Review Article

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Novel Insights into the Health Importance of Natural Honey

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Abstract

Honey is a sweet, flavourful liquid substance with several beneficial constituents. Extensive research has shown the therapeutic promise of the use of honey in enhancing health values and improving body systems. This manuscript documents the ancient medicinal uses of honey and provides evidence-based data demonstrating its benefits in animal models, patients, and healthy individuals. Several reports by various researchers are discussed regarding health indices and biomarkers used following apitherapy. These include physiological processes in virtually all animal and human organs. The responses of body systems after oral and systemic administration of honey are also mentioned. Honey is also evaluated for its wide acceptability as a complementary and alternative medicine for most ailments. All types of honey exhibit different biochemical activities and show greater variability in their potency as apitherapeutic agents than conventional medicines. The mechanisms of action conferring honey's protective effects, as suggested by various authors, are documented. These entail synergistic interaction of the bioactive physical and chemical constituents of honey to produce the desired beneficial effects. The use of apitherapy in synergy with chemotherapy to manage microbial and cancer ailments is also helpful in reducing drug-induced cytotoxicity. The mechanistic insights into the overall protective, preventive, and therapeutic effects of honey portend the presence of a unique factor, a 'synergistic multiple ingredients factor', designated SMIF.

Keywords: *honey, therapeutic, bioactivity, phytochemical, nutraceutical, apitherapy, health, diabetes mellitus, hypertension, medicine*

Introduction

Natural honey can be defined as a sweet, flavourful liquid substance of high nutritional value and immense therapeutic benefit (1). This natural product is produced mainly by bees from the secreted nectars of various flowers; this type is regarded as blossom or floral honey. A less common type, honeydew or forest honey, is produced from the exudates of plant sucking insects called aphids. Natural honey has more than 300 constituents, but its main composition is sugars, primarily fructose and glucose, with small amounts of fructo-oligosaccharides (1,2). The contents of raw honey vary in different geographical locations. These compositional varieties are greatly influenced by the botanical origin of the honey, which is a consequence of the diet of the bees. It is noteworthy that, irrespective of its floral source, honey contains phytochemicals, flavonoids, catalase, phenolic acids, ascorbic acid, antibiotic-rich inhibine, tocopherols, and peptides, and most of these substances work in synergy to provide its beneficial effects (1–3). The other substances identified in natural honey include proteins, amino acids, enzymes (amylase, catalase, invertase, oxidase), and vitamins (including niacin, riboflavin, and pantothenic acid), as well as minerals (mainly calcium, copper, iron, magnesium, manganese, phosphorus, potassium and zinc) (3,4). Some of these macro and micronutrients found in natural honey, as documented in previous reviews by Eteraf-Oskouei and Najafi (1) and by Ajibola et al. (5) with modifications by Ajibola (6), are listed in Table 1. The other chemical components of honey also identified by these reviewers (1,5), with inputs from Rashed and Soltan (4), are shown in Table 2.

The oral consumption of raw honey by man has been in vogue for centuries. An abundance of reports confirm that pure natural honey is the most ancient sweetener and has been in use since antiquity (1). The numerous bioactive substances found in honey interact uniquely and work in synergy to contribute to SMIF (6); thus, honey serves as a complementary and alternative medicine (CAM) for most diseases. The traditional and therapeutic use of NH has

Table 1: Some macro and micro nutrients of natural honey (Mean(SD))*

Proximate analyses	Amount	Proximate analyses	Amount
Water (%)	15.92 (SD 0.07)	Protein (%)	0.42 (SD 0.06)
Carbohydrate (g/100g)	88.97 (SD 1.71)	Fat (%)	0.53 (SD 0.01)
Fructose (g/100g)	43.35 (SD 0.02)	Thiamine (mg/100g)	0.01 (SD 0.00)
Glucose (g/100g)	37.64 (SD 0.01)	Riboflavin (mg/100g)	0.02 (SD 0.00)
Sucrose (g/100g)	2.03 (SD 0.05)	Niacin (mg/100g)	0.15 (SD 0.01)
Maltose (g/100g)	2.75 (SD 0.02)	Vitamin B5 (mg/100g)	0.07 (SD 0.03)
Oligosaccharides (g/100g)	3.11 (SD 0.08)	Pyridoxine (mg/100g)	0.17 (SD 0.02)
Erlose (g/100g)	0.81 (SD 0.06)	Folic acid (mg/100g)	0.006 (SD 0.00)
Melezitose (g/100g)	0.09 (SD 0.03)	Ascorbic acid (mg/100g)	2.35 (SD 0.25)
Glycaemic sugars (%)	76.71 (SD 1.55)	Vitamin K (mg/100g)	0.025 (SD 0.00)
Energy (MJ/Kg)	15.56 (SD 0.21)	Other nutrients (%)	0.53 (SD 0.00)

*Adapted from Eteraf-Oskouei and Najafi (1), Ajibola et al. (5), Ajibola (6).

Table 2: Chemical elements found in natural honey*

Element	Amount	Element	Amount
Aluminium (Al)	0.01 – 2.4	Magnesium (Mg)	0.7 – 13
Arsenic (As)	0.014 – 0.026	Manganese (Mn)	0.02 – 2
Barium (Ba)	0.01 – 0.08	Molybdenum (Mo)	0 – 0.004
Boron (B)	0.05 – 0.3	Nickel (Ni)	0 – 0.051
Bromine (Br)	0.4 – 1.3	Phosphorus (P)	2 – 15
Cadmium (Cd)	0 – 0.001	Potassium (K)	40 – 3500
Calcium (Ca)	3 – 31	Rubidium (Rb)	0.040 – 3.5
Chlorine (Cl)	0.4 – 56	Selenium (Se)	0.002 – 0.01
Chromium (Cr)	0.01 – 0.3	Sodium (Na)	1.6 – 17
Cobalt (Co)	0.1 – 0.35	Silicon (Si)	0.05 – 24
Copper (Cu)	0.02 – 0.6	Strontium (Sr)	0.04 – 0.35
Fluoride (F)	0.4 – 1.34	Sulphur (S)	0.7 – 26
Iodide (I)	10 – 100	Vanadium (V)	0 – 0.013
Iron (Fe)	0.03 – 4	Zinc (Zn)	0.05 – 2
Lead (Pb)	0.001 – 0.03	Zirconium (Zr)	0.05 – 0.08
Lithium (Li)	0.225 – 1.56		

*Data in mg/100g, Adapted from Eteraf-Oskouei and Najafi (1), Rashed and Soltan (4), Ajibola et al. (5).

been to abate infections, mitigate ailments, give health benefits to patients, and provide succour to healthy individuals (5–7).

The wide acceptability and successful use of honey as a CAM and apitherapeutic agent has prompted several studies aimed at gaining some scientific insights and generating evidence-based data. Collation of some of these scattered data is also required for further investigation of honey's nutraceutical properties and its relevance in modern day health care. Hence, the documentation of the known medicinal uses of honey in one manuscript becomes imperative for providing further insight into the apitherapeutic and health values of natural honey.

Haematology

The daily intake of natural honey is associated with various beneficial effects on haematological parameters and blood concentrations of metabolic catalysts, namely enzymes and minerals (7). The use of natural honey in apitherapy has been shown to ameliorate anaemic effects, thereby providing succour to patients. One dietary enrichment study (8) confirmed an enhanced haematological value in adult rats fed Nigerian Jungle honey when compared to controls. The authors found improved haemoglobin concentration, elevated red blood cell counts and enhanced haematocrit values in the raw honey eaters. In a similar experimental study from another laboratory, Chepulis (9), also reported improved haematological profiles and immunity boost in rats nurtured with 10% New Zealand forest honey as a dietary supplement. This researcher also documented a higher lymphocyte count and enhanced phagocytosis by neutrophils in rats fed natural honey relative to control rats. This aligns with a previous study that verified that prebiotics can improve immunity (10) and that honey contains oligosaccharides and other prebiotics (1). In a clinical trial in California, human participants given either of two honey treatments in showed the benefits of haematoprotection and enhanced haematopoiesis (11). In addition, natural honey has immuno-protective ingredients. According to Al-Waili and Haq (12), the oral consumption of Asian polyfloral honey from Al-Theed City, UAE stimulates and increases antibody production during various immune responses against the T-cells antigens of the thymus- independent and dependent origin.

