Bugs as Drugs, Part 1: Insects. The "New" Alternative Medicine for the 21st Century?

E. Paul Cherniack, MD

Abstract
Insects and insect-derived products have been widely used in folk healing in many parts of the world since ancient times. Promising treatments have at least preliminarily been studied experimentally. Maggots and honey have been used to heal chronic and post-surgical wounds and have been shown to be comparable to conventional dressings in numerous settings. Honey has also been applied to treat burns. Honey has been combined with beeswax in the care of several dermatologic disorders, including psoriasis, atopic dermatitis, tinea, pityriasis versicolor, and diaper dermatitis. Royal jelly has been used to treat postmenopausal symptoms. Bee and ant venom have reduced the number of swollen joints in patients with rheumatoid arthritis. Propolis, a hive sealant made by bees, has been utilized to cure aphthous stomatitis. Cantharidin, a derivative of the bodies of blister beetles, has been applied to treat warts and molluscum contagiosum. Combining insects with conventional treatments may provide further benefit.
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E. Paul Cherniack, MD – The Geriatrics Institute, University of Miami Miller School of Medicine, Division of Geriatrics and Gerontology, and the Geriatrics and Extended Care Service and Geriatric Research Education, and Clinical Center (GRECC) of the Miami Veterans Affairs Medical Center
Correspondence address: Miami VA Medical Center, Room 1D200, 1201 NW 16th Street, Miami, FL 33125
Email: evan.cherniack@va.gov

Introduction: Why Insects?

Insects and other arthropods provide ingredients that have been a staple of traditional medicine for centuries in parts of East Asia, Africa, and South America. While many of these ingredients have not been evaluated experimentally, an increasing number have been shown in preliminary trials to have beneficial properties. Although medical practitioners in more economically robust countries may prefer conventional treatments, it may be more a result of squeamishness rather than science. Furthermore, in parts of the world where conventional medical care is scarcer than arthropods used by folk healers, insects may represent a feasible substitute in some cases. In sub-Saharan Africa alone, the World Health Organization estimates that $20 billion will be needed to replace the shortage of 800,000 conventional health care workers by 2015.[1] Globally ubiquitous, arthropods potentially provide a cheap, plentiful supply of healing substances in an economically challenged world.

Maggots

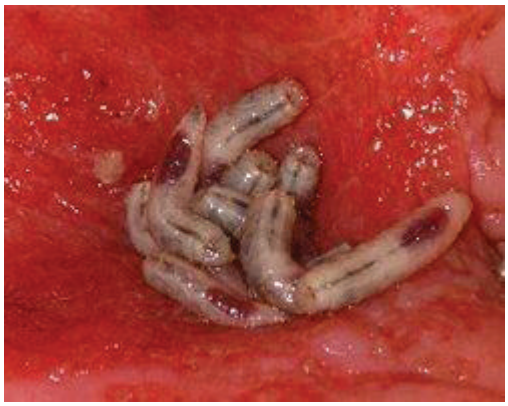
The most well-studied medical application of arthropods is the use of maggots – the larvae of flies (most frequently that of *Lucilia sericata*, a blowfly) that feed on necrotic tissue.[2] Traditional healers from many parts of the world including Asia, South America, and Australia have used "larval therapy,"[3] and records of physician use of maggots to heal wounds have existed since the Middle Ages.[3] Figure 1 depicts maggots on a wound.

Fly larvae aid in wound healing via a number of mechanisms: (1) larval secretions break the larger adhesion molecules, fibronectin and collagen, into smaller fragments that promote fibroblast aggregation and tissue repair;[4] (2) larvae eat necrotic tissue that would otherwise form a nidus for infection, liquefying such tissue and aiding its digestion;[4] (3) maggots release antibacterial substances, some of which are produced by *Proteus mirabilis* bacteria that live naturally in the larval intestine; and (4) ingested bacteria are destroyed within maggots.[3]

Maggots commercially grown under sterile conditions are used in wound healing. In one application technique, a hole is cut in a hydrocolloid dressing over a wound.[3] The maggots are lifted out of a container on a piece of nylon netting, which is folded together and taped onto the dressing over the hole after removal of the moisture in the maggot growth medium. A piece of gauze is placed over the nylon and taped in place.[3]

