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From entomophagy to entomotherapy

Panuwan Chantawannakul[1, 2]

[1]*Department of Biology, Faculty of Science, Chiang Mai University, 50200, Thailand,* [2]*Environmental Science Research Center (ESRC), Faculty of Science, Chiang Mai University, Chiang Mai, 50200, Thailand*

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1. ABSTRACT

Insects are the most diverse group of organisms with one million species that account for 80% of the world's species. Particularly in East Asia, edible insects serve as a source of nutrients. Among these, silkworms and honeybees are well-known sources of food and have been used for the treatment of a large number of human disorders. This review focuses on the utilization of insects as food (entomophagy) as well as for their pharmacological properties (entomotherapy) that have been tested *in vitro* as well as *in vivo.*

2. INTRODUCTION

Insects account for 80% of the world's species and are the most diverse group of organisms. With one million species that fall in 24 orders, Coleoptera, Diptera, Hymenoptera, and Lepidoptera predominate and more than 2,100 different species are edible (1). "Entomophagy" is common in many cultures, particularly in East Asia. Edible insects are a healthy and sustainable source of high-quality protein which are rich in amino acids, fatty acids, and various micronutrients, such as the minerals copper, iron, magnesium, manganese, phosphorous, selenium, and zinc as well as the vitamins riboflavin, biotin, and, in some cases, folic acid (2-3).

"Entomotherapy" is defined as preventative or therapeutic use of insects and insect-derived products (4-5). Honey, royal jelly, propolis, bee pollen, bee wax, and bee venom from honeybees have been used since ancient times (6), and are potentially beneficial to humans due to their biomedical properties. Honeybee products are also regarded as a potential source of natural antioxidants due to their heterogenous phenolic, polyphenol content and flavonoid constituents that varies based on floral sources as well as the processing, handling, and storage of the product (7-8). Although, insects and their products is regarded to be valuable resources as medicine, such uses require further work to substantiate the value of these as medicine.

In this review, the history, and modern use of edible insects and products, particularly honey products, are summarized in addition to their potential use in preventive medicine based on recent scientific findings.

3. EDIBLE INSECTS AND BEE PRODUCTS

3.1. Traditional use and ethnobiological records

Insects have been as traditional medicines (9). In the Roman empire, the use of insects for medical purposes was recorded in *Naturalis historiae* (4). Most of the insects used were from the Orders Coleoptera, Hymemoptera, Orthoptera, and Hemiptera, and were employed in the treatment of disorders of the skin, digestive, respiratory, reproductive, circulatory, nervous, neuromuscular, and immunological systems as well as other diseases. Ethnobiological data have been recorded in many parts of the world. For example, in Europe, the oil extracted from the May beetle larvae (*Melolontha vulgaris*) was applied to wounds (10). At least 50 and 210 insect species in Brazil and Mexico, respectively, have been reported for use for medical purposes (11). In China, the medical use of crude drugs derived from insects was reported in the "herbal" *Jingshi Zhenglei Daguang Bencao* (A.D.1108) (12). Many insects have been recorded in traditional medicine to exhibit anti-cancer activities. These uses include use of *Bombyx mori* and *Apis mellifera* for lung cancer, *Tabanus mandarinus* (Chinese horse fly) and *Gryllotalpa unispina* (giant mole cricket) for liver cancer, *Cyclopelta parva* (dadap bug) for esophageal cancer, *Hueckys sanguea* (red lady bug) for skin cancer, *Blatta orientalis* (oriental cockroach) for renal cancer, and *Cryptotympana japonensis* (black cicada) for thyroid cancer (13).

Members of Coleoptera (e.g. the Palm beetle (*Pachymerus nucleorum*), scarab (*Strategus aloeus*), scarab (*Megasona acaeon*), and Blister beetle (*Lytta versicatoria*)) have been used for treatment of earaches, as aphrodisiacs, and to treat urinary disorders (14-17). Hemiptera (e.g. *Hyechys sanguinea*) have been used to treat migraine and ear infections (18). Orthoptera (e.g. the grasshopper (*Tropidacris* sp.), crickets (*Brachytrupes* sp.), and mole cricket (*Gryllus assimilis*)) have been used to treat skin diseases, defective mental development, and urine retention (4, 17, 19).