Dental Effect

The oral use of raw honey can positively influence dental health and oral wellness, and is assuming importance during dental surgery (13). A very recent article indicates that the use of Asian polyfloral honey as an apitherapeutic agent mitigates pain associated with tooth extraction and prevents oral infections, such as gingivitis and dental caries, in patients undergoing orthodontic treatment (13). According to Mohapatra et al. (14), raw and processed honey have a broad-spectrum antibacterial activity with high potential for the reduction of dental caries susceptibility (13,14). In addition to the carioprotective potential of New Zealand manuka honey, English et al. (15) report, and Atwa et al. (13) concur, that this natural product prevents dental plaque and gingivitis as well as other oral ailments. The report from Steinberg and co-researchers also show that raw honey is non-cariogenic or less cariogenic than sugar (16).

Natural honey is not only non-cariogenic, but is also anti-cariogenic, as shown by Khamverdi and co-workers, who evaluated the antibacterial potency of Iranian honey (17) in apitherapy. The oral health effect of honey is due to its antibacterial potential, which prevents bacterial growth, thereby mitigating the pathogenesis of dental caries (13,16). In addition, recent research shows that eating raw honey is safe and does not give rise to oral health hazards such as gingivitis and periodontal disease (15). In this study (15), volunteers who chewed New Zealand manuka honey as "honey leather" had highly significant reductions in mean plaque scores (0.99 reduced to 0.65; $P = 0.001$) compared to the control group, suggesting a potential therapeutic role for honey in oral health.

As discussed in previous studies, the non-cariogenic potential of honey might be due to the protective role of honey's synergistic constituents (1,5,6). These chemical substances include calcium, fluoride, phosphorus and other colloidal constituents of honey. In summary, honey is a potent analgesic agent in dental surgery, in addition to its nutraceutical value when consumed by individuals and/or used as an apitherapeutic agent in the management of patients with oral ailments.

Eye Disorders

The therapeutic use of natural honey in the treatment and management of eye ailments is on record. The ancient use of honey as curative substance for eye diseases cuts across geographical barriers, and involves people from Attica, Europe, India, Asia and Africa (18–20). In India, the indigenous population still continues the use of floral honey as an apitherapeutic ointment to cure eye diseases to date (19). The efficacy of honey as a potent apitherapeutic agent in the management of eye infections was also recently shown by Salehi and co-workers, in their clinical trial on vernal keratoconjunctivitis patients (21). These authors show the relevance of natural honey in modern ophthalmology by documenting effective treatment of these patients by topical honey application. The African people in Mali also used natural honey for therapeutic control of measles (18). Natural honey was mostly applied on the eyes for the prevention of the corneal scarring sequelae of measles and other eye infections (19–22).

Clinical trials involving more than 100 patients harbouring various ophthalmological pathologies, including blepharitis, conjunctivitis and keratitis, showed unresponsiveness to conventional treatment. This prompted the topical administration of different types of honey, which resulted in astounding successful healing (21,22). In an extensive review on why honey is effective as a medicine, various honey types were noted as potent agents of apitherapy for ophthalmology in Asia and Eastern Europe (22). According to the findings reported in the reviewed manuscripts, the antimicrobial and anti-inflammatory properties of honey are highly beneficial in the treatment of different eye ailments. These ailments could be caused by chemical and thermal injuries to the eyes, as well as by conjunctival and corneal infections (21,22).

The apitherapeutic use of varieties of honey in the field of ophthalmology is comprehensively discussed by Ajibola et al. (5) in a review on the nutraceutical value of honey. The ophthalmological effects of natural honey mentioned by these researchers in their recent discourse are further elaborated above as honey therapy against various eye pathologies. This current review aligns with the extensive study by Ajibola et al. (5) that documented the efficacy of honey in the traditional and orthodox management of eye infections, including blepharitis, conjunctivitis, keratitis, measles, and corneal opacity

Cardiovascular Diseases

The oral administration of medical honey abates cardiovascular risk factors in animal models, human participants, susceptible healthy individuals, and patients (23–26). Inferences drawn from these studies suggest that, in contrast to refined sugars, patients with heart ailments can consume this natural sweetener, honey, without any health hazard (25,27). Other studies involving animal models and human participants nurtured with natural honey relative to controls (fed a fructose/sucrose mixture) report higher blood concentrations of antioxidants, which reduce the risk of development of cardiovascular diseases (23,25,26).

In 2012, some nutritional physiologists performed a comparative study in male rats fed sugar or South African monofloral sunflower honey (27). They found that excessive sugar consumption significantly ($P < 0.05$) elevated blood concentrations of circulating substrates (glucose and triglycerides) amidst several pathological changes, including hypercholesterolaemia, hyperinsulinaemia, and hepatomegaly, and significantly increased ($P < 0.001$) visceral adiposity and fat molecules in the liver (27). These risk factors of cardiovascular diseases were not seen in the honey-fed rats during the study. The absence of these pathologies confirms the cardioprotective capability of sunflower honey; thus, natural honey intake is devoid of health hazards (5,27). These results justify the conclusion that eating natural honey instead of artificial sugars has health benefits (23). Experimental procedures and clinical trials also affirm the apitherapeutic value and the significance of eating honey in mitigating cardiovascular ailments, as shown by health index records (25,26). Gharekhani et al. (24) give credence to this affirmation in their test of the efficacy of natural honey on cardiac arrhythmias and infarct size when it is used during ischemia in isolated rat hearts.

Hypertension and diabetes mellitus are important risk factors in patients with cardiovascular diseases. The apitherapeutic and beneficial effects of Malaysian honey have been demonstrated in animal models with hypertension alone (28), or with hypertension and diabetes (29), as well as those of Nigerian Jungle honey in a clinical trial involving healthy human participants (30). This cardiovascular section can be concluded with the 'cure all' claim associated with therapeutic potency of honey, as the literature search shows its positive influence as an apitherapeutic agent on various body organs and systems, ranging from the body metabolic sites (e.g., the liver) to the heart, kidney, blood and gastrointestinal tract.

Metabolic Effects

Natural honey is also beneficial as a glycaemic food in maintaining blood-sugar concentration (31,32). Several studies show that oral consumption of varieties of honey abates metabolic disorders in animal models, patients and susceptible healthy individuals (25,31–33). In one dietary supplementation study, male and female rodents were fed diets enriched with either South African sunflower honey or liquid sugar from 7 days old to 13 weeks of age in order to compare their metabolic health and to document the effects of natural honey against metabolic dysfunction and/or syndrome (6). Metabolic syndrome is a condition characterized by central obesity, hyperglycaemia, hypertension and dyslipidaemia, and thus increased susceptibility to diabetes mellitus and other metabolic ailments (34). In male rodents, sugar significantly ($P < 0.05$) elevates the blood concentrations of glucose and triglycerides and promotes enhanced visceral adiposity, hypercholesterolaemia, hyperinsulinaemia, hepatomegaly, and accumulation of fat droplets in the liver (31). These risk factors, which are associated with metabolic dysfunctions, were not seen in the honey-nurtured or in female rodents in this trial, which indicated the health potentials of monofloral sunflower honey. These results confirm the conclusion drawn from one study done elsewhere, by Busserolles and other researchers, that eating natural honey instead of artificial sugars has health benefits (23). The trials involving animal models and human participants also affirm the apitherapeutic value of medicinal honey in the management and control of metabolic diseases. Several biomarkers confirm this, including reduction in the plasma concentrations of total cholesterol and low density lipoprotein (LDL)-cholesterol (23,25,26); triglycerides (25,26), and glucose in healthy humans, as well as in patients with diabetes mellitus and C-reactive protein (23,25,26,32) and patients with elevated blood concentrations of high density lipoprotein (HDL)-cholesterol (23,25,26).

