The Adaptive Significance of Self-medication

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Not all pharmacists are human: other species also use medicinal substances to combat pathogens and other parasites. Self-medicating behaviour is a topic of rapidly growing interest to behaviourists, parasitologists, ethnobotanists, chemical ecologists, conservationists and physicians. Although most of the pertinent literature is anecdotal, several studies have now attempted to test the adaptive function of particular self-medicating behaviours. We discuss the results of these studies in relation to simple hypotheses that can provide a framework for future tests of self-medication.

Animals wage a continuous battle against parasites using a variety of defence mechanisms, ranging from simple behavioural avoidance to complex immune responses. One poorly understood mechanism is self-medicating behaviour, i.e. defence against parasites by one species using substances produced by another. (We do not cover inorganic medicines; see Ref. 1.) Purported cases of self-medication include bizarre behaviours that have long tickled the fancy of naturalists, but which have seldom been investigated with rigour.

For example, kodiak bears (*Ursus arctos*) chew the root of *Ligusticum* spp., spit the resulting mixture of saliva and juice onto their paws and rub it thoroughly into their fur (S. Sigstedt, unpublished AAAS symposium proceedings, 1992). This behaviour may serve a medicinal function as suggested by the fact that *Ligusticum* is routinely used by humans against viral and bacterial infections[2]. In fact, Navajo Indians consider it to be among their most important medicinal plants and, according to Navajo legend, it was the bear that taught the Navajos to use the root and informed them of its medicinal powers.

Most of the literature on self-medication is similarly anecdotal[1]. However, several recent studies have tested the adaptiveness of different forms of self-medication. Last year a symposium was also devoted to this topic, otherwise known as 'zoopharmacognosy' (E. Rodriguez and R. Wrangham, unpublished AAAS symposium proceedings, 1992).

Research on self-medication can provide a shortcut to the discovery of new human medicines[1,4]. Such shortcuts are critical since only a fraction of potential medicinal sources can be assayed, particularly in regions of vanishing habitat. Just as modern medicine has benefited from the medicinal practices of indigenous peoples[5], it can benefit from the medicinal practices of other animals. First, it is necessary to test the effect of a particular behaviour on parasites and whether this effect leads to an increase in host fitness. Next, it is desirable to work out the proximal mechanisms by which the medicinal substance works. For the purposes of this review we restrict our attention to the first step – testing the adaptive function of self-medication.

Self-medication can be classified into four categories according to the mode of contact: ingestion, absorption, topical application and proximity. The adaptiveness of each of these categories can be determined by jointly testing the following three hypotheses: (1) the medicinal substance is deliberately contacted by the medicator; (2) the substance is detrimental to one or more parasites when contacted (namely viruses, fungi, bacteria, protozoa, helminths and/or arthropods); and (3) the detrimental effect on parasites leads to an increase in host fitness. Here we review some of the recent empirical evidence for the adaptive function of each category of self-medication in the context of these hypotheses.

Ingestion

Humans are not the only animals to control parasites by ingesting medicinal compounds. Huffman and Seifu[6] observed marked improvement in the condition of a sick chimpanzee (*Pan troglodytes*) that consumed the juice of *Vernonia amygdalina*, '... a naturally occurring plant of known ethnomedicinal value ...' (Fig. 1). Observations like these provide only circumstantial evidence (Table 1), but this may be the best evidence possible in cases where it is neither feasible nor ethical to conduct manipulative experiments.