In Hymenoptera, wasps, stingless bees, and honey bees have been used as traditional medicine. One of the most well-known insects in this group are bees, which have also been used extensively in folk medicine. In Nepal, bee pollen has been used as a tonic for the elderly (5). Propolis, a plant resin collected by honey bees, is also used as an antiseptic and anti-inflammatory agent in the treatment of wounds and burns. Propolis is a resinous material that bees collect from plant exudates. Bees use these materials to block holes and cracks, as glue to repair combs, make the entrance to hives easier to defend by narrowing the hive entrance, and to embalm dead organisms inside their hives. Propolis has been used in various pharmaceutical products due to its therapeutic properties, such as antimicrobial and antioxidant activities, in both folk and modern medicine used both externally and internally. The hives of stingless bees and European honey bees (*A. mellifera*) are good sources of propolis (6).

Royal jelly, a bee larval food provided by young nurse bees, is used to treat asthma, anorexia, gastrointestinal ulcers, arteriosclerosis, anemia, hypotension or hypertension, anorexia, gastrointestinal ulcers, and postmenopausal symptoms (9, 20). Moreover, the venom of honeybees has been used to ameliorate the symptoms of inflammatory and autoimmune disorders, including multiple sclerosis (MS), arthritis, rheumatism, chronic pain, neurological diseases, asthma, and dermatological conditions (21). Bee venom was used in ancient Greece for the anti-arthritic properties of apitoxin, which enhances blood flow to ischemic regions. The application of bee stings in treatment of human disease is known as "apipuncture". Similarly, other insect venoms such as ant venom and wasp venom have been recorded for medicinal use such as treatment of arthritis (22-23).

The order Orthoptera has also been traditionally used for treatment of human disorders, for example, in Africa, powder of dried grasshoppers has been used to alleviate the pain of severe headaches (24). The mole cricket, *Gryllotalpa africana*, has been used in Korean traditional medicine for retention of urine, urolithiasis, edema, lymphangitis and furuncles (25). In Latin America, the

Table 1. Examples of the nutritional composition and energy content of edible insects

Nutrition	Common and scientific name of insects									
	House cricket (*Gryllus bimaculatus*)	**Short tail cricket** (*Diestrammena marmorata*)	**Coconut rhinoceros beetle** (*Oryctes rhinoceros*)	**Bombay locust** (*Patanga succincta*)	**Paper wasps** (*Vespa affinis*)	**Giant water bug** (*Lethocerus indicus*)	**Silkworm pupae** (*Bombyx mori*)	**Bamboo worm** (*Omphisa fuscidentalis*)	**Giant honey bee** (*Apis dorsata*)	**Subterranean ants** *Carebara castanea*)
Protein (%)	75.01	69.31	65.33	74.92	49.36	38.99	53.64	33.01	41.26	41.72
Fat (%)	19.29	17.67	17.73	12.7	20.15	28.33	32.7	56.89	30.84	53.36
Fiber (%)	9.71	17.93	25.89	15.19	2.12	16.3	3.27	9.28	1.9	16.7
Ash (%)	5.04	3.67	3.97	3.43	3.83	23.7	5.51	1.76	3.82	2.49
Moisture content (%)	2.04	3.6	4.43	4.33	6.89	3.24	9.33	2.09	9.25	2.24
Energy (cal/g)	5853	5828	5913	5416	5339	4944	6337	7783	5932	7561

* Nutritional composition values were obtained from studied edible insect samples collected in Thailand

house cricket, *Acheta domesticus*, was used for the treatment of scabies, asthma, eczema, lithiasis, earache, oliguresis, rheumatism, urine retention, urinary incontinence and ophthalmological problems (26).

Some insects of the order Hemiptera, are known to have medicinal values. For example, the stinkbug (*Encosternum delegorguei*) in Zimbabwe and South Africa decrease hypertension and have been used to cure asthma and heart diseases (27). The edible Chinese stinkbug, *Aspongopus chinensis*, has also been employed to relieve pain, and to treat nephropathy and kidney disease in China (28). The bedbug (*Cimex lectularius* and *C. hemipterus*) was employed in the treatment of urinary disorders, epilepsy, piles, alopecia, headache, constipation, ulcer, arthritis, hair loss, snake bites and to stop somnolence (29).