Key words: maggots, honey, wounds, surgery, burns, bee, propolis, cantharidin, molluscum, ant, beetle, pityriasis, royal jelly, ulcers, larva, tinea

Figure 1. Maggots on a Wound



In one study, maggots were grown *in vitro* and placed in the wounds of 30 individuals after bacterial swabs of the wounds were taken.[5] The patients had arterial or venous stasis ulcers, diabetic or pressure ulcers, or chronic postoperative wounds. Secretions taken either from maggots grown on sterile plates or from wound sites sampled from 1-5 days after the introduction of larvae were studied for antibacterial properties. Larval secretions successfully suppressed *Staphylococcus aureus* growth *in vitro*. *In vivo*, 51 wounds (83.2%) healed, with reduced bacterial counts within the wounds.

Maggots were also used to treat chronic leg wounds in several patient series. In one case series involving 34 leg wounds of at least three months duration in subjects ages 32-84, 85 percent of the wounds healed.[6] Of the healed wounds, 93 percent resolved within 7-10 days. In a second series, 70 patients, ages 25-94 with wounds of at least six weeks duration, were given treatment with one-day-old larvae added at a concentration of 5-10 larvae/cm^2.[2] Eighty-six percent of the subjects had a 66- to 100-percent reduction of wound size. During treatment, 35 percent of subjects perceived more pain, 25 percent less pain, and 46 percent no difference in pain. In a third case series, larval therapy was applied to 70 chronic wounds; 43 percent of the wounds were completely debrided, and 29 percent were partially debrided.[7] There are also case reports of the successful use of maggots for treating the wound of a terminally ill patient[8] and for non-healing venous ulcers.[9]

One study examined the factors that predict better outcomes of larval therapy in a series of 117 wounds. Greater wound depth, older patient age, and presence of septic arthritis portended a worse outcome.[10]

Larval therapy has also been evaluated in controlled trials. In a randomized trial, 267 subjects with venous or arterial ulcers at least 25-percent covered with necrotic material were assigned to receive maggots or a conventional hydrogel dressing.[11] Although there was no difference in rate or timing of healing between groups, the maggot-treated wounds were debrided significantly faster (2.31 days; $p<0.001$). On the other hand, subjects treated with maggots had a significantly higher pain score (approximately 40 points higher on a 150-point analog scale; $p<0001$). In another trial involving diabetic leg ulcers, non-healing wounds were treated with either maggots, a conventional hydrogel, or the conventional therapy followed by larval treatment.[12] Wounds treated with maggots had significantly less necrotic tissue after two weeks. Thus, there is limited evidence that larval therapy can provide wound healing for lower extremity ulcers comparable to conventional treatment. A systematic review concluded that, in appropriate patients, use may be safe and effective.[13] Maggots may be appropriate especially when conventional therapies cannot be used, or in parts of the world where larvae are more easily obtainable than conventional treatment.

Honey Treatment

Honey is another insect-derived substance that has been used in wound healing and for treatment of other disorders, such as infections and irritable bowel syndrome. Therapeutic effects of honey have been documented from ancient times and it is still used in African folk medicine.[14,15] Honey composition varies widely throughout the world depending on the species of bee and plants the bees feed on, both of which influence the honey's antioxidant and antimicrobial properties.[16-18] Four phenolic compounds in honey – p-hydroxybenzoic acid, naringenin, pinocembrin, and chrysin – are antimicrobials and antioxidants. The carbohydrate in honey is also antimicrobial.[16,17] Honey also has antimutagenic properties.[19]

Wound Healing

The best studied use of honey is for wound healing. Honey promotes wound healing through osmotic properties that serve to moisturize the wound bed and reduce the risk of maceration. It also works via anti-inflammatory processes that reduce exudate and inhibit fibrin that adheres eschar to the wound bed, impairing tissue repair.[20]

Honey has been used to heal wounds in numerous situations. Many studies have found dressings that contain honey comparable to conventional dressings. In a randomized, double-blind, placebo-controlled trial, 100 patients who had toenail surgery were assigned to receive either a honey-coated dressing or a conventional paraffin dressing.[21] There was no significant difference between groups in days taken to heal the wounds.