Fortunately, such experiments are possible in other systems. Several plant–insect studies show conclusively that herbivores combat parasites using chemicals derived from their host plants (citations in Ref. 7). For example, Krischik *et al.*[8] showed that nicotine ingested by the tobacco hornworm (*Manduca sexta*) reduces colony growth and toxicity of *Bacillus thuringiensis*, leading to an increase in the survivorship of the

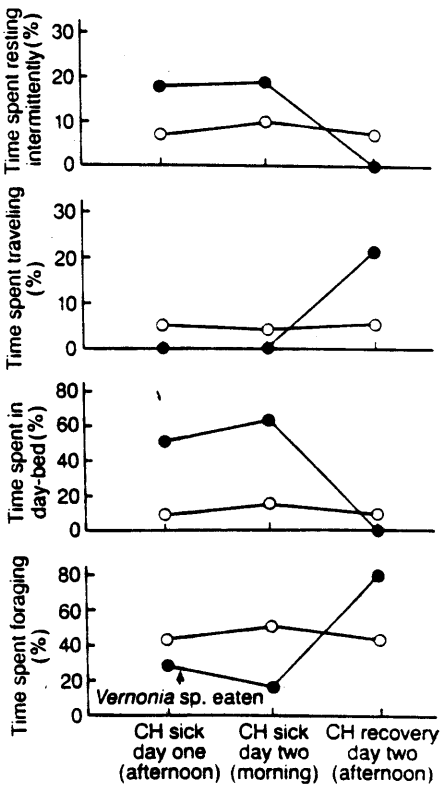

Fig. 1. Circumstantial evidence for self-medication by a sick chimpanzee (CH). During routine focal animal observations, CH (●) appeared to be in ill health compared to 'control' individuals (○) observed at the same time of day. CH showed signs of full recovery within 24 hours of ingesting *Vernonia amygdalina*, a plant of known ethnomedicinal value which was not consumed by the other individuals observed. *Drawn by B.L. Hart from data in Ref. 6.*

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Table 1. Tests of the adaptiveness of self-medication

					Adaptive hypotheses			
Mode of contact	Self-medicator	Medicinal source	Medicinal substance	Parasite	Substance contacted by medicator[a]	Substance detrimental to parasites[a]	Increased fitness of medicator[a]	Refs
Ingestion	Chimpanzee	*Vernonia* shoot	Vernonin, other 'bitter principles'	Protozoa, helminths	Y	y[b]	y	6
	Tobacco hornworm	Tobacco leaf	Nicotine	Bacteria	Y	Y	Y	8
	Spanish dancer nudibranch	Sponge	Macrolide	Fungi	Y	y[b]	–	9,10
Absorption	Chimpanzee	*Aspilia* leaf	Thiarubrine A	Viruses, bacteria, fungi,helminths	y[c]	y[b]	–	11–16
Topical application	Kodiak bear	*Ligusticum* root	Cumarines	Viruses, bacteria	Y	y[b]	–	2[d]
	Pipit, Starling	Ants	Formic acid	Mites, lice	Y	y/N	–	32,33[e]
	Grackle	Lime rind	Lime oil vapour	Lice	Y	y[b]	–	f
Proximity	Gall-wasp	Oak leaf	Tannin	Fungi	Y	y[g]	y[g]	19,20
	Starling	Aromatic plants, e.g. wild carrot	Monoterpenes, sesquiterpenes	Bacteria, mites, lice	Y	Y	N	22–24

[a] Y, hypothesis supported; N, hypothesis rejected; y, circumstantial support; –, untested.
[b] Detrimental *in vitro* or in other species, e.g. humans.
[c] Leaves massaged between tongue and surface of the mouth which may facilitate absorption, but ingestion also occurs.
[d] S. Sigstedt, 1992 unpublished AAAS symposium proceedings.
[e] A. Bennett and D. Clayton, unpublished.
[f] D. Clayton and J. Vernon, unpublished.
[g] Gall-wasp survival negatively correlated with fungal infestation which was negatively correlated with tannin level of surrounding leaves.

hornworm. This study provides strong support for all three adaptive hypotheses (Table 1) and confirms that animals may indeed combat parasites through the ingestion of compounds produced by other organisms.

Medication by ingestion may be common in many other groups of animals. To give a marine example, the shell-less Spanish dancer nudibranch (*Hexabranchus sanguineus*) defends itself against predators using macrolides derived from sponges upon which it feeds[9]. Macrolides also have fungicidal properties[10] so the Spanish dancer may rely upon sponges for defence against fungi as well as predators.