Unlike artificial sugars, this natural sweetener, honey, can be consumed by diabetic patients with beneficial results (25,32,33). However, there is need for caution and honey consumers, especially diabetic patients, should still be wary of possibilities for health hazard(s). As mentioned by Ajibola and colleagues in their study on the nutraceutical value of honey and contributions to human health, honey, like any other products with human involvement, is not devoid of contamination and adulteration (5). Some apiculturists feed the bees in their colonies with refined sugars, while some honey vendors even engage in the crude, inimical, and unwholesome practice of direct honey adulteration with sugars and other artificial sweeteners (5,6,33). As such, if diabetic patients consume a honey sample that is adulterated with as high as 70% artificial sugars, their health conditions may deteriorate.

In one study, Bahrami and colleagues showed that eating honey by certain diabetic patients can worsen glycaemic control (35). Erejuwa provides possible explanations for such a potential negative effect of honey in diabetic patients (33), including the ingestion of higher than pharmacological doses of honey without therapeutic monitoring and/or consumption of honey with a low fructose: glucose ratio, as used in Bahrami's clinical trial (33,35). Hence, natural honey should be provided in its genuine, original state and administered at appropriate therapeutic doses for desired positive results. Nonetheless, the metabolic effects of natural honey seen in evidence-based data, including studies on diabetic rodents and human patients, can be described as beneficial apitherapy, since only one out of several documents report any detrimental response from honey-fed diabetic patients.

Antimicrobial & Antiparasitic Effects

The antimicrobial potential of natural honey is the most widely investigated apitherapy, alongside its use in wound management. To date, several studies have been conducted on different bacterial species to investigate the antibacterial properties of honey from different geographical locations of the world (2,5,13,36–40). Most bacteria, viruses and fungi are sensitive to medicinal honey, as it is a very effective broad-spectrum antimicrobial agent (1,2,3,6,41,42). Researchers have demonstrated the antimicrobial activity of natural honey against *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, as well as other Gram-positive and Gram-negative bacteria (2,3,13). These authors opine that the formation of hydrogen peroxide (H_2O_2) enhances the antibacterial capability of honey.

Glucose + H_2O + O_2 --------Gluconic acid + H_2O_2

Hydrogen peroxide is produced through the action of enzymes, mainly glucose oxidase, in natural honey. The hypopharyngeal gland of the bee facilitates the enzymatic secretion of glucose oxidase into the nectar of flowers during honey production (3), (39). In general, apitherapeutic investigations on the antibacterial activities of honey show both bacteriostatic and bactericidal effects (13), and these could be due to peroxide and non-peroxide constituents of honey (39,40,43).

Treatment with natural honey is also of therapeutic value against Candida albicans, Leishmania parasites, *Trichophyton mentagrophytes*, and influenza and rubella viruses, as well as other pathogenic microbes (2,5,13,41,42). In addition, other studies also document the anti-mycotic effects of honey (22,37,43). Cutaneous and superficial fungal infections, like athlete's foot and ringworm, are sensitive to apitherapy. This sensitivity partially results from fungal growth inhibition and is partially due to prevention of secondary infection by opportunists like bacteria (22,36). Many microorganisms and parasites sensitive to natural honey have been identified by different researchers (2,3,5,12–14,22,36,39,41,44) as shown in Table 3.

Note that, in addition to its antimicrobial effect, the nematicidal potential of natural honey has also been demonstrated on the model nematode, Caenorhabditis elegans (44). Honey from different botanical origins shows nematicidal capability against the developmental stages of this worm. This antiparasitic action of honey could be due to reproductive anomalies seen as defects in laying and hatching of eggs by the parasite. The nematicidal activity of honey is so high that dilution does not affect honey's apitherapeutic potency. Thus, if the concentration of honey is reduced to about 0.03%, it will still cause profuse defects in the nematode's eggs, while about 6% concentrated honey is required to cause abnormalities during the hatching of the eggs. According to these authors, the main sugar constituents of honey did not contribute to the nematicidal activity; instead, this activity could be due to the bioactivity of other constituents manifesting as 'synergistic multiple ingredient factors' (6,44).

The various studies discussed in this section show that diluted and/or undiluted natural honey has antiseptic, anthelminthic and antimicrobial (antibacterial, antimycobacterial, antimycotic, antiparasitic, antiviral) activities when used alone; while it shows enhanced antipathogenic potency when apitherapy is combined with chemotherapy. This synergistic potency was shown in an in vitro study by Watanabe et al. (41) using New Zealand manuka honey in combination with antiviral chemotherapeutic agents (zanamivir or oseltamivir) against influenza virus. The reports

Table 3: Some microorganisms and parasites sensitive to natural honey*

Actinomyces pyogenes	*Nocardia asteroids*
Bacillus anthracis	*Proteus species*
Caenorhabditis elegans	*Pseudomonas aeruginosa*
Campylobacter coli	*Rubella virus*
Campylobacter jejuni	*Salmonella cholerae-suis*
Candida albicans	*Salmonella typhi*
Corynebacterium diphtheria	*Salmonella typhimurium*
Echinococcus parasite	*Serrata marcescens*
Enterococcus avium	*Shigella species*
Enterococcus faecalis	*Staphylococcus aureus*
Enterococcus faecium	*Stenotrophomonas maltophilia*
Enterococcus raffinosus	*Streptococcus agalactiae*
Epidermophyton floccosum	*Streptococcus dysgalactiae*
Escherichia coli	*Streptococcus faecalis uberis*
Haemophilus influenza	*Streptococcus mutans*
Helicobacter pylori	*Streptococcus pneumonia*
Influenza virus	*Streptococcus pyogenes*
Klebsiella pneumonia	*Streptococcus uberis*
Leishmania parasite	*Trichophyton mentagrophytes*
Microsporum canis	*Trichophyton tonsurans*
Microsporum gypseum	*Trichophyton rubrum*
Mycobacterium tuberculosis	*Vibrio choleriae*

*Adapted from Alvarez-Suarez et al. (2), Olaitan et al. (3), Ajibola et al. (5), Al-Waili and Haq (12), Atwa et al. (13), Mohapatra et al. (14), Molan (22), Basualdo et al. (36), Vit and Huq (39), Watanabe et al. (41), Sajid and Azim (44).

of potent inhibitory activity by these authors demonstrate a potential enhanced apitherapeutic value of honey.

Apitherapy & Chemotherapy of Wounds

Medical honey is an antiseptic agent, effective against burns, ulcers (including recalcitrant ones), surgical wounds (even when infected), fungating wounds, pressure sores, and cancer or broken skin (42). According to an expert, applying honey topically as dressings in surgical patients was successful where conventional treatments (including radiation therapy) failed to produce the desired results (42). In one study, Ajibola (45) also obtained excellent results from experimentally created surgical wounds in West African Dwarf (WAD) goats treated with Nigerian Jungle honey as an apitherapeutic agent. The researcher documented epithelialisation and enhanced contraction of the honey treated wounds when compared with untreated wounds.

An abundance of evidence supports the topical application of medical honey for different types of wounds. These include apitherapeutic studies involving the use of honey in hospital surgical wards and laboratory experimentation (45–47). The presence of various bioactive substances in honey (2,4,48) gives rise to its different biological properties (5,6) promoting wound healing amidst other several protective effects, as shown by molecular evidence from several studies (39,49–51). Comprehensive overviews of the effects of honey on various types and classes of wounds are available in Molan's popular treatise: "Why honey is effective as a medicine" (22), and a recent publication by Ajibola (42) titled: "Physiological effects of natural honey on wounds in animals."

The apitherapeutic use and application of honey for wound care also involves paediatric patients (51). Honey causes enhanced epithelialisation and minimises scar formation with an anti-microbial effect. These researchers opine that medical honey is a safe and natural substance that induces wound healing at a greater rate than conventional methods of treatment.

The key findings for the use of honey in wound management are intertwined with those of the previous section (Antimicrobial & antiparasitic effects). These entail wound dressing with honey as an age-long practice, pre-dating antibiotic use (22,42). Honey is a potent broad-spectrum antibacterial agent, with both bacteriostatic and bactericidal properties (hydrogen peroxide, antioxidants, lysozyme, polyphenols, phenolic acids, flavonoids, methylglyoxal and bee peptides) higher than those of conventional drugs (1,14,40,43). Antibiotic-resistant microbes are sensitive to honey treatment (38–40); Medical grade wound honey care creams, gels, impregnated gauzes and dressings for wound management have been developed for public use (39,42). Minor cuts, bruises, chronic ulcers, burns, diabetic foot, gangrene, oncological wounds and other wounds, such as those caused by surgical removal of tumours, radiotherapy, and mucositis sequelae to chemotherapy, have been successfully treated with honey (22,39,42).

