Supplemental Materials Table S1. Primer Sequences used for qPCR across experiments in this work.

Category	Target	Forward Primer	Reverse Primer	Reference
Immunity	Hymenoptaecin	CTCTTCTGTGCCGTTGCATA	GCGTCTCCTGTCATTCCATT	[1]
	Abaecin	AGATCTGCACACTCGAGGTCTG	TCGGATTGAATGGTCCCTGA	[1]
	Apidaecin	TAGTCGCGGTATTTGGGAAT	TTTCACGTGCTTCATATTCTTCA	[1]
	PGRP-LC	TCGGAGCGAGATAGTGCATT	CCATCTGCGGTTGTCACTTC	[1]
	Cytochrome P450 (*CYP9Q1*)	ATCCTGGCCAAGTGCAGCTTC	CAGCTCCTTCAATTGGATCAGCAAC	[2]
	Defensin-1	TGTCGGCCTTCTCTTCATGG	TGACCTCCAGCTTTACCCAAA	[1]
	AmEater	CATTTGCCAACCTGTTTGT	ATCCATTGGTGCAATTTGG	[1]
Host reference	Actin	TTGTATGCCAACACTGTCCTTT	TGGCGCGATGATCTTAATTT	[1]
	Arp1	CCAAAGACCCAAGCTCCCTA	TGGCTTATTGGTTTATGTTTTTCGT	[3]
	RPS5	AATTATTTGGTCGCTGGAATTG	TAACGTCCAGCAGAATGTGGTA	[4]
Parasites and microbiome	*Gilliamella apicola*	GTATCTAATAGGTGCATCAATT	TCCTCTACAATACTCTAGTT	[4]
	Snodgrassella alvi	CTTAGAGATAGGAGAGTG	TAATGATGGCAACTAATGACAA	[4]
	Lotmaria passim	CGAAGTGCACATATATGCTTTAC	GCCAAACACCAATAACTGGTACT	[5]
	N. ceranae	AGAAACTACAACAGCATCACTGGGA	AGTGAATATTCCAATTCCCAACGACTT	qNc40sRP [6]
	N. ceranae	TATTGTAGAGAGGTGGGAGATT	GCTATGATCGCTTGCC	[7]
	Trypanosome (universal)	GTGCAGTTCCGGAGTCTTGT	CTGAGCTCGCCTTAGGACAC	[3]
Virus	IAPV	GCGGAGAATATAAGGCTCAG	CTTGCAAGATAAGAAAGGGGG	[8]
	VDV/DWV-B	GCCCTGTTCAAGAACATG	CTTTTCTAATTCAACTTCACC	[9]

	LSV	GTCATCCCAAGAGAACCACTYAC	CRCACYGACATGAAGAAATGAGGTC	[10]
	DWV-A	GAGATTGAAGCGCATGAACA	TGAATTCAGTGTCGCCCATA	[11]
Nutrition/age/immunity	Vitellogenin (Vg)	TCTTCCCCTTCGATAAACACA	GTTTCGGTGGGGAAACTGT	[12]
	Vitellogenin (Vg)	TCGACAACTGCGATCAAAGGA	TGGTCACCGACGATTGGATG	Schwarz *et al.* 2016)
	Endochitinase	TATCGAAAGGACGTCGGCAG	TCACGCCGATGAACGAGTAG	[13]
	α-glucosidase	TACCTGGCTTCGTGTCAAC	ATCTTCGGTTTCCCTAGAGAATG	[14]
	Trehalase	GTTCGGATGGACTAACGGGG	CGTCCTCGTATCCAACCTCC	[13]
	mrjp1	TGACATACATTACGAAGGAGTCCA	ATCCGAAGAAGAGAACGCCA	[15]
Structural integrity of gut	Peritrophin	GCAAACGAGATTTCAATGGCAATCTTCAG	CACATTGGTAATTGTATAGTACGTTCGCATC	[2]

Additional Material and Methods by Experiment

Chrysin, Cucurmin, Hesperidin, Tocopherol, and Vanillin:

Adult winter bees were collected from a colony at the Bee Research Lab, Beltsville, MD and fed in a laboratory cup experiment, as in the previous experiment, with the following natural products at 100pm in 1:1 v/v sugar water: Cucurmin, Vanillin, Tocopherol, Hesperidin, Chrysin (a flavone found in honey, propolis), with 30 bees/cup and 8 reps of each treatment or control. After 6 days, RNA was extracted using the bag extraction method scaled down for 15 bees/cup, cDNA and qPCR were also performed as outlined in the BEEBOOK [16]. For this trial we targeted by qPCR: RpS5, Hymenoptaecin, AmEater, Vg, DWV, LSV, VDV, Trypanosome, and *Nosema ceranae*.

Cacao (Raw), Cacao (Roasted), Limonene, Tyrosine (low dose), and Tyrosine (high dose):

Adult bees were collected using the bump method from colonies at the Bee Research Lab, Beltsville, MD. Thirty adult bees were temporarily knocked out with CO_2 and placed in experimental cups. Eight replicate cups were run for each of the following compounds: Tyrosine (low), Tyrosine (high), and Limonene fed at 100ppm in 1:1 v/v sugar water, or 1:1 v/v sugar water only for the control. Two sets of experiments were run to reach 8 reps/treatment due to high mortality with incubator problem, along with one set of 8 for the control. Mortality was recorded daily and mortality was recorded for 5 days. Dead bees were removed, and remaining bees were frozen at -80^{0}C until nucleic acid extraction. RNA was extracted following the Bulk Extraction, cDNA synthesis, and qPCR protocols [16] for each of the treatments or control. For this trial we targeted by qPCR: RpS5, DWV, and VDV.

Astragalus, Calendula, Cat's Claw, Echinacea, Elderberry, Garlic Oil, Ginger, Licorice, Olive Leaf, Oil of Oregano (non-significant results and not reviewed in paper):

Ten extracts were tested for survival and antiviral activity in honeybees: Astragalus (*Astragalus propinquus*), Calendula (*Calendula officinalis*), Cat's Claw (*Uncaria tomentosa*),

Echinacea (*Echinacea*), Garlic Oil (*Allium sativum*), Ginger (*Zingiber officinale*), Licorice (*Glycyrrhiza glabra*), Olive Leaf (*Olea europaea*), Oil of Oregano (*Origanum vulgare*), Elderberry (*Sambucus*). 1:1 v/v *v/v* Sugar water was the control. All preparations were prepared in sterile water at 100 ppm v/v. Newly-emerged bees were collected and hand-fed a suspension of cloned DWV (10^8 copies per 5ul fed per bee) before treatment with the natural products, which was added to top feeders with 1:1 v/v v/v sugar water (final concentration 100ppm) REF?. After 7 days, all dead bees were removed and remaining live bees were frozen at -80^0C until processing. RNA was extracted following the Bulk Extraction, cDNA synthesis, and qPCR protocols [16]

Garlic oil and oil of oregano (A):

Further testing was done on two antivirals which showed promise, garlic oil and oil of oregano, at higher concentrations. Doses were raised to 1,000ppm and tested for survival and analysis following the same experimental setup as previous, however with 10 replicate cups per treatment. Newly emerged bees were collected, and 15 bees were placed in each of 10 cups per treatment. All bees were fed either: sugar water, sugar water + natural product +DWV, or sugar water +DWV. After seven days, all live bees were frozen at -80°C until processing. RNA was extracted following the Bulk Extraction, cDNA synthesis, and qPCR protocols [16]. RpS5 was used as a housekeeping gene and DWV levels were measured.

Cat's Claw, Elderberry Garlic Oil, Olive Leaf, and Oil of Oregano (B):

Five of the most promising treatments from the initial experiment , Cat's Claw, Garlic Oil, Olive Leaf, Oil of Oregano, Elderberry, were selected for this assay in un-inoculated adult bees, relying on natural infections in a colony showing symptoms of deformed wings, and presumably DWV. With the possibility of natural *Nosema* infections, this was also screened for. Adult bees were collected from two colonies at the Bee Research Lab, Beltsville, MD. Each treatment or control consisted of 5 cups (replicates) of 30 bees/cup per treatment, for each of the two colonies. Bees were fed with top feeders either 1:1 v/v sugar water (control), or 1:1 v/v sugar water with 1,000ppm of the treatment for 7 days. RNA was extracted using the bag extraction method for 30 bees/cup, cDNA and qPCR were also performed, all as outlined in the BEEBOOK

[16]. For this trial we targeted by qPCR:RpS5 (control gene), DWV and *Nosema ceranae* (qNC40sRp).

Garlic oil (C):

Garlic oil, which showed the most promise and was not toxic to bees at higher levels was tested at an increased dose, 10,000ppm, to see is viral infection could be further reduced when orally inoculated with DWV. This dose was not toxic to bees in initial testing of the product (data not shown). Ten newly emerged bees were placed into each of 30 cups. Controls consisted of sugar water only, or DWV-fed for the DWV control. After 7 days, RNA was extracted following the Bulk Extraction, cDNA synthesis, and qPCR protocols [16] for each of the treatments or control.

Beta carotene:

Beta carotene (a strong antioxidant), was tested for inhibition of viral and *Snodgrasella alvi* (a constitutive gut microbiome member) and its effect on immune genes in honeybees. Frame captured non-age-controlled bees were collected from brood frames in the field. In the lab, bees were put under CO_2 and sorted into rearing cages. Two cups of 30 bees were incubated with beta-carotene feeding *ad libitum* for 6 days (≥97.0% , (UV), Sigma 22040; 2000ppm in 50% sucrose solution). Control cups were fed 50% sugar water solution. Whole bees were individually extracted, two from each of the experimental cups (total 6). These were compared to ten controls which we additionally used for another experimental control in parallel. We extracted total RNA from individual bees using TRIzol™ and following the protocol outlined in the BEEBOOK [16]. DNase treatment and cDNA synthesis was carried out as in [17] with the following modifications: a variable input of total RNA was used (1µl of input), we replaced Superscript II with Protoscript II (NEB) and increased the synthesis reaction to 60 minutes from 50 minutes. The cDNA reaction mixture was diluted with 80µl of nuclease-free water before qPCR). Using qPCR, we targeted *RpS5* (reference gene), *Arp1* (reference gene), Abaecin, Hymenoptaecin, Apidaecin, PgrpLC, Vg, AmEater, MRJP1, Cytochrome, Defensin-1, DWV-A, VDV, Endochitinase, Glucosidase, Trehalase, Peritrophin and *S. alvi*. A 20 µl qPCR reaction consisted of the following: 1 × HOT FIREPol®

EvaGreen® HRM Mix (Solisbiodyne, Estonia), 250nM each primer, 1µl of template and nuclease-free water. Reactions were run in singlets. qPCR thermocycling was as follows: 95°C for 12 minutes, then 50 cycles of 95°C for 10 seconds, then 55°C, 58°C, or 60°C (as appropriate for specific primers) for 15 seconds, and 72°C for 15 seconds (with data acquisition). Thermocycling was immediately followed with a melt curve analysis as follows: Melt curve ramping was done from 60°C to 95°C in 5 degrees Celsius increments, each held for 10 seconds.

A subsequent trial was done with four cups of 30 bees per treatment. The protocols, from collection to qPCR, remained as above, except the number of targets was reduced based on our interests: *Arp1* (reference gene), abaecin, AmEater, and VDV were run. In total, there were twelve beta-carotene samples compared with twelve controls.

Berberine, Cinnamic Acid, Carvacrol, and Ginger:

Five natural products were tested. Newly emerged bees were collected from frames collected at the Bee Research Lab, Beltsville, MD and caged in a 34°C laboratory incubator with 55% relative humidity. Newly-emerged bees were collected and placed in experimental cups. Bees were fed 5ul/bee of a *DWV clone derived viu*s at 10^8 /ul suspension. Top feeders were prepared and Five cups of 15 bees/cup were then fed by top-feeders with 100ppm of the following natural products: Cinnamic Acid, Ginger, Carvacrol, Berberine or 1:1 *v/v* sugar water for the Control. Survival was monitored every other day for 7 days. RNA was extracted following the Bulk Extraction, cDNA synthesis, and qPCR protocols [16] for each of the treatments or control. For this trial we targeted by qPCR: DWV, AmEater, hymenoptaecin, and Vg. RPS5 was used for normalization.

Cinnamic Acid, Ginger, Carvacrol, and Fumagillin (non-significant results and not reviewed in paper):

The experiment was conducted as above, preparing 4 cups of 20 bees each. The bees were again fed *Nosema* spores at 1,000ppm followed by natural products at 100ppm. Berberine was dropped due to its toxicity to the bees and Fumagillin was added as a control, as Fumagillin is the industry standard for treating *Nosema* with known effect on *Nosema* infections in the field.

Cinnamic Acid, Ginger, Carvacrol, and Fumagillin were fed at 200ppm in 1:1 v/v sugar water, or sugar water only for the control. Mortality was measured for 6 days. At the end of incubation, RNA was extracted following the Bulk Extraction, cDNA synthesis, and qPCR protocols [16] for each of the treatments or control. For this trial we targeted by qPCR: DWV, AmEater, hymenoptaecin, and Vg. RPS5 was used for normalization.

Carvacrol, Decanoic Acid, Octanoic Acid, Cinnamic Acid, Ginger, and Fumagillin (non-significant results and not reviewed in paper):

In continuation of the previous experiment and to increase replicates for Carvacrol, Cinnamic Acid, Ginger and Fumagillin, and to add two additional treatments (Decanoic Acid and Octanoic Acid), the experiment was again prepared as above. Newly emerged bees were collected and hand-Fed *Nosema* spores in 5ul at 1000ppm. RNA was extracted following the Bulk Extraction, cDNA synthesis, and qPCR protocols [16] for each of the treatments or control. For this trial we targeted, by qPCR: DWV, AmEater, hymenoptaecin, and Vg. RPS5 was used for normalization.

Capric Acid, Farnesol, Coco Oil, Caprylic Acid, Lauric Acid and Fumagillin (non-significant results and not reviewed in paper):

In this experiment natural products were tested in bees hand-fed *Nosema* spores. All newly emerged bees were collected as in previous experiments, with 3 cups of 15 bees/cup which were hand-fed 5ul of a *Nosema* suspension at 1000ppm *Nosema* spores in 1:1 v/v sugar water. The bees were then fed *ad libitum* 100ppm of the following natural products or sugar water controls: Fumagillin, Capric Acid, Farnesol, Coco Oil, Caprylic Acid, Lauric Acid. RNA was extracted following the Bulk Extraction, cDNA synthesis, and qPCR protocols [16] for each of the treatments or control. For this trial we targeted by qPCR: RpS5, DWV, *Nosema*, Hymenoptaecin, AmEater, Vg, *Lotmaria, Gilliamella*.

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