However, in a single-blind study (blind to the investigator who examined the wounds), honey proved inferior in healing time to a conventional iodine dressing in 57 patients who had total avulsion toenail surgery, but comparable in wound-healing time to standard treatment after partial avulsion surgery.[22]

In a case series, eight patients (ages 22-83) with leg wounds that had not healed in a month were given once- or twice-weekly applications of honey on a non-adhesive dressing.[23] After a month of treatment there was an average 54.8-percent reduction in wound size, from a baseline mean wound size of 5.62 to 2.25 cm^2.[23]

Two open (unblinded) trials also found significant wound healing with honey. In a randomized, controlled, but open trial, a honey dressing was compared to a conventional hydrogel dressing in 108 subjects (ages 30-68) with venous ulcers that were at least half-covered in slough.[24] By three months, healing had occurred in a significantly greater number of honey-treated wounds compared to those treated by hydrogel (44% versus 33%; p=0.047).[24] In a longer open trial of 368 patients, a honey dressing was compared to a calcium alginate dressing.[25] After three months, there was no statistically different wound-healing rate between groups (55.6% versus 49.7%).[25]

Honey has also been used to treat infected wounds. In one investigation, 50 women with post-abdominal hysterectomy or caesarian-section wound infections were randomized to receive a topical application of honey or a local iodine/ethyl alcohol antiseptic twice daily.[26] Patients receiving honey had an average infection-healing time of six days versus 14.8 days in the iodine/ethyl alcohol antiseptic group (p<0.05).[26] Sixteen other less methodologically rigorous studies have also outlined the utility of honey in wound healing.[27] Two systematic reviews conclude that honey may be beneficial in the treatment of wounds, but the quality of the studies was low.[27,28]

Burns

Several studies, most conducted by the same investigator, have examined the use of honey in the treatment of burns. In one randomized, controlled trial, 104 subjects with burns covering 5-40 percent of their bodies were divided into two groups. One had 15-30 mL undiluted honey applied to the burn, the other received a conventional topical cream of silver sulfadiazine applied to gauze covering the burn.[29] Subjects treated with honey had a significantly shorter healing time (7.4 days versus 13.4 days; p<0.001).

In a similar second investigation, 50 patients with burns were randomly divided into two groups and treated with either honey or silver sulfadiazine.[30] All of the honey-treated burns healed after one week compared to 84 percent of burns treated with silver sulfadiazine (p<0.001).

In another trial by the same group, honey was compared to a conventional polyurethane film dressing in 92 subjects.[31] Burns treated with honey healed in a mean 10.8 days versus 15.3 days for the polyurethane film group (p<0.001).

In two other studies of burn healing, honey dressings were compared to dressings made from potato peels or human amniotic membranes. One hundred patients with burns received dressings containing either honey or boiled potato peels.[32] After 15 days of treatment, all honey-treated burns resolved, compared to only half the wounds treated with potato peels.[32] The second trial featured patients with partial-thickness burns (less than 40 percent of body surface) who were given honey dressings (n=42) or amniotic membrane dressings (n=24).[33] In the honey group, wounds healed in an average of 9.4 days, compared to 17.5 days in the group receiving amniotic membrane dressings (p<0.001). A Cochrane systematic review concluded that honey induced more rapid healing times in mild-to-moderate superficial and partial thickness burns than conventional dressings.[34]

Miscellaneous Uses

Several other uses have been suggested for honey, including the treatment of infectious diseases, skin conditions, gastrointestinal disorders, and allergic rhinitis. Thirty subjects with seborrheic dermatitis and dandruff were randomized to obtain honey or no treatment.[35] The treatment group applied a 90-percent honey mixture diluted in water to the scalp every other day for a month. Those given honey had a complete resolution of symptoms after two weeks, whereas 75 percent of those who had no treatment had a recurrence of symptoms.[35]

Honey successfully treated hydatid disease in rats,[36,37] but did not cure leishmaniasis in 100 individuals with skin manifestations.[38] In an observation-only study, patients who used honey for tinea infections and pityriasis versicolor improved.[39] A combination of honey and starch inhibited the growth *in vitro* of *Escherichia coli* and *Staphylococcus aureus*.[40]

In a study of 169 children (ages eight days to 11 years) with gastroenteritis, honey (50 mL/L electrolyte-glucose solution) safely reduced the length of time of diarrhea by two days compared to a standard solution without honey.[41] It should be noted that honey is usually not recommended for children under one year of age due to the potential for acquiring botulism.

