of the total carbohydrates are oligosaccharides, in total about 25 different di- and trisaccharides.
• The Glycemic Index of honey varies from 32 to 85, depending on the botanical source which is lower than sucrose (60 to 110). Fructose-rich honeys such as acacia honey have a low GI.
• Besides, honey contains small amounts of proteins, enzymes, amino acids, minerals, trace elements, vitamins, aroma compounds and polyphenols.

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Paper 21

- Honey has been shown to possess antimicrobial, antiviral, antiparasitory, antiinflammatory, antioxidant, antimutagenic and antitumor effects.
- Due to its high carbohydrate content and functional properties honey is an excellent source of energy for athletes.
- Most of the health promoting properties of honey are only achieved by application of rather high doses of honey such as 50 to 80 g per intake.

CONCLUSION

Due to variation of botanical origin honey differs in appearance, sensory perception and composition. It contains mainly carbohydrates. The glycemic index of honey varies from 32 to 87, depending on botanical origin and on fructose content. The main nutrition- and health relevant components are the carbohydrates, which make it an excellent energy source especially for children and sportsmen.

Besides its main components, the carbohydrates fructose and glucose, honey contains also a great number of other constituents in small and trace amounts, producing numerous nutritional and biological effects: antimicrobial, antioxidant, antiviral, antiparasitic, antiinflammatory, antimutagenic, anticancer and immunosuppressive activities.

Different nutritional studies have confirmed various effects after honey ingestion, e.g. enhanced gastroenterological and cardiovascular health. Besides, honey showed physiological effects on blood health indicators as well as effects on hepatitis A and radiation mucositis patients. However, it should be pointed out that most of these studies were based on relatively high honey intakes of 50 to 80 g. Honey compositions, and also its different biological effects, depend to a great extent on the botanical origin of honey. This fact was often not considered in the reviewed studies.

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