These various beneficial effects of apitherapy involve several mechanisms, as suggested by different workers (1,22,39,42), using varieties of honey from different geographic, botanic and entomologic origins, and can be summarised as follows: the physicochemical properties of honey curtail malodour of wounds and infected sites; the hygroscopic nature of honey facilitates moisture withdrawal from infected sites and surrounding tissues, thereby dehydrating bacteria, yeasts and other microbes; a protective layer forms between the wound bed and the highly viscous honey dressing; the low pH inhibits bacterial growth; a synergistic interaction occurs with the phenolic acids and other non-peroxide bioactive phytochemicals contained in honey.

Cancer Therapy

The anti-inflammatory properties of different honey types confer the capability to mitigate the pathogenesis of cancer (52). The potential of various honey types of different botanic, geographic and entomologic origins as anti-cancer agents is also documented in a number of studies (39,49,50). A review on honey and cancer by Othman (52) describes honey as a natural cancer "vaccine", due to the observed reduction in prolonged inflammation, a risk factor for the pathogenesis of cancer. Due to its high antioxidant content, natural honey shows anti-tumour activity by inhibiting proliferation and enhancing the early death of various cancer cells (52). These cancer cells include carcinomas, sarcomas, cancer cell lines, experimental cancers, bone cancer and breast cancer (39,50,53–56). The processes involved in the anti-mutagenic and anti-tumour activities of natural honey appear to be multifactorial, and include the release of cytotoxic hydrogen peroxide and scavenging of reactive oxygen species (55,57); cyclooxygenase-2 inhibition by honey constituents like flavonoids (2,4,11,48,58); and cancer cell apoptosis via mitochondrial membrane depolarisation (39).

Honey shows inhibitory effects on cancer cell proliferation through cell death, so its use in cancer management is highly beneficial and does not hamper the health of cancer patients. This is due to the fact that natural honey is highly selectively cytotoxic against tumour or cancer cells, while it is non-cytotoxic to normal cells. This observation was made by Fernandez-Cabezudo and co-workers in a melanoma animal model that showed improved host survival and tumour growth inhibition following intravenous administration of New Zealand manuka honey combined with chemotherapy (59). This selectivity of cell destruction, in which host cells are preserved and 'unwanted or killer cells' are destroyed, was further investigated by Erejuwa et al. (60) in a recent molecular study. These workers propose that honey's mechanisms of action on the development and progression of cancer include cell cycle regulation, activation of the mitochondrial apoptosis pathway, induction of mitochondrial outer membrane permeabilisation, induction of apoptosis, modulation of oxidative stress, amelioration of inflammation, modulation of insulin signalling and inhibition of angiogenesis.

Overall, the experimental and clinical oncological investigations of this natural product confirm that honey has antimetastatic, antiproliferative and anticancer effects on various forms of tumours or cancer cells. These include adenomas, carcinomas, melanomas, breast cancer, and liver and colorectal cancer cell lines. Others are prostate, bladder, endometrial, kidney, skin, cervical, Ehrlich ascites tumour (EAT) of the peritoneum (39), oral and bone cancer cells. The treatment and control of these different cancer cells with the use of natural honey involves the inhibition of cancer pathways such as AKT-PI3, Mtor and caspases by bioactive honey constituents. Fernandez-Cabezudo et al. (59) reports the inhibition of caspases in an in vitro oncological study of three different cancer cell lines: colorectal carcinoma (CT26), human breast cancer (MCF-7) and murine melanoma (B16.F1). The findings demonstrate the anti-proliferative effect of 0.6% (w/v) New Zealand manuka honey being mediated via the activation of a caspase 9-dependent apoptotic pathway. This leads to the induction of caspase 3 and reduced Bcl-2 expression, with consequent deoxyribonucleic acid (DNA) fragmentation and cell death. Gao et al. (61) demonstrate that chrysin, a constituent of natural honey, reverses the anticancer drug resistance of doxorubicin by down-regulating some cancer pathways (PI3K-Akt and ERK) to inhibit hepatocellular carcinoma. The modulation of these cancer pathways is also corroborated by Yaacob and colleagues (50) with the apitherapeutic use of Malaysian tualang honey on breast cancer cell lines.

In addition to the antioxidant, apoptotic and anti-proliferative potentials of honey, it also possesses anti-tumour necrosis factor (anti-TNF), anti-inflammatory, estrogenic and immunomodulatory activities (39,50). The study of oncology shows that carcinogenesis involves the molecular processes of initiation, promotion and progression stages of cancer cells, all of which can be modulated with the use of honey. Hussein et al. (49) demonstrated the modulation of the initiation stage of cancer in a rodent model treated with Gelam honey from Malaysia. These workers report that honey inhibited the production of pro-inflammatory mediators [nitric oxide (NO), prostaglandin E2 (PGE2), interleukin-6 (IL-6) and TNF-α] in carrageenan-induced acute paw oedema in rat cancer models. The application of Egyptian honey in apitherapy has also been shown to reduce experimental tumour implantation in mice (39). The findings show that the anti-tumour activity of honey occurs through the activation of macrophages, T-lymphocytes and B-lymphocytes in the Ehrlich ascites tumour (EAT) in the peritoneum of the mice.

Apitherapy has been shown to be potentially complementary to anticancer chemotherapy. Previous studies show enhanced inhibition of carcinogenesis and suppression of cancer cells growth when the natural medicine, honey or its bioactive constituents, is combined with chemotherapy of various anticancer drugs such as tamoxifen (50), paclitaxel (59), doxorubicin (61), 5-fluorouracil and cyclophosphamide (39). In addition, the synergistic use of honey in combination with chemotherapy reduces the required dosage of drugs and consequently eliminates drug-induced adverse effects such as cytotoxicity of viable body cells associated with chemotherapy and radiotherapy in cancer management.

The potential of various natural honey types from different botanic, geographic and entomologic origins as anti-cancer agents is also documented in other studies (39,49,50). However, it suffices to conclude from the overall literature search that the multifactorial processes involved in the anticancer activity of honey emanate from the bioactivity of its several phytochemicals and other constituents, namely apigenin, chrysin, galangin, pinobanksin, pinostrobin, pinocembrin, acacetin, caffeic acid, polyphenols, phenyl esters, quercetin and kaempferol (39,58), and this portends that these nutraceutical and biochemical components contribute to the therapeutic potency of honey by synergy. According to one oncological report (39), the synergistic effects of quercetin and kaempferol in reducing cell proliferation at 4 and 14 days single exposure in the human gut (HuTu-80, Caco-2) and breast cancer cells (PMC42) were associated with decreased expression of nuclear proliferation antigen Ki67 and total protein levels in treated cells relative to controls.

Children's health

The inclusion of natural honey in the diet of infants confers health benefits on children. Some studies have shown that honey-nourished infants have improved memory and enhanced growth, as well as being less anxious and showing better performance as they grow (62,63). The investigation by Ramenghi and others (63) on the palatability of honey for infants indicated a high tolerance level and acceptability of this natural sweetener in honey-fed babies, and they cry less than those given sterile water. A comparison between honey and sucrose inclusion in children's nutrition revealed improved haematology and calcium utilization, digestion devoid of problems, with lighter and thinner faeces in the children treated with natural honey relative to those nurtured with sucrose (62). Other findings documented in this study were appreciable skin colour, reduced susceptibility to diseases, and healthy weight gain (62). In their 12-month behavioural study on animal models, Chepulis and co-workers give scientific credibility to this beneficial practice (64). During the trial, eight-week-old rodents were fed with either New Zealand forest honey-enriched diet or diet containing sucrose, while a third group was given a diet devoid of sugar and served as the control. Similar results were obtained during the experimental procedure and actual practice. The findings prompted the conclusion that early introduction of honey in the diet is beneficial and facilitates memory retention and improves cognitive ability in adult life (64). The benefits of including natural honey in an infant's diet were attributed to honey's effects on the digestion process of the neonates, coupled with the action of prebiotic honey constituents (oligosaccharides) on the intestinal flora of these children (65).

In the opinion of Ajibola (6), formed from his findings in another nutritional study involving feeding honey from South Africa to neonatal animal models, the feeding of unadulterated, unprocessed natural honey to children could be beneficial in place of sweets and other sugary substances that they often have an appetite for. This assertion is supported by the recent findings of Weissenstein and colleagues (51) from an exclusive neonatal study on the apitherapeutic use of honey on paediatric patients, involving about 80 trials. These authors conclude that the use of medical honey is safe and encouraging for paediatric nutrition (51). The use of honey in infants and children also includes treatment of diaper dermatitis by topical application of a mixture containing honey, olive oil, and beeswax for a course of seven days (66), and as cough syrup for infection due to upper respiratory tract infection (URTI) (67).

Other health benefits

The other beneficial health effects of varieties of natural honey and apitherapeutic practices include treatment of general body pain, chest pain, menstrual pain, fatigue, vertigo, postnatal disorders, male impotence, and respiratory distress such as cough, bronchitis, pharyngitis, throat aches, and urinary tract infection (URTI) (1,22,39,43,67,68). These effects might be connected with the high energy content of honey, in addition to its effects against bacterial infection and inflammatory processes (42,51,68). In one reproductive study, Zaid et al. (69) reported the effects of tualang honey from Malaysia on menopausal rodents. The observation of uterine atrophy prevention informed the suggested use of honey as an alternative to hormone replacement therapy by these authors.

The contributions of medical honey in radiology and nuclear medicine have also been documented (70). According to Makpol et al. (70), Malaysian Gelam honey attenuates radiation-induced cell death and radiation-induced deoxyribonucleic acid (DNA) damage by promoting cell cycle progression and inhibiting apoptosis, indicating its molecular mechanism as a radioprotector against radiation damage. However, apitherapeutic management with honey prior to radiation exposure is advisable as it provides the best beneficial effect against ionizing radiation (70).

Another important medicinal use of natural honey is its age-long therapeutic effect against gastrointestinal tract ailments (22,71,72). Present statistics support this ancient practice, as honey is being used for the management and control of gastrointestinal pathologies like ulcers, diarrhoea, gastritis and gastroenteritis (73–75). The potency of this natural product as a gastro-protective agent, as reported by Osato et al. (76), includes inhibition of Helicobacter pylori, the causative agent of gastritis and peptic ulcers. The protective and other health benefits of honey are due to its bioactive constituents interacting synergistically for positive effects, as proposed by Ajibola (6). This hypothesis of SMIF in honey has also been mentioned by other researchers. Eteraf-Oskouei and Najafi (1) concur with this proposition that most compounds in honey work together to produce a synergistic antioxidant effect. Vit and Huq (39) also lend credence to the synergism of the phytochemicals of natural honey in their 'Systematic reviews on interventions with honey in cancer.'

Mechanisms of Action

The mechanistic effects surrounding the various protective actions of natural honey have been investigated in several studies and have generated various probable explanations. These include the mechanisms suggested to be responsible for the antimicrobial, anti-inflammatory, antidiabetic, gastro-, hepato-, and cardioprotective (73,74), as well as anticancer (56,59,60) potentials of natural honey. The antimicrobial activity of honey entails several phenomena, as follows: first, honey draws water out of the surroundings, thereby dehydrating potentially infective organisms (37). Hence, little or no water is made available to promote yeast and bacterial growth by this singular action of honey. This hygroscopic action of honey, coupled with its high sugar content, hinders the growth of bacteria and other microbes (4,5,37). Second, natural honey has a low pH, which confers high natural acidity on honey to inhibit some pathogens. In addition, the production of hydrogen peroxide by glucose oxidase, an enzymatic constituent of honey, contributes to its antibacterial activity (22). Alvarez-Suarez et al. (2) and Olaitan et al. (3), as well as Vit and Huq (39), opine that the non-peroxide components of honey, such as the phytochemicals, oligosaccharides, organic acids, lysozyme, organic acids and other bioactive substances, also contribute to its mechanistic potential. These biochemical constituents are very important and helpful in the efficacy of honey as a broad-spectrum antibiotic and potent apitherapeutic agent.

The mechanisms of action of this natural product on diabetes and other metabolic diseases have been attributed to its influence on metabolic and neuronal activities within the gastro-intestinal tract (GIT). According to Al Swayeh and Ali (74), consumption of natural honey sensitizes the sensory nerves in the GIT, causing proprioception as a result of capsaicin. This mechanism entails some processes, such as ulcer index reduction, permeability of blood vessels in the GIT, and enhanced muscular activity of the stomach. The processes have been further explained by other authors through the documentation of the effect of dandelion honey consumption in ameliorating the ill effects of acidity in the stomach by about 50% (80). Other research shows that honey reduces the rate of passage of sugars in the GIT after intake of natural honey, unlike the rate observed following ingestion of a glucose/fructose mixture (81). This reduces the ulcerative effects and provides succour for diabetic patients, as well as alleviating the ill effects of diarrhoea. This mechanism can explain the observed effects of the medicinal uses of honey in infants and children to abate bacterial diarrhoea. Similarly, natural honey reduces the pathogenesis and duration of diarrhoea caused by viruses, contrary to results obtained from conventional therapy (72). Thus, natural honey is an excellent antidiabetic, antidiarrhoeal and antimicrobial agent.

Most of the protective and mechanistic effects of honey emanate from the antioxidant constituents of natural honey. One experimental pathological investigation by Ali (73), on rats with gastric lesions, suggested that the therapeutic effect of honey was due to its antioxidant constituents (2,39). According to Ali (73), natural honey enhances the non-protein sulfhydryl antioxidant capacity to ameliorate ethanol-induced ulcer lesions in rodents. Further establishment of the mechanism of honey as a chemotherapeutic agent was obtained by monitoring the concentration of endogenous antioxidant glutathione in N-ethylmaleimide (NEM)-damaged liver of animal models pretreated with Anzer honey in Ankara, Turkey (79). The results showed a reduction in the antioxidant concentration in proportion to the level of the damage, thereby confirming the importance of endogenous glutathione, enhanced by the antioxidant constituent of honey, as a gastro- and hepatoprotective agent. The hepatoprotection was suggested to be mediated through some processes of the non-protein sensory substance, sulfhydryl antioxidant.

The 'cure-all' effects of natural honey can partly be attributed to its hepatoprotective potential, as the liver is the chief metabolic site of the entire body. In one molecular study, honey produced by stingless bees from Ecuador (Meliponinae) prevented DNA damage, as shown by measured antioxidant capacity (77). Other authors also have significantly contributed to mechanistic insights into honey's action through its chemotherapy against the oxidative stress and cell death (apoptosis) caused experimentally by hepatic obstructive jaundice (78). Natural honey curtails the ill effects of bile duct ligation to preserve the ultrastructural anatomy of the liver. The conclusion can be drawn that the antioxidant constituents, anti-inflammatory activity, free radical scavenging capability, reduction in necrotized tissue and the provision of a rich energy source are among the more important mechanisms of honey's effects (3,36), including the cardioprotective effect (24).

In addition to the cyto- and organoprotective properties of natural honey, its anticancer potential has been established to be due to multifactorial processes. These mechanisms include the release of cytotoxic hydrogen peroxide and the scavenging of reactive oxygen species (55,57); inhibitory effects on the proliferation of cancer cells through programmed cell death, as shown with the intravenous administration of New Zealand manuka honey combined with chemotherapy on melanoma cells in animal model (59). The other is the well discussed inhibition of cyclooxygenase-2 by the synergistic phytochemical constituents of natural honey, such as phenols and flavonoids (2,4,11,39,48,58,61). An inhibitory mechanism of Malaysian tualang honey on experimental breast cancer cells was also proposed by Kadir and colleagues (56), while Fernandez-Cabezudo et al. (59) reported the mechanistic effects of New Zealand manuka honey on melanoma cells. The conclusions of these workers on their mechanistic insights into rodent cancer models align with the summary of Erejuwa et al. (60) from their very recent investigation into the development and progression of cancer. In their contributions while investigating the influence of honey and its constituents on cancer, Othman (52) and Kumazaki and co-workers (82) also concur with above suggested mechanisms of inhibition of cell proliferation and induction of apoptosis and cell cycle arrest.

Another mechanism of antimutagenic potential of honey is the antiproliferative action on cancer cells through apoptosis induced by Tualang, Gelam and Nenas honeys from Malaysia; Indian honey and other honey types (39). This mechanism involves the working of bioactive constituents of honey in synergy to produce the anticancer effects. The honey constituents identified with antimutagenicity are chrysin, galangin, pinobanksin, pinostrobin, pinocembrin, acacetin, caffeic acid, polyphenols, hesperetin, naringin, phenyl esters, quercetin, kaempferol and apigenin (39,58). These flavonoids interact uniquely and work in synergy to give the desired beneficial bioactive effects. The antiproliferative and apoptotic effects of the phenolic constituents of honey on target cells can be better explained as the product of interactions of these phenols and other antioxidants with membrane and intracellular receptors causing mitochondrial membrane depolarisation, as well as nitric oxide synthase inhibition. Vit and Huq (39) provide further explanation of the synergistic roles of the bioactive substances in curtailing cancer pathways as follows: hesperetin and naringin can inhibit nitric oxide (NO) production induced by lipoxygenase (LPS); quercetin, caffeic acid, chrysin and ellagic acid down-regulate the nuclear factor-κB to reduce the biosynthesis of iNOS and consequently of NO. In general, phenolics are antioxidants and antitumour agents, and as such act as specific free radical scavengers to block tumour necrosis factor (TNF-α)-mediated cytotoxicity. Their antioxidant activity plays a role in preventing free radical damage, a common occurrence in cancer cell growth (39).

The evidence for synergism of honey is further provided by the enhanced cancer suppression when chrysin is used in conjunction with a chemotherapeutic agent (61), when compared with the rate of inhibition of the metastatic growth of cancer cells observed when chrysin is used alone (83). In addition, the antitumour and antimutagenic activities of certain chemotherapeutic drugs, such as 5-fluorouracil and cyclophosphamide (39), and tamoxifen (50), are facilitated by honey administration. The synergistic growth-inhibitory effect of some cinnamic acid derivatives from the honey constituent, propolis, on human colon cancer cell lines occurs by both intrinsic and extrinsic apoptotic signalling transduction pathways (82). According to these authors, the synergy of these propolis derivatives (Artepilin C, Baccharin and Drupanin) enhances the decreased expression levels of the cancer target gene MAPK-Erk5, even in drug-resistant colon cancer cells. These studies provide supporting evidence for the synergistic action of honey. Hence, the summary of the mechanistic insights into the overall protective effects of honey portends the presence of a unique 'synergistic multiple ingredients factor' (6). The conclusion of Ajibola (6), derived from an extensive experimental study of the effects of South African monofloral honey on metabolism in growing rodents, aligns with the summary of Eteraf-Oskouei and Najafi (1). In their overview of the traditional and modern uses of natural honey in diseases, these authors also conclude that honey constituents work together in synergy to produce beneficial effects. The hypothesis of this unique factor, SMIF, has been supported by these various authors (1,39,50).

Conclusion

The oral and topical uses of honey as CAM show therapeutic promise, as honey improves functional body systems, reverses pathological conditions and gives enhanced health values. Natural honey contains antioxidants, phytochemicals and other bioactive substances that produce desired beneficial effects in almost all organs of the human and animal body. The different honey types show biochemical activities, adding value to honey's apitherapeutic potency and promoting natural honey as a choice therapeutic agent, even when conventional therapy appears ineffective. The superior efficacy of honey, coupled with its wide application in apitherapy, makes it a complementary and alternative medicine for most ailments, including cancer. The biological, physical and chemical properties derived from honey's constituents interact uniquely and work synergistically to bring forth the desired beneficial effects. Hence, the mechanistic insights into the overall protective effects of honey indicates the presence of a unique 'synergistic multiple ingredients factor'.

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Conflict of Interest

None

Funds

None

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References

1. Eteraf-Oskouei T, Najafi M. Traditional and modern uses of natural honey in human diseases: A review. *Iran J Basic Med Sci*. 2013; **16(6)**:731–742.

2. Alvarez-Suarez JM, Tulipani S, Diaz D, Estevez Y, Romandini S, Giampieri F, et al. Antioxidant and antimicrobial capacity of several monofloral Cuban honeys and their correlation with color, polyphenol content and other chemical compounds. *Food Chem Toxic*. 2010;**48(8–9)**:2490–2499. doi: 10.1016/j.fct.2010.06.021.

3. Olaitan PB, Adeleke EO, Ola OI. Honey: A reservoir for microorganisms and an inhibitory agent for microbes. *Afr Health Sci*. 2007;**7(3)**:159–165.

4. Rashed MN, Soltan ME. Major and trace elements in different types of Egyptian mono-floral and non-floral bee honeys. *J Food Compos Anal*. 2004; **17**:725–735.

5. Ajibola A, Chamunorwa JP, Erlwanger KH. Nutraceutical values of natural honey and its contribution to human health and wealth. *Nutr Metab (Lond)*. 2012;**9**:61. doi: 10.1186/1743-7075-9-61.

6. Ajibola A. *Effects of dietary supplementation with pure natural honey on metabolism in growing Sprague-Dawley rats* [(Phd thesis) Johannesburg, South Africa]: University of the Witwatersrand; 2013. wiredspace.wits.ac.za/jspui/bitstream/10539/14403/1/AJIBOLA's%20Thesis.pdf.

7. Al-Waili NS. Effects of daily consumption of honey solution on haematological indices and blood levels of minerals and enzymes in normal individuals. *J Med Food*. 2003;**6**:135–140.

8. Ajibola A, Idowu GO, Amballi AA, Oyefuga OH, Iquot IS. Improvement of some haematological parameters in albino rats with pure natural honey. *J Biol Sci Res*. 2007;**2(1)**:67–69.

9. Chepulis LM. The effects of honey compared with sucrose and a sugar-free diet on neutrophil phagocytosis and lymphocyte numbers after long-term feeding in rats. *J Compl Integrat Med*. 2007;**4(1)**:1–9.

10. Schley PD, Field CJ. The immune-enhancing effects of dietary fibres and prebiotics. *Brit J Nutr*. 2002;**87**:S221–S230. doi: 10.1079/BJN/2002541.

11. Schramm DD, Karim M, Schrader HR, Holt RR, Cardetti M, Keen CL. Honey with high levels of antioxidants can provide protection to healthy human subjects. *J Agric Food Chem*. 2003;**51(6)**:1732–1735. doi: 10.1021/jf025928k.

12. Al-Waili NS, Haq A. Effect of honey on antibody production against thymus-dependent and thymus-independent antigens in primary and secondary immune responses. *J Med Food*. 2004;**7(4)**:491–494. doi:10.1089/jmf.2004.7.491.

13. Atwa AA, AbuShahba RY, Mostafa M, Mohamed IH. Effect of honey in preventing gingivitis and dental caries in patients undergoing orthodontic treatment. *Saudi Dent J*. 2014;**26(3)**:108–114. doi: 10.1016/j.sdentj.2014.03.001.

14. Mohapatra DP, Thakur V, Brar SK. Antibacterial efficacy of raw and processed honey. *Biotech Res Int*. 2011:2011;**6**. doi: 10.4061/2011/917505.

15. English HK, Pack AR, Molan PC. The effects of manuka honey on plaque and gingivitis: A pilot study. *J Int Acad Periodont*. 2004;**6(2)**:63–67.

16. Steinberg D, Kaine G, Gedalia I. Antibacterial effect of propolis and honey on oral bacteria. *Am J Dent*. 1996;**9(6)**:236–239.

17. Ahmadi-Motamayel F, Hendi SS, Alikhani MY, Khamverdi Z. Antibacterial activity of honey on cariogenic bacteria. *J Dent (Tehran)*. 2013; **10(1)**: 10–15.

18. Imperato PJ, Traore A. Traditional beliefs about measles and its treatment among the Bambara of Mali. T*rop Geog Med*. 1969;**21(1)**:62–67.

19. Mahawar MM, Jaroli DP. Animals and their products utilized as medicines by the inhabitants surrounding the Ranthambhore National Park, India. *J Ethnobiol Ethnomed*. 2006;**2**:46. doi: 10.1186/1746-4269-2-46.

20. Emarah MH. A clinical study of the topical use of bee honey in the treatment of some occular diseases. *Bull Islamic Med*. 1982;**2**:422–425.

21. Salehi A, Jabarzare S, Neurmohamadi M, Kheiri S, Rafieian-Kopaei M. A double blind clinical trial on the efficacy of honey drop in vernal keratoconjunctivitis. *Evid Based Compl Altern Med*. 2014:**2014**;4. doi: 10.1155/2014/287540.

22. Molan P. Why honey is effective as a medicine. 1. Its use in modern medicine. *Bee Wrld*. 1999;**80**:79–92.

23. Busserolles J, Gueux E, Rock E, Mazur A, Rayssiquier Y. Substituting honey for refined carbohydrates protects rats from hypertriglyceridemic and prooxidative effects of fructose. *J Nutr*. 2002;**132(11)**:3379–3382.

24. Gharekhani A, Najafi M, Ghavimi H. Acute administration of natural honey protects isolated heart in normothermic ischemia. *Iran J Pharm Res*. 2012;**11(4)**:1275–1284.

25. Yaghoobi N, Al-Waili N, Ghayour-Mobarhan M, Parizadeh SM, Abasalti Z, Yaghoobi Z, et al. Natural honey and cardiovascular risk factors; effects on blood glucose, cholesterol, triacylglycerol, CRP, and body weight compared with sucrose. *Sci Wrld J*. 2008;**8**:463–469. doi: 10.1100/tsw.2008.64.

26. Earnest CP, Lancaster SL, Rasmussen CJ, Kerksick CM, Lucia A, Greenwood MC, et al. Low versus high glycemic index meals carbohydrate gel ingestion during simulated 64 km cycling time trial performance. *J Strength Cond Res*. 2004;**18(3)**:466–472.

27. Ajibola A, Chamunorwa JP, Erlwanger KH. Long-term dietary supplementation with natural honey does not predispose growing male rats to metabolic syndrome. *BMC Proceedings*. 2012;**6(S3)**:3. doi:10.1186/1753-6561-6-S3-P3.

28. Erejuwa OO, Sulaiman SA, Ab-Wahab MS, Sirajudeen KN, Salleh MS, Gurtu S. Honey supplementation in spontaneously hypertensive rats elicits antihypertensive effect via amelioration of renal oxidative stress. *Oxid Med Cell Longev*. 2012;**2012**:374037. doi: 10.1155/2012/374037.

29. Erejuwa OO, Sulaiman SA, Ab-Wahab MS, Sirajudeen KN, Salleh MS, Gurtu S. Differential responses to blood pressure and oxidative stress in streptozotocin-induced diabetic wistar-kyoto rats and spontaneously hypertensive rats: Effects of antioxidant (honey) treatment. *Int J Mol Sci*. 2011;**12(3)**:1888–1907. doi: 10.3390/ijms12031888.

30. Aluko EO, Olubobokun TH, Enobong IB, Atang DE. Comparative study of effect of honey on blood pressure and heart rate in healthy male and female subjects. *Br J Med Med Res*. 2013;**3(4)**:2214–2221.

31. Ajibola A, Chamunorwa JP, Erlwanger KH. Dietary supplementation with natural honey promotes growth and health of male and female rats compared to cane syrup. *Sci Res Essay*. 2013;**8(14)**:543–553. doi: 10.5897/SRE12.659.

32. Al-Waili NS. Natural honey lowers plasma glucose, C-reactive protein, homocysteine, and blood lipids in healthy, diabetic, and hyperlipidemic subjects: Comparison with dextrose and sucrose. *J Med Food*. 2004;**7**:100–107.

33. Erejuwa OO. The use of honey in diabetes mellitus: is it beneficial or detrimental? *Int J Endocrinol Metab*. 2012;**10(1)**:444–445. doi: 10.5812/ijem.3628.

34. Ford ES, Giles WH. A comparison of the prevalence of the metabolic syndrome using two proposed definitions. *Diabetes Care*. 2003;**26(3)**:575–581. doi: 10.2337/diacare.26.3.575.

35. Bahrami M, Ataie-Jafari A, Hosseini S, Foruzanfar MH, Rahmani M, Pajouhi M. Effects of natural honey consumption in diabetic patients: an 8-week randomized clinical trial. *Int J Food Sci Nutr*. 2009;**60(7)**:618–626. doi: 10.3109/09637480801990389.

36. Basualdo C, Sgroy VS, Finola MM, Marioli J. Comparison of the antibacterial activity of honey from different provenance against bacteria usually isolated from skin wounds. *Vet Microbiol*. 2007;**124**:375–381.

37. Küçük M, Kolayl S, Karaoğlu Ş, Ulusoy E, Baltacı C, Candan F. Biological activities and chemical composition of three honeys of different types from Anatolia. *Food Chem*. 2007;**100**:526–534.

38. Agbagwa OE, Frank-Peterside N. Effect of raw commercial honeys from Nigeria on selected pathogenic bacteria. *Afr J Microbiol Res*. 2010; **4(16)**:1801–1803.

39. Vit P, Huq F. 2013. Systematic reviews on interventions with honey in cancer. pp. 1-9. In Vit P & Roubik DW, eds. *Stingless bees process honey and pollen in cerumen pots*. Facultad de Farmacia y Bioanálisis, Universidad de Los Andes; Mérida, Venezuela. http://www.saber.ula.ve/handle/123456789/35292 ISBN: 978-980-11-1551-9.

40. Zainol MI, Mohd Yusoff K, Mohd Yusof MY. Antibacterial activity of selected Malaysian honey. *BMC Compl Altern Med*. 2013;**13**:129. doi: 10.1186/1472-6882-13-129.

41. Watanabe K, Rahmasari R, Matsunaga A, Haruyama T, Kobayashi N. Anti-influenza viral effects of honey in vitro: Potent high activity of manuka honey. *Arch Med Res*. 2014;**45(5)**:359–365. doi: 10.1016/j.arcmed.2014.05.006.

42. Ajibola A. *Physiological effects of natural honey on wounds in animals*. 1st ed. S. Lynch (KG, Germany): LAP; 2014.

43. Israili ZH. Antimicrobial properties of honey. *Am J Ther*. 2014;**21(4)**:304–323. doi: 10.1097/MJT.0b013e318293b09b.

44. Sajid M, Azim MK. Characterization of the nematicidal activity of natural honey. *J Agric Food Chem*. 2012;**60(30)**:7428–7434. doi: 10.1021/jf301653n.

45. Ajibola AA. *Honey in the post-surgical wound management in goats* [DVM dissertation (Ibadan)]:, Nigeria: University of Ibadan; 1995.

46. Oryan A, Zaker R. Effects of topical application of honey on cutaneous wound healing in rabbits. *Zentralb Veterinarmed A*. 1998;**45(3)**:181–188.

47. Efem SEE. Clinical observations on the wound healing properties of honey. *Br J Surg*. 1988;**75(7)**:679–681.

48. Chua LS, Abdul-Rahaman NL, Sarmidi MR, Aziz R. Multi-elemental composition and physical properties of honey samples from Malaysia. *Food Chem*. 2012;**135(3)**:880–887. doi: 10.1016/j.foodchem.2012.05.106.

49. Hussein SZ, Mohd Yusoff K, Makpol S, Mohd Yusof YA. Gelam honey inhibits the production of proinflammatory, mediators NO, PGE2, TNF-α and IL-6 in carrageenan-induced acute Paw edema in rats. *Evid Based Compl Altern Med*. 2012;**2012**:13. doi: 10.1155/2012/109636.

50. Yaacob NS, Nengsih A, Norazmi MN. Tualang honey promotes apoptotic cell death induced by tamoxifen in breast cancer cell lines. *Evid Based Compl Altern Med*. 2013;**2013**:9. doi: 10.1155/2013/989841.

51. Weissenstein A, Luchter E, Bittmann S. Medical honey and its role in paediatric patients. *Br J Nurs*. 2014;**23(6)**:S30–S34.

52. Othman NH. Honey and cancer: Sustainable inverse relationship particularly for developing nations: A review. *Evid Based Compl Altern Med*. 2012;**2012**:10. doi: 10.1155/2012/410406.

53. Sewllam T, Miyanaga N, Onozawa M, Hattori K, Kawari K, Shimazui T, et al. Antineoplastic activity of honey in an experimental bladder cancer implantation model: In vivo and in vitro studies. *Int J Urol*. 2003;**10**:213–219.

54. Abdel Aziz A, Rady HM, Amer MA, Kiwan HS. Effect of Some honey bee extracts on the proliferation, proteolytic and gelatinolytic activities of the hepatocellular carcinoma Hepg2 cell line. *Aus J Basic Appl Sci*. 2009;**3(3)**:2754–2769.

55. Attia WY, Gabry MS, El-Shaikh KA, Othman GA. The anti-tumor effect of bee honey in Ehrlich ascite tumor model of mice is coincided with stimulation of the immune cells. *Egypt J Immunol*. 2008;**15(2)**:169–183.

56. Kadir EA, Sulaiman SA, Yahya NK, Othman NH. Inhibitory effects of tualang honey on experimental breast cancer in rats: A preliminary study. *Asian Pac J Cancer Prev*. 2013;**14(4)**:2249–2254.

57. Al-Jabri A, Al Mahrooqi Z, Nzeako B, Nsanze H. Inhibition effect of honey on the adherence of Salmonella to intestinal epithelial cells in vitro. *Int J Food Microbiol*. 2005;**103(3)**:347–351.

58. Michaluart P, Masferrer JL, Carothers AM, Subbaramaiah K, Zweifel BS, Koboldt C. Inhibitory effects of caffeic acid, phenethyl ester on the activity and expression of cyclooxygenase-2 in human oral epithelial cells and in a rat model of inflammation. *Cancer Res*. 1999;**59(10)**:2347–2352.

59. Fernandez-Cabezudo MJ, El-Kharrag R, Torab F, Bashir G, George GA, El-Taji H, et al. Intravenous administration of manuka honey inhibits tumor growth and improves host survival when used in combination with chemotherapy in a melanoma mouse model. *PLoS One*. 2013;**8(2)**:e55993. doi: 10.1371/journal.pone.0055993.

60. Erejuwa OO, Sulaiman SA, Wahab MS. Effects of honey and its mechanisms of action on the development and progression of cancer. *Molecules*. 2014;**19(2)**: 2497–2522. doi:10.3390/molecules19022497.

61. Gao AM, Ke ZP, Shi F, Sun GC, Chen H. Chrysin enhances sensitivity of BEL-7402/ADM cells to doxorubicin by suppressing PI3K/Akt/Nrf2 and ERK/Nrf2 pathway. *Chemico-Biological Interactions*. 2013;**206(1)**:100–108. doi: 10.1016/j.cbi.2013.08.008.

62. Bianchi EM. Honey: Its importance in children's nutrition. *Am Bee J*. 1977;**117**:733.

63. Ramenghi LA, Amerio G, Sabatino G. Honey, a palatable substance for infants: from De Rerum Natura to evidence-based medicine. Eur J Paed. 2001; 160:677–678.

64. Chepulis LM, Starkey NJ, Waas JR, Molan PC. The effects of long-term honey, sucrose or sugar-free diets on memory and anxiety in rats. *Physiol Behav*. 2009;**97(3–4)**:359–368. doi: 10.1016/j.physbeh.2009.03.001.

65. Rivero-Urgell M, Santamaria-Orleans A. Oligosaccharides: Application in infant food (review). *Early Hum Dev*. 2001;**65**:43–52.

66. Al-Waili NS. Clinical and mycological benefits of topical application of honey, olive oil and beeswax in diaper dermatitis. *Clin Microbiol Inf*. 2005;**11(2)**:160–163.

67. Heppermann B. Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. Bet 3. Honey for the symptomatic relief of cough in children with upper respiratory tract infections. *Emerg Med J*. 2009;**26(7)**:522–523.

68. Meda A, Lamien EC, Millogo J, Romito M, Nacoulma OG. Ethnopharmacological communication therapeutic uses of honey and honeybee larvae in central Burkina Faso. *J Ethnopharm*. 2004;**95**:103–107.

69. Zaid SM, Sulaiman SA, Sirajudeen NM, Othman NH. The effects of tualang honey on female reproductive organs, tibia bone and hormonal profile in ovariectomised rats – animal model for menopause. *BMC Compl Altern Med*. 2010;**10**:82. doi: 10.1186/1472-6882-10-82.

70. Makpol S, Ahmad TAFT, Jubri Z, Rajab NF, Yusof N, Yusof YAM. Gelam honey acting as a radioprotectant agent in gamma-irradiated human diploid fibroblasts. *J Med Plants Res*. 2012;**6**.

71. Salem SN. Honey regimen in gastrointestinal disorders. *Bull Islamic Med*. 1981;**1**:358–362.

72. Haffejee IE, Moosa A. Honey in the treatment of infantile gastroenteritis. *Br Med J*. 1985;**290**:1866–1867.

73. Ali ATMM. Natural honey exerts its protective effects against ethanol-induced gastric lesions in rats by preventing depletion of glandular non protein sulfhydryls. *Trop Gastroenterol*. 1995;**16**:18–26.

74. Al Swayeh OA, Ali ATMM. Effect of ablation of capsaicin sensitive neurons on gastric protection by honey and sucralfate. *Hepato-Gastroenterol,* 1998;**45(19)**: 297–302.

75. Gharzouli K, Amira S, Gharzouli A, Khennouf S. Gastro protective effects of honey and glucose-fructose-sucrose-maltose mixture against ethanol-, indomethacin-, and acidified aspirin induced lesions in the rat. *Exp Toxic Path*. 2002;**54(3)**:217–221. doi: 10.1078/0940-2993-00255.

76. Osato MS, Reddy SG, Graham DY. Osmotic effect of honey on growth and viability of Helicobacter pylori. *Dig Dis Sci*. 1999;**44(3)**:462–464.

77. Guerrini A, Bruni R, Maietti S, Poli F, Rossi D, Paganetto G. Ecuadorian stingless bee (Meliponinae) honey: A chemical and functional profile of an ancient health product. *Food Chem*. 2009;**114(4)**:1413–1420. doi: 10.1016/j.foodchem.2008.11.023.

78. Kilicoglu B, Gencay C, Kismet K, Kilicoglu S, Erguder I, Erel S, et al. The ultrastructural research of liver in experimental obstructive jaundice and effect of honey. *Am J Surg*. 2008;**195(2)**:249–256. doi: 10.1016/j.amjsurg.2007.04.011.

79. Korkmaz A, Kolankaya D. Anzer honey prevents N-ethyl maleimide-induced liver damage in rats. *Exp Toxic Path*. 2009;**61(4)**:333–337. doi: 10.1016/j.etp.2008.07.005.

80. Baltuskevicius A, Laiskonis A, Vysniauskiene D, Ceksteryte V, Racys J. Use of different kinds of honey for hepatitis A treatment and for reduction of increased acidity of gastric juice. *Zemdirbyste Mokslo Darbai*. 2001;**76**:173–180.

81. Pokorn D, Vukmirovic V. *Velocity of gastric emptying of saccharides after administering honey and pure invert sugar*. III International Apitherapy, Symposium 11–15 September 1978, Portoroz, Yougoslava. Bukarest: Apimondia, pp. 277–279.

82. Kumazaki M, Shinohara H, Taniguchi K, Yamada N, Ohta S, Ichihara K, et al. Propolis cinnamic acid derivatives induce apoptosis through both extrinsic and intrinsic apoptosis signaling pathways and modulate of miRNA expression. *Phytomedicine*. 2014;**21(8–9)**:1070–1077.

83. Lirdprapamongkol K, Sakurai H, Abdelhamed S, Yokoyama S, Maruyama T, Athikomkulchai S, et al. A flavonoid chrysin suppresses hypoxic survival and metastatic growth of mouse breast cancer cells. *Oncol Rep*. 2013;**30(5)**:2357–2364. doi: 10.3892/or.2013.2667.