Rats given experimentally-produced inflammatory bowel disease were protected from colonic inflammation by honey.[42]

Thirty-six patients with allergic rhinoconjunctivitis took unpasteurized honey, a commercially processed honey, or a placebo (corn syrup) for 10 days.[43] Keeping a log of the clinical manifestations of the illness, the patients noted no difference in symptoms regardless of treatment group.

Honey and Beeswax

Honey has been combined with beeswax, a complex carbohydrate, as a vehicle to create medicinal compounds. A mixture of honey, beeswax, and olive oil, a combination that is antibacterial *in vitro*,[44] has been piloted in the treatment of several skin disorders.[45] A compound was created using equal proportions of the aforementioned components and was either administered in pure form or further mixed with a topical steroid, betamethasone, in three different ratios (1:1, 2:1, or 3:1 – compound:steroid).[45] Two sets of patients were tested, 11 subjects with psoriasis (ages 20-60 years) and 21 subjects with atopic dermatitis (ages 5-16 years). Both groups included some subjects who were already being treated with topical steroids. Each group was subdivided into a beeswax mixture and placebo group or a beeswax mixture and steroid group.[45]

Subjects with atopic dermatitis had lesions on one side of the body treated with the beeswax mixtures and on the other side with a placebo cream.[45] If there was a response to experimental treatment after two weeks, subjects continued the treatment for another three weeks with the placebo cream replaced by the beeswax mixture. The second group of atopic patients had the 1:1 beeswax mixture:steroid applied to lesions on one-half of their bodies and a steroid plus placebo in a 1:1 ratio mixture applied to the other half. If there was response to the beeswax mixture after two weeks, subjects were switched to progressively higher concentrations of the beeswax mixture (i.e., 2:1, 3:1). If there was a response to a 3:1 mixture, subjects were switched to the 100-percent beeswax mixture.

In the psoriasis patients, a similar design was used, but each group had a three-week trial with each compound rather than two weeks. In atopic dermatitis patients who had had no prior treatment, after two weeks subjects who received the beeswax mixture had statistically fewer skin lesions on the sides of the body to which this mixture was applied compared to the other side (6.7 ± 5.3 versus 14 ± 4.8 lesions, respectively; p=0.0129). Patients with psoriasis who had previously been given steroids also had fewer lesions on the beeswax-treated side after two weeks (7.1 ± 3.7 versus 10.4 ± 1.3; p=0.0235), but the differences were no longer statistically significant after three weeks.[45]

A honey and beeswax mixture was also administered to patients with two other skin disorders: tinea in various locations and pityriasis versicolor.[39] Twenty-seven patients with pityriasis versicolor and 23 patients with either tinea corporis, cruris, or faciei participated (average age mid-20s).[39] The subjects applied the mixture topically every eight hours for three weeks. If there was a response, the patients continued to use the mixture until a cure was obtained. Burning, scaling, erythema, and pruritis were each rated on a 0-4 scale by the investigator and summed to give a total score for each subject. There was a statistically significant reduction in the summed score in the 14 subjects with tinea cruris – from 8.5 at baseline to 1.0 at week four ($p<0.00001$). A complete cure was observed in 79 percent of pityriasis versicolor patients. The mean scale score of 7.1 at baseline decreased to 1.0 after three weeks, although statistical significance was not reported. Similarly, in the eight patients with tinea corporis, a 62-percent cure rate was reported and the mean scale score decreased from 8.7 at baseline to 1.3 after three weeks; again, there is no record of statistical significance.

In an uncontrolled trial, 12 infants with diaper rash were treated topically with a honey, olive oil, and beeswax mixture.[46] Skin erythema was rated on a five-point scale, and an initial mean score of 2.91 was decreased to 0.66 on day seven ($p<0.05$).[46]

In pilot trials on animals, a mixture of alcohols derived from beeswax called D-002 was tested on experimentally-induced organ injury. In one trial, rats who received gastric injuries from the non-steroidal anti-inflammatory drug indomethacin were given injections of different doses of D-002 or placebo.[47] Those animals given D-002 had progressively smaller ulcer sizes with larger doses of D-002 (50-200 mg/kg).[47] In another study, rats with acute liver injury induced by intraperitoneal injections of carbon tetrachloride were either given oral doses of 25 or 100 mg/kg D-002 or placebo.[48] The rats receiving D-002 had less liver damage upon biopsy.[48]

Royal Jelly

Royal jelly is a complex mixture of sugars, lipids, vitamins, and proteins secreted from the mandibular and hypopharyngeal glands of worker bees. It sustains both the queen and other bees.[49] It is widely used in traditional Oriental medicine, with 31.3 percent of respondents in one Hong Kong survey having used it.[50,51]

Animal and *In vitro* Studies

Several royal jelly constituents are estrogenic, including 24-methylenecholesterol, 10-hydroxydecanoic acid, 10-hydroxy-trans-2-decenoic acid, and trans-2-decenoic acid.[49] Royal jelly stimulates osteoblasts and collagen production in mice[51] and restores estrogenic function in the uteri of ovariectomized rats.[52] Royal jelly increased wound healing in punctured tympanic membranes of guinea pigs after three months.[53] One of the constituent proteins stimulated the proliferation of rat hepatocytes *in vitro* and stimulated the production of albumin.[54]

Royal jelly has been used to alter immunity and suppress infectious diseases. It can also stimulate antibody production in mice[55] and suppress auto-antibody production in lupus-prone mice.[56] The compound blocked cell adhesion factors released by *Pseudomonas aeruginosa*,[57] and *Staphylococcus aureus* growth was inhibited *in vitro* by royal jelly (and by a combination of honey and royal jelly).[58] Pseudomonas adhesion factors were also blocked by royal jelly.[59] One peptide in royal jelly suppresses interleukin-4, which is released by T cells to stimulate an allergic response in mice.[60]

Royal jelly may have anti-atherogenic effects. Peptides present in royal jelly inhibited angiotensin-converting enzyme and lowered systolic blood pressure in rats.[61]

Clinical Evidence

Several studies from the 1960s in foreign-language journals in Europe observed significant reductions in lipid levels in small numbers of human subjects given royal jelly.[62]

A compound containing royal jelly, Melbrosia, which also contains flower pollen, was piloted to treat menopausal symptoms. Sixty healthy postmenopausal women with symptoms took two Melbrosia tablets daily for two weeks and then one tablet daily for 10 weeks.[63] Questionnaires of menopausal and depression symptoms yielded a statistically significant reduction in symptom scores.

Royal jelly can induce hypersensitivity and asthma.[50,64] In one survey, 7.4 percent of attendees at an asthma clinic in Hong Kong had a positive skin test to royal jelly,[50] and cases of asthma have also been reported.[64]

Insect Venom

Bee Venom

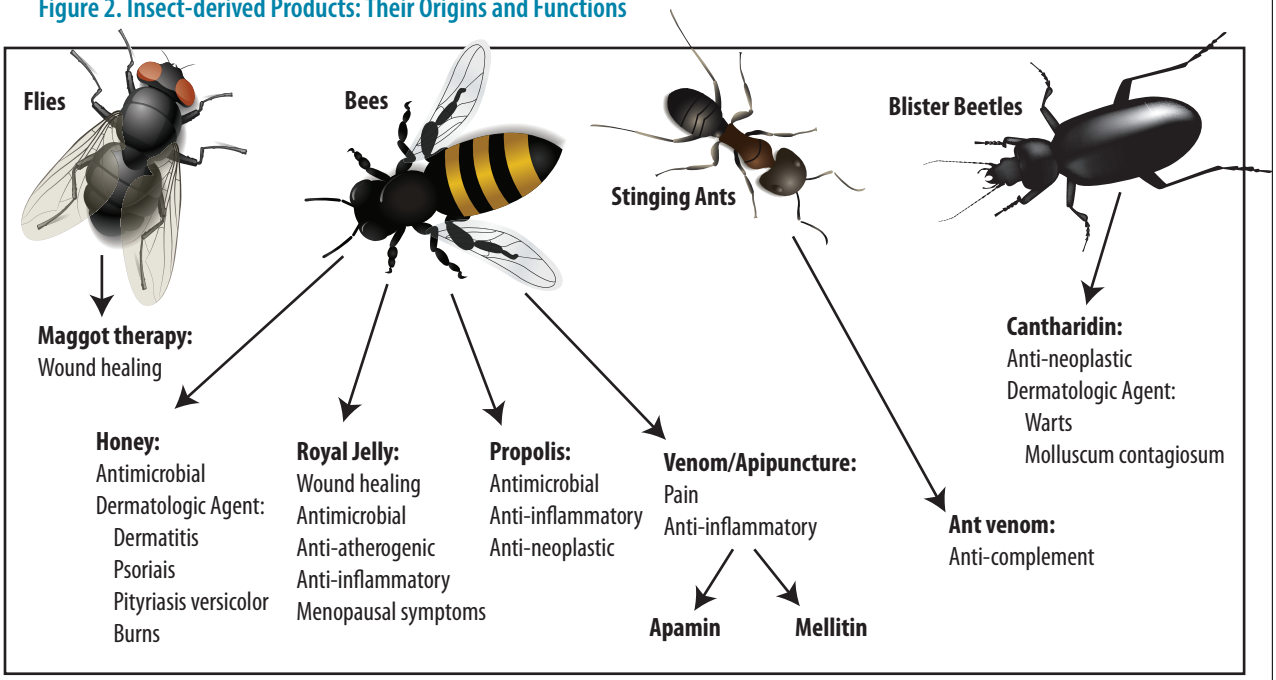
Bee venom is a compound containing immunoreactive and neuroactive peptides, enzymes, glucose, fructose, and water.[65] It is used to treat pain in traditional Oriental medicine.[66]

Inflammation/Arthritis

Bee venom constituents have anti-inflammatory properties, including suppression of phospholipase A_2, free radical production, and alpha-1 acid glycoprotein gene expression, and activation of nitrous oxide.[65,67-69] Other anti-inflammatory mechanisms include inhibition of inflammatory gene activation (in mouse macrophages), reduction of cyclooxygenase-2 (COX-2) activation, mRNA expression, decrease of inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β), and superoxide production.[66,69] *In vivo* in the mouse, the anti-inflammatory effect of bee venom is at least in part under neural regulation.[70] Mice who received hind limb bee venom injections and had lesions in the contralateral but not ipsilateral locus coeruleus demonstrated suppression of the inflammatory response, as measured by leukocyte count in the exudate.[70]

One possible application is the treatment of arthritis. The paws of rats with adjuvant-induced arthritis were injected with 0.8-1.6 mcg bee venom daily for two weeks. Paws of bee venom-treated rats had 25-percent less swelling ($p<0.05$) than rats who received an adjuvant alone.[71] In an *in vitro* human trial, bee venom induced apoptosis of synovial fibroblasts in subjects with rheumatoid

Figure 2. Insect-derived Products: Their Origins and Functions



Adapted from a drawing by Maggie Cherniack

arthritis.[72] Rats with chemically-induced pancreatitis that received three doses of 0.25 mg/kg bee venom had significantly better histological appearance of the pancreas and lower levels of lipase, amylase, and inflammatory cytokines than rats that received a placebo.[73]

Multiple Sclerosis

Bee venom has been piloted as a treatment for multiple sclerosis (MS). In a preliminary study, nine subjects, ages 21-55, were treated with 0.025-2.0 mg bee venom injected daily for two weeks followed by weekly injections for one year. There were four different dosing schedules; two with gradually increasing doses. No side effects were observed. Neurological examinations showed improvement in two subjects, no change in two, and worsening in the other five.[74]

Bee venom was tested in a randomized crossover trial of 26 MS patients (25 completed). They were assigned to receive no treatment or 20 bee stings daily, three times a week for six weeks, then crossed over to the other group. There was no improvement in symptom ratings on questionnaire during the treatment phase.[75]