Absorption

Absorption of medicinal substances across skin or mucous membranes is another potential mode of self-medication. Chimpanzees massage *Aspilia* leaves with the tongue for up to 25 seconds before swallowing the leaves whole, which are not digested but emerge intact in the faeces[11]. Massaging of the leaves may facilitate absorption of Thiarubrine A, a potent antibiotic present in *Aspilia*[12–16]. Because Thiarubrine A is unstable under gastric acidic conditions[12], absorption across the buccal membrane prior to ingestion may be the only possible route of medicinal contact[1]. But this does not explain why *Aspilia* leaves are ultimately swallowed rather than spat out. Further work is needed to determine the relative importance of absorption and ingestion as modes of contact with medicinal compounds such as Thiarubrine A, and to measure the ultimate impact of such behaviour on host fitness (Table 1).

Topical application

Examples of topical application include the kodiak bear behaviour already mentioned, although the evidence for medication in this case is purely circumstantial (Table 1). Bears are not the only mammals that perform topical application. White-faced monkeys (*Cebus capucinus*) rub *Dieffenbachia* leaves and *Annona* fruits into their fur, followed by vigorous scratching (J.R. Oppenheimer, PhD thesis, University of Illinois, 1968). Given that scratching may facilitate absorption of medicinal compounds through the skin, topical application and absorption are not necessarily exclusive modes of contact. Apparently no test of the impact of topical application on mammal parasites has been carried out.

A better known example of topical application is the 'anting' behaviour of birds, during which a bird grasps an ant in its bill and rubs it frenetically through its plumage. The fact that birds ant exclusively with ants that secrete acid or other pungent fluids suggests that anting may play some role in ectoparasite defence[17]. Although anting behaviour has been observed in well over 200 bird species, its function is still largely a mystery and a source of controversy[17,18]. Several workers have performed tests of the adaptive function of anting with mixed results (Box 1).

Proximity

Animals may even self-medicate from a distance. Gall-wasps developing in galls near tannin-rich leaves have lower rates of fungal attack and higher emergence rates than wasps developing in galls near tannin-poor leaves, even within a single oak[19]. Furthermore, variation in tannin levels across oak species is positively correlated with (1) density of individual galls per leaf, and (2) number of species of wasps infesting an oak[20]. These results suggest that gall-wasps rely on host tannins for protection against fungi, even though they have no direct contact with the tannin. Taper and Case[20] claimed '... reduction in mortality due to fungus attack can be brought about by the artificial application of tannic acid to leaves with cynipid galls on them.' Unfortunately, no further details were provided so evidence related to the second and third adaptive hypotheses remains circumstantial (Table 1).

A more thoroughly tested form of proximal medication is the suggestion that birds combat ectoparasites by weaving insecticidal green vegetation into their nests[21]. Clark and Mason[22] provided strong support for the first adaptive hypothesis (Table 1) by showing that European starlings (*Sturnus vulgaris*) select particular species of plants with antibacterial, insecticidal and miticidal properties. In a subsequent experiment they provided support for the second hypothesis by documenting lower infestations of blood-sucking mites in nests containing such vegetation[23]. In contrast, Clark and Mason[23] were unable to confirm the third hypothesis. Although young from nests with high mite loads had lower haemoglobin levels than young from low-load nests, there were no significant differences in the weights or feather development of the two groups.

In an independent experiment with starlings, Fauth *et al.*[24] noted that young from nests with low mite loads had significantly fewer scabs and higher body masses than young from nests with high mite loads. On the other hand, they detected no difference in the fledging success or post-fledging survival of the two groups. In concluding their paper, Fauth *et al.* proposed that green vegetation does not have a medicinal function but plays some role in mate selection or pair-bonding. Considering the demonstrated effect of mites on nestling haemoglobin and body mass, however, it is possible that mites have a negative impact on host fitness restricted to harsh years. Additional field work is needed to test this possibility.

Box 1. Does anting behaviour control ectoparasites?

Many authