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The medicinal value of phytochemicals is hindered by pathogen evolution of resistance

Alison Duncan[1] and Sara Magalhães[2]

1 ISEM, University of Montpellier -- Montpellier, France
2 CE3C: Centre for Ecology, Evolution and Environmental Changes -- Lisboa, Portugal
Correspondence to Alison Duncan (alison.duncan@umontpellier.fr)
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A recommendation of

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As plants cannot run from their enemies, natural selection has favoured the evolution of diverse chemical compounds (phytochemicals) to protect them against herbivores and pathogens. This provides an opportunity for plant feeders to exploit these compounds to combat their own enemies. Indeed, it is widely known that herbivores use such compounds as protection against predators [1]. Recently, this reasoning has been extended to pathogens, and elegant studies have shown that some herbivores feed on phytochemical-containing plants reducing both parasite abundance within hosts [2] and their virulence [3].

Suffering less from parasites is clearly beneficial for infected herbivores. Why then, is this behaviour not fixed in nature? There are, at least, two possible explanations. First, feeding on 'medicinal', often toxic, plants may impose costs upon uninfected individuals. Second, parasites may evolve resistance to such chemicals. Whereas the first possibility has been explored, and is taken as evidence for 'self-medication' [3], the second hypothesis requires investigation.

A recent study by Palmer-Young *et al.* [4] fills this gap. This article reports evolution of resistance to two different phytochemicals, alone and in combination, in the trypanosome *Crithidia bombi*, a bumble bee (*Bombus impatiens*) parasite. To

show this, the authors experimentally evolved a strain of *C. bombi* in the presence of thymol, eugenol or both simultaneously. These phytochemicals are commonly found in the nectar of several plant species, in particular those of the Lamiaceae, a family containing several aromatic herbs. Prior to selection both phytochemicals reduced *C. bombi* growth by about 50%. However, *C. bombi* rapidly evolved resistance in both single and the double phytochemical treatments. Moreover, no cost of resistance was detected when evolved parasites were placed in the ancestral, phytochemical-free environment. Therefore, resistance to phytochemicals would be expected to spread rapidly in natural populations of *C. bombi*. Clearly, thus, the herbivore strategy of sequestering plant secondary chemical compounds as a defence against their pathogens should fail. The question then is 'why do they still do it'? Can self-medication work in the longer-term for bumblebees?

Well, yes. The very fact that resistance evolved shows that resistance is not fixed in natural *C. bombi* populations. This is surprising considering that resistance is not costly. This might be due to a number of reasons. Firstly, there may be costs of resistance that were not detected in this experiment. Second, it may not be possible to evolve universal resistance to the heterogeneity present in the phytochemical environment. Indeed, phytochemical environments are highly varied in time and space and bumblebees will visit different plants presenting different phytochemical cocktails throughout the season. Furthermore, migration of bees from populations exposed to different phytochemicals may prevent the fixation of one resistance type.

Or, it may be self-behaviour itself that prevents the evolution of resistance? Indeed, in the same way that infected bees seek cooler temperatures to slow growth of a parasitoid fly [5], they may also seek a more varied diet with diverse phytochemicals to which the parasite cannot evolve, but which reduces parasite growth. Further understanding of arthropod self-medication may thus be instrumental to prevent the observed worldwide decline of pollinators [6]. Furthermore, it may inform on mechanisms that prevent rapid evolution of drug resistance in other systems.

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