Pain

Bee venom may influence pain regulation. On one hand, there is evidence that bee venom or its constituents promote pain through the activation of spinal neurons,[69] and in fact, people do perceive bee stings as being painful or hyperesthetic. Bee venom application by plantar injection in rats increases a marker of neuronal activity, c-fos gene expression, in nociceptive neurons of the dorsal horn of the spinal cord.[76] The nociceptive activity of bee venom is mediated by spinal neurons utilizing NMDA as a neurotransmitter.[69] Descending neurons from the rostral medial medulla, capsaicin-sensitive peripheral afferent neurons, and spinal pathways involving protein kinases A and C, 5-hydroxytryptamine, and neurokinin are also involved in the induction of hyperesthesia.[69]

Apipuncture

On the other hand, bee venom promotes the expression of genes in spinal neurons that down-regulate pain.[69] The acupuncture needle coated with bee venom has been utilized to treat pain.[69] Bee venom acupuncture, or apipuncture, had an anti-nociceptive effect on chemically-induced pain in rats by formalin.[69,77] An opioid receptor antagonist did not reverse the pain-relieving effects of apipuncture, but a serotonin-antagonist and an α_2-receptor antagonist did.[69]

Several clinical trials in Korea have been performed using apipuncture to treat arthritis. In an uncontrolled trial, 20 subjects were given apipuncture to proximal and distal phalangeal joints twice weekly for three months. Subjects had significantly fewer tender and swollen joints and less pain and morning stiffness after therapy.[78]

In a controlled study of rheumatoid arthritis, 80 subjects were given either twice-weekly injections of bee venom or a placebo for three months. Those treated with bee venom had a significantly lower number of swollen joints and less morning stiffness.[79]

One uncontrolled and one controlled trial published in Korean but not translated showed no statistically significant improvement in knee joint function after apipuncture.[80]

Ant Venom

Ant venom has also been used to treat arthritis. In one study, 15 subjects with rheumatoid arthritis were administered the venom of the South American tree ant Pseudomyrmex.[81] Patients were given daily subcutaneous injections of 1 mL (600 mcg venom in neutral sugar) or a 0.1 mg/cc histamine placebo for 10 days.[81] There was a significant reduction in the number of swollen joints in those who received ant venom (from 16.8 ± 4.3 initially to 8.5 ± 5.4), an improvement not seen in the control group ($p<0.015$).[81]

Individual Constituents of Insect Venom

Individual constituents of insect venoms have anti-inflammatory properties that may make them useful in the treatment of several disorders. Mellitin is a 26 amino-acid peptide that comprises almost half of all dried bee venom by volume (and is also present in wasp venom).[65,82] Mellitin suppressed pro-inflammatory cytokine nuclear factor kappaB (NF-κB) in rats[71] and inhibited phospholipase A_2 *in vitro*.[83] However, in human fibroblasts, pro-inflammatory genes and reactive oxygen species were up-regulated.[84] Mellitin was also found to lyse lipids[84] and stop the formation of matrix metalloproteinase, a degradation product of cartilage that is increased in human chondrocytes in osteoarthritis patients.[85]

Apamin (which comprises two percent of dry weight of bee venom and is also a wasp venom constituent) and adolapin are peptides that reduce inflammation in chemically-induced paw edema in rats.[82,86,87] Hornet venom contains a peptide, masroparan-1, that is an anti-inflammatory and antibacterial agent.[88] Ant venom has anti-complement components.[81]

Propolis

Propolis is a hive sealant made by bees from plant resins.[89] It includes many polyphenols, including resveratrol, and has been used in Egypt and Greece in folk medicine since antiquity.[89] Propolis possesses anti-inflammatory properties and has *in vitro* antimicrobial,[90-92] antiviral,[93] estrogenic,[94] and antineoplastic activity.[89] Propolis inhibits expression of the p24 antigen by HIV-infected T cells[95] and retards leukemia cells in culture.[96]

Propolis has also been studied for prevention of dental caries in rats and humans.[97] The bee-derived compound inhibits caries-causing Streptococci *in vitro*. Volunteers who rinsed their mouths with 10 mL of a 0.2-percent propolis solution for 1.5 minutes had lower oral Streptococcal counts both 10 minutes and one hour after the rinse,[98] but other subjects who tried a 10-percent propolis mix did not have reduced dental plaque formation.[99] Nineteen patients with aphthous stomatitis were randomized to receive propolis (500 mg/day) or a placebo for six months.[100] Subjects who took the propolis had a greater reduction in number of sores (26.5% versus 12.5%; $p<0.05$) than those who took the placebo.[100]

Standardization of medicinal propolis may be problematic, as variation in composition can occur based on the species of bee, its geographic location, and the plant species the bees use to manufacture propolis.[97]

Cantharidin

Cantharidin is a terpenoid derived from the bodies of several types of blister beetle, including *Mylabris phalerata* and *M. cichorii* (Chinese blister beetles) and *Lytta vesicatoria* (Spanish fly). Dried bodies of these beetles are ingredients of traditional Chinese and Vietnamese medicine used to

Table 1. Summary of Insect-derived Treatments

Treatment	Potential Uses	Human Studies	Randomized, Controlled Trials
Maggots	Wound healing	√	√
Honey	Wound healing, burns, skin diseases, infections, neoplasms	√	√
Royal Jelly	Menopausal symptoms, infections	√	
Bee, Ant Venom	Rheumatoid arthritis, pain, neoplasms	√	√
Propolis	Aphthous stomatitis, infections, neoplasms	√	√
Cantharidin	Skin diseases, neoplasms	√	

treat esophageal cancer, hepatoma, and skin diseases.[101,102] Although cantharidin has a long history in European and African folk medicine as an aphrodisiac, it is more likely to cause toxicity after ingestion, including priapism or even death.[101] Cantharidin has been found to inhibit the growth of human leukemia cell lines *in vitro*.[103] In contrast to other chemotherapeutic agents, cantharidin acts on leukemia progenitor and stem cells.[104] Several derivatives of cantharidin also retard the growth of prostate, colon, oral, cervical, and gall bladder cancer cell lines.[102,105-113]

One analogue, norcantharidin, also reduced the production of molecules that promote tumor cell adhesion and metastasis.[110] It is believed to suppress protein phosphatase, increase oxidative stress within cancer cells, down-regulate the gene STAT3, and activate the Bax genes that induce cell apoptosis by up-regulating the MAPK/ERK and p53 pathway genes.[102,103,105,114] Cantharidin stopped the production of P-gp, a membrane transport protein that creates chemotherapeutic drug resistance in a hepatoma cell line.[115]

Topical cantharidin in a 0.7-percent concentration has been used as treatment for warts and molluscum contagiosum for at least 40 years.[101] Application causes blister formation that heals within a week.[101] Retrospectively, 90 percent of the parents of 300 children treated with cantharidin for molluscum contagiosum reported resolution of lesions; improvement was reported in another eight percent.[116] Adverse reactions, including burning, pain, erythema, or temporary blistering were reported in 37 percent of patients.[116]

Conclusions and Future Directions

Insect-based medicine has had a long history in folk tradition and is coming under increasing interest and scrutiny for incorporation into evidence-based medicine (Table 1). Insect-based products that refine arthropod-derived substances with conventional technology have recently been developed and may yield further benefits. One product, an extract from maggot secretia, was embedded into a hydrogel and preliminarily tested in wounds.[117] Microspheres have also been created from beeswax and used to deliver indomethacin in controlled-release form to prevent drug toxicity.[118]

An important question that remains to be addressed is whether arthropod-based medicine is cost-effective. Regarding the maggot therapy, the cost was comparable to wound treatment with a conventional hydrogel dressing.[119] Other cost comparisons have not been made.

Given the long history of arthropod-derived medicine, one might wonder why insect-based treatment has not advanced further. Perhaps, as Robert Pemberton wrote in response to the relative absence of insect-based medicine in many parts of the world (the traditional medicine of the Far East is an exception), "The absence of arthropod-based drugs in the West is probably related to negative cultural attitudes towards arthropods. The enormous richness and diversity of arthropods and the use of many species as drugs against common and important diseases in South Korea and elsewhere, suggest that arthropods are a large, unexplored and unexploited source of potentially useful compounds for modern medicine."[120]

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