Besides the four orders described above, the silkworm (*B. mori* L., 1758) which is a member of Lepidoptera, has been used in Chinese traditional medicine for at least three thousand years (13) and the larvae of certain flies have been employed for centuries as beneficial agents to heal infected wounds (30).

Even though in some cases, the scientific validity of use has been established, nevertheless, the pharmacological significance of insects, particularly the efficacy of insect-based medicines, has been questioned. Yet, there is increasing interest in demonstrating the scientific validity of medical properties of insects and to prove the pharmaceutical properties of natural products in mice, rats, and, recently, in fruit flies (31).

3.2. Nutritional factors

More than 50 species of known insects are edible. The most common insects consumed in Asian countries are locusts, beetles, crickets, giant water bugs, cicada, ant eggs, silkworm pupae, and bamboo caterpillars. The global population is expected to reach 9 billion in 2050; therefore, a safe, clean, and nutritious food will be urgently needed. Insects are promoted as alternative sustainable source of human food and animal feed worldwide. Insect farming is regarded as environmentally friendly due to their less waste production, less land and water requirement, smaller energy input, and low greenhouse gas emissions, resulting in a lower environmental footprint. We previously reported that these insects are a good source of protein and fiber (Table 1). Most insects contain approximately 60% protein (32) including essential amino acids, such as isoleucine, leucine, lysine, methionine, and phenylalanine, which are suitable for human consumption (Table 2). Insects, therefore, have been proposed as a new source of alternative protein in the future. Insects are also known to be a good source of lipids, particularly in their larval and nymphal stages. Our preliminary results of a

Table 2. Amino acid contents of edible insects

Amino acids	Common and scientific name of insects									
	House cricket (*Gryllus bimaculatus*)	**Short tail cricket** (*Diestrammena marmorata*)	**Coconut rhinoceros beetle** (*Oryctes rhinoceros*)	**Bombay locust** (*Patanga succincta*)	**Paper wasps** (*Vespa affinis*)	**Giant water bug** (*Lethocerus indicus*)	**Silkworm pupae** (*Bombyx mori*)	**Bamboo worm** (*Omphisa fuscidentalis*)	**Giant honey bee** (*Apis dorsata*)	**Subterranean ants** *Carebara castanea*)
Essential Amino acids(mg/g)										
Isoleucine	2.892	3.205	6.036	4.814	2.19	6.437	3.946	4.718	2.45	3.308
Leucine	4.954	4.65	6.098	5.22	12.89	6.899	4.879	5.258	15.97	3.987
Lysine	10.32	3.54	12.156	1.945	8.41	6.512	8.844	4.013	5.06	6.923
Methionine	0.698	1.243	1.38	0.769	4.16	1.355	1.35	1.798	3.95	1.037
Phenylalanine	3.366	5.611	7.856	5.381	6.99	8.076	4.264	15.953	8.31	4.111
Tyrosine	1.105	2.23	6.007	5.293	4.74	6.074	2.363	6.008	3.01	1.867
Total aromatic a.a.[1]	**4.471**	**7.841**	**13.863**	**10.674**	**11.73**	**14.15**	**6.627**	**21.961**	**11.32**	**5.978**
Threonine	16.386	4.663	6.648	4.84	1.39	5.456	5.928	4.947	1.32	2.911
Valine	5.081	2.451	4.155	2.606	13.86	7.42	2.632	3.336	7.05	1.688
Histidine	0.912	3.901	1.928	1.479	4.46	2.353	5.005	1.647	6.38	1.129
Total essential a.a.	**45.714**	**31.494**	**52.264**	**32.347**	**59.09**	**50.582**	**39.211**	**47.678**	**53.5**	**26.961**
Non-essential Amino acids(mg/g)										
Aspartic acid	Nd.	12.512	23.659	13.002	8.35	6.151	Nd.	19.567	5.55	3.717
Serine	4.142	4.273	3.979	4.088	11.68	5.469	5.293	5.733	7.66	2.797
Glutamic acid	0.552	0.659	3.22	0.743	17.21	0.976	1.783	2.098	11.61	Nd.
Proline	9.444	7.259	14.512	15.148	5.32	6.7	8.928	11.485	6.48	17.043
Glycine	17.694	6.662	9.497	6.915	3.52	7.794	8.469	7.067	2.32	4.158
Alanine	7.87	6.049	12.093	12.29	10.48	5.583	7.44	9.571	12.79	14.202
Arginine	9.986	4.663	6.648	4.84	3.59	5.456	5.928	4.947	2.39	2.911

[1]Phenylalanine + tyrosine, a.a.= amino acids, Nd. Not detected, * Amino acid contents were obtained from studied edible insect samples collected in Thailand

nutritional study of edible insect in Thailand found that the Bamboo worm (*Omphisa fuscidentalis*) consists of 56.89% lipids and provides 778 kcal/100 g (Table 1). Insect lipids are composed of polyunsaturated fatty acids, of which major essential fatty acids are linoleic and α-linolenic acids. In addition, insects contain other nutritive elements such as vitamins and mineral (33).

The insect farming industry has been promoted as an alternative sustainable food source due to an increasing demand of consumers in recent years. The production of honey from *A. mellifera* and *A. cerana* for human consumption as well as the silk natural textile production from silkworm are allowed to be the most striking achievement of insect industries. These insects may be domesticated; however, cricket farming has recently become more popular, particularly in European markets. In the European Union, insects that may be used as food are the yellow mealworm (*Tenebrio molitor*), lesser mealworm (*Alphitobius diaperinus*), tropical banded cricket (*G. sigillatus*), and migratory locust (*Locusta migratoria*) (32, 34). New legislation in Europe on insect food has been in effect since January 2018 and the scientific evidence are required in terms of food safety (e.g. microbial contamination). In the US and Canada, edible insects are regarded as food, and, thus, have to comply with food standards. Since edible insects have traditionally been consumed in Asia, they are widely sold in markets.

3.3. Pharmacological properties for preventive medicine

Since honey bees and silkworms have contributed to the development of an industry that

Table 3. Examples of arthropod-derived chemicals and products mentioned as pharmaceutical and medical resources

Taxon	Common name	Molecules/Products	Pharmaceutical/Medical action	References
Amblyomma americanum	Lone star tick	Calreticulin	Inhibition of angiogenesis	(90)
		Amblyomin-X	Induction of tumor cell death	(91)
Antheraea mylitta	Tasar silkworm	Peptide fraction II	Anti-bacterial (MDR Gram-negative bacteria)	(92)
		Sericin (from cocoon)	Anti-oxidant	(93)
Blaberus giganteus	Cockroach	Chitin film	Anti-bacterial	(94)
Bombyx mori	Silk worm	35-kDa protein	hepatoprotection, antioxidant	(95)
		Silk (cocoons), Cecropin B	Anti-microbial	(96)
Calliphora vicina	Blow flies and bottle flies	Alloferon	Antiviral, Anti-tumor (in rats)	(97)
Calosoma sycophanta	Forest caterpillar hunter	Pygidial gland secretion	Anti-microbial	(98)
Catharsius molossus	Dung beetle	Glycosaminoglycan	Anti-cancer, Anti-inflammatory	(99)
Chrysomya megacephala	Oriental latrine fly	Larvae Excretions-secretions	Anti-bacterial (*E. coli*)	(100)
Clanis bilineata	Two-lined velvet hawkmoth	Chitosan of larval skin, extract oil	Anti-oxidant	(101, 102)
Curculio caryae	Pecan weevil	Pupal cell	Anti-fungal	(103)
Eupolyphaga sinensis	Chinese medicinal cockroach	EPS72 (protein)	Anti-human lung cancer	(104)
Galleria mellonella	Greater wax moth (larva)	Apolipophorin III	Anti-bacterial	(105)
Gryllodes sigillatus	Tropical house cricket	Peptides	Antioxidant, Anti-inflammatory	(106)
Haemaphysalis longicornis longicornis	Bush tick	Troponin I-like	Inhibition of angiogenesis of vascular endothelial cells proliferation and induction of apoptosis	(107)
		Haemagin	Disruption of angiogenesis wound healing	(108)
Hermetia illucens	Black soldier fly	Trx-stomoxynZH1	Anti-microbial	(109)
Hydropsyche angustipennis	Caddisfly	Silk (cocoons)	Biomaterials in medicine	(110)
Ixodes scapularis	Tick	sialostatin L	Anti-inflammatory	(111)
		Salivary gland extracts	Inhibition of endothelial cell proliferation and angiogenesis	(112)
		Ixolaris	Anti-tumor	(113)
Ixodes persulcatus	Taiga tick	Persulcatusin	Anti-bacterial	(114)
Musca domestica	Housefly	Protein-enriched fraction/extracts (PE)	Anti-pro-inflammation	(115)
		Crude extract	Antitumor activity	(116)
		Cecropin	Apoptosis-inducing activity	(117)
Myrmecia gulosa	Australian bull ant	Secretions	Anti-microbial	(118)

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Table 3. Contd...

Taxon	Common name	Molecules/Products	Pharmaceutical/Medical action	References
Nasonia vitripennis	Jewel wasp	Venom	Anti-inflammatory (inhibits NF-κB signaling in mammalian cells)	(119)
Polyrhachis dives	Chinese black ants	Non-peptide nitrogen compounds	Anti-inflammatory	(120)
Sarcophaga bullata	Grey flesh fly	Lectin	Cytotoxic effects	(121)
Spodoptera litura	Cutworm	Cecropin-like peptides	Anti-bacterial	(122)
Tabanus bovinus	Pale giant horse-fly	Crude whole body extracts	Cytotoxic effects, Anti-angiogenic activities	(123, 124)
Tenebrio molitor	Mealworm beetle	Peptides	Antioxidant, Anti-inflammatory	(106)
Tetramorium bicarinatum	Guinea ant	Bicarinalin	Anti-microbial	(125)
Apis mellifera	Honey bee	Honey and royal jelly	Wound healing	(126-129)
		Royal jelly	Anti-bacterial, Anti-angiogenesis, Anti-allergic	(51, 130-132)
		Propolis	Killing human pancreatic cancer cells, Localized plaque psoriasis treatment.	(133, 134)
Apis mellifera, Apis cerana	Honey bee	Venom	Anti-tumor (in lung and cervix cancer cells), Inhibition of arthritic inflammation and bone changes (in rat), Skin wrinkle improvements, Anti-bacterial	(135-139)
Apis mellifera, Vespa sp.	Honey bee, Wasp	Venom peptide (Melittin)	Anti-HIV, Anti-bacterial, Anti-cancer cells, Anti-inflammatory	(140-144)
		Venom peptide (Apamin)	Anti-cancer, Treatment of Parkinson's disease (in rats)	(58, 145)
Vespa sp.	Wasp	Venom peptide (Mastoparan)	Antimicrobial, Anti-cancer	(146, 147)

uses insects to produce food, more scientific information has been accumulated for them than for other insect species. Edible insects with their experimentally demonstrated pharmacological properties are listed in Table 3. Their pharmacological activities, including antioxidant, antimicrobial, anti-cancer, and anti-inflammatory effects, have been examined in various experiments; for example, silk protein from silkworms has been shown to possess anti-microbial properties, while peptides from the tropical house cricket exert both antioxidant and anti-inflammatory effects. The bush cricket (*Brachytrupes orientalis*) is a popular edible insect in North East India and its extract exhibits antioxidant activities (35). Peptides of the wax moth (*Galleria mellonela*), yellow mealworm (*T. molitor*), and silkworm (*Bombyx mori*) were shown to inhibit angiotensin-converting enzyme (ACE) activity *in vitro*, causing blood vessels to constrict (36). Hence, these edible insects may be a source of health-promoting food for the treatment of cardiovascular diseases.

Honey, the most consumed product derived from insects, contains many active constituents and antioxidants, such as polyphenols (37). Polyphenols are phytochemicals, a generic form for the several thousands of plant-based molecules with antioxidant activities. Important honey polyphenols, such as kaempferol, quercetin, galangin, chrysin, gallic acid, ellagic acid, benzoic acid, and caffeic acid, are derived from floral sources (38). Honey phenols exhibit many biological activities that include antibacterial and anti-inflammatory activities as well as antioxidative stress activity. They have also been shown to promote wound healing and prevent gastric ulcers. The antimicrobial properties of honey are derived from hydrogen peroxide produced by glucose oxidase, an enzyme secreted from the hypopharyngeal gland of honey bees and a non-peroxide substance derived from plants. For example, methylglyoxal from Manuka flowers has been shown to contribute to the non-peroxide properties of Manuka honey. Honey is used to promote wound healing based on its osmotic properties, moisturize wounds, reduce maceration, and inhibit fibrin-adhering eschar to wounds that may impair tissue repair (39). Honey is also used to treat infectious diseases, skin conditions, gastrointestinal disorders, and allergic rhinitis. In patients with gastroenteritis, honey (50 ml/l electrolyte-glucose solution) safely reduced the duration of diarrhea by two days from that with a standard solution without honey (40). The chemical and biomedical properties of honey are influenced by plant sources. In Thailand, various types of honey are produced and consumed, such as longan, coffee, lychee, sunflower, and wild honey. Pattamayutanon *et al.* (41) reported that coffee honey produced by *A. cerana* exhibited strong antioxidant activity (IC_{50} = 1.788 ± 0.329 mg/mL). It had the lowest IC50, reflecting its strong free-radical reduction activity, and the highest phenolic (1308.62 ± 27.83 mgGAE/kg) and flavonoid contents (0.152 ± 0.015 mgQE/g). The volatiles from coffee honey produced by *A. cerana* are 2-furanmethanol, butyryl lactone, phenylmethanol, anisaldehyde, anise alcohol, and 3,4,5-trimethyl-phenol. Besides their influence on the aroma of honey, the type and proportion of volatiles in honey affect its therapeutic properties, including antioxidant, antibacterial, and even immunomodulatory activities (42).

Propolis is composed of pharmacologically active molecules, such as polyphenols, sesquiterpene quinones, coumarins, steroids, amino acids, and inorganic compounds. It exhibits antimicrobial activities against various microorganisms, including bacteria, protozoa, fungi, and viruses. The presence of polyphenols in propolis contributes to its pharmacological and biological properties. Brazil propolis is well known because it is rich in flavonoids, prenylated derivatives of p-coumaric acids, lignans, and terpenoids (43). Propolis has also been reported to suppress cancer cell growth (44-46). *Tetragonula laviceps* is one of the stingless bee species that is commonly kept for commercial purposes in Thailand and South East Asia. Based on taxonomic markers, *T. laeviceps* propolis exhibited the highest antimicrobial activity and is composed of prenylated xanthones (e.g. α-mangostin, mangostanin, and ϒ-mangostin), which have been identified as major secondary metabolites of mangosteen (*Garcinia magostana*), a pericarp found in India, Myanmar, Malaysia, the Philippines, Sri Lanka, and Thailand (47). The antibacterial activity of *T. laeviceps* against *Staphylococcus epidermidis*, a skin pathogen, confirmed its use in traditional medicine. *Tetrigona melanoleuca* propolis contains dammar, a tri-terpenic resin produced by trees in the family Dipterocarpaceae. Dammar exhibits antiviral activity and is a protective agent against low-density lipoprotein oxidation (48).

Royal jelly, a larval food of honey bees, is rich in nutrients and biological compounds, such as proteins, lipids, and vitamins. The main biologically active compound is 10-hydroxy-trans-2-decenoic acid (10-HDA), which has been reported to exhibit anticancer activity (49). Antimicrobial peptides, such as royalactin and royalisin, are also present in royal jelly (50, 51).

Bee venom contains immunoreactive and neuroactive peptides, enzymes, glucose, fructose, and water (52). Melittin, a major component of bee venom peptides possesses anti-inflammatory, antibacterial, and antifungal properties and also exerts cytotoxic effects against cancer cells (53). Other peptides in bee venom (apamin, adolapin, mast cell degranulation peptide, and phospholipase A2) also possess anti-inflammatory properties (54-57). Hyaluronidase in bee venom has been shown to increase capillary permeability (58). When eight different types of cancer cell lines were treated with bee venom *in vitro*, the findings obtained showed dose-dependent growth inhibition in all cell lines, with the highest rate of cell death being observed in the HEPG2 (liver cancer), A549 (lung cancer), and HEP-2C (larynx cancer) cell lines, and the lowest in the HCT116 cell line (colon cancer) (59).

3.4. From lab mice to fruit fly models

Even though some of the information on the bioactivity of edible insects and their products are currently available, the effects of edible insect peptides and their products on small animals need to continue being investigated for further development (34). Honey bee products are the most studied insect products in animal models. Besides *in vitro* research on antimicrobial and antioxidant activities, Malaysian Tualang honey collected from the giant honey bee (*Apis dorsata*) has been examined and reported to exert potentially protective effects against chronic cerebral hypofusion-induced neurodegeneration by reducing neuronal loss and inhibiting neural death in the hippocampus of rats (60). Neurodegenerative disorders affect the neurons of the nervous system (dysfunction or death of nerve cells), resulting in the loss of memory, inability for self-care, loss of communication ability, and personality changes, leading to difficulties in social functions. Commonly known neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), MS, and stroke, are caused by the aging process in addition to increased oxidative stress; therefore, the antioxidant properties of bee products and edible insects have the potential to block this process via dietary intake. The consumption of antioxidant foods has been proposed to attenuate oxidative damage, improve cognitive performance, and slow down the deterioration in memory and learning associated with aging. Dietary phenols in honey have also been reported to prevent neurodegenerative diseases. Luteolin, a flavonoid found in honey, exhibited neuroprotective activity against microglia-induced neuronal cell death and promoted spatial working memory by preventing microglia-associated inflammation in the hippocampus of aged rats (61). A previous study also reported that honey reduced neuroinflammation and caspase-3 activity after kainic acid (KA)-induced status epilepticus in rats (62). Quercetin, kaempferol, ferulic acid, chrysin, and chlorogenic acid in honey have been shown to exhibit neuroprotective activity in rat models (63-70). Caffeic acid, another important phenolic acid and antioxidant, which is found in honey, suppressed neuroinflammation in the brain tissues of mice (71). Tualang honey has been shown to improve short- and long-term memory as well as the neuronal proliferation of hippocampal regions in rats (72). Similarly, the consumption of honey with a high antioxidant content decreased deteriorations in brain function during aging and, thus, reduced anxiety and improved spatial memory in rats (73).

Gastric ulcers are a major issue worldwide and there is, as of yet, no effective treatment. Manuka honey was previously shown to significantly reduce the ulcer index and maintain the glycoprotein content, and these effects were attributed to its antioxidant properties. It also reduced mucosal myeloperoxidase activity, lipid peroxidation, and the levels of inflammatory cytokines (TNF-α, IL-1β, and IL-6) to lower than those in the untreated control group. In addition, rats treated with Manuka honey showed a normalized cell cycle distribution and significantly reduced apoptosis in the gastric mucosa. These findings demonstrated that Manuka honey is effective in the treatment of chronic ulcers and preservation of mucosal glycoproteins (8).

Honey has been reported to exert protective effects against metabolic syndromes (74). Metabolic syndromes (e.g. cardiovascular disease, hypertension, and diabetes) are linked to lifestyle choices. The anti-obesity effects of honey were previously reported in a rat model (75, 76). The hypoglycemic effects of stingless bee honey and giant honey bee honey have been tested in rats (77-79). Royal jelly was found to ameliorate diet-induced obesity and glucose intolerance in mice (80). Furthermore, Seo *et al.* showed that the daily intake of yellow mealworms attenuated weight gain in obese mice by increasing lipid accumulation and triglyceride levels in adipocytes (81).

Brazilian green propolis contains prenylated phenylpropanoids and flavonoids and exhibits antioxidative and anti-inflammatory activities. Furthermore, its extract suppressed acetaminophen-induced hepatocellular necrosis by modulating cytokine expression in rats (82). Luteolin is a flavonoid found in honey that exhibited neuroprotective activity against microglia-induced neuronal cell death and enhanced spatial working memory by preventing microglia-associated inflammation in the hippocampus of aged rats (83). Among flavonols (quercetin, kaempferol, galangin, fisetin, and myricetin), flavones (apigenin, acacetin, chrysin, luteolin, genkwanin, wogonin, and tricetin), phenolic acids (caffeic acids), and flavanones (hesperidin), quercetin has been shown to enhance the apoptotic activities of anti-CD95 and rTRAIL (recombinant tumor necrosis factor-related apoptosis-inducing ligand) in acute lymphocytic leukemia (84). Apigenin and acacetin not only induce caspase-dependent apoptosis in human leukemia cells *in vitro*, the former also induced the apoptosis-mediated inhibition of U937 leukemic cell xenografts in mice (85).

In an *in vivo* study, the administration of bee venom to carcinoma-bearing rats significantly reduced their body weight, ascites tumor volume, packed cell volume, viable tumor cell numbers, and tumor cell count and increased their mean survival time. These findings suggest that the bee venom studied is applicable as an effective anticancer agent (59). Bee venom also exerts neuroprotective effects. For example, when bee venom phospholipase A2 (PLA2) was injected into a mouse model of PD, the second most common neurodegenerative disorder, it attenuated neurotoxicity and enhanced motor functions (86). Melittin in bee venom reduced the expression of inflammatory proteins in a transgenic mouse model of amyotrophic lateral sclerosis (ALS). These findings suggest that melittin has potential as an agent to regulate the immune system in organs with the loss of motor neurons caused by ALS (87).

The *Drosophila melanogaster* genome project was completed in 2000. Approximately 75% of human disease-causing genes have functional orthologues in *Drosophila*. *Drosophila* is a good model organism because it has a short life span and produces a large number of offspring. It has been used to investigate degenerative diseases related to the nervous system, such as neurodegradation, AD, PD, sleep disorders, and aging. *Drosophila* has also been used as an animal model of neurodegradation, AD, PD, sleep disorders, ALS, and cancer (31). However, limited information is currently available on edible insects and insect-derived products tested using *Drosophila* models. When *Drosophila* was fed the boiled and freeze-dried powder of silkworms (*B. mori*), their life span increased and the symptoms of rotenone-induced PD were attenuated (88). Yamanashi *et al.* reported that when flies were fed freeze-dried royal jelly, royal jelly influenced the adult physiology via a shorter developmental time, prolonged longevity, and increased female fecundity (89). These findings suggest that royal jelly maintains certain bioactivities in multicellular organisms and *Drosophila* mutants may be a useful model to study lifestyle- and age-related diseases. A *Drosophila* model of the knockdown of ubiquilin, which induces severe morphological defects in neuromuscular junctions (NMJs), has been used to examine edible insect proteins and honey bee products. When *Drosophila* mutants were fed food supplemented with coffee honey, bee venom, and wasp protein, the number of boutons was significantly higher in the three treatment groups than in the control. These findings suggest that these insect products have neuroprotective properties. Furthermore, the anti-inflammatory activities of coffee honey, royal jelly, and melittin were demonstrated in the *Drosophila* model.

4. SUMMARY AND PERSPECTIVES

Due to the large diversity of insects, they may be an alternative food source and preventive medicine for humans. Pharmacological and chemical analyses of insects and their products as well as medicinal properties warrant further investigation in multicellular organisms to reaffirm that the same effects are achievable in humans. Insect-derived compounds may be used as alternative medicine in the 21st century. Quality control for commercial processes, reductions in pesticides, and barcoding for taxonomy are also needed for food safety and to maintain the benefits of edible insects and insect-derived products as an alternative diet and in preventive medicine.

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Send correspondence to: Panuwan Chantawannakul, Department of Biology, Faculty of Science, Chiang Mai University, 239 Huay Kaew rd, T. Suthep, A. Meung, Chiang Mai, Thailand 50200, Tel: 6653943346, Fax: 66538922, E-mail: panuwan@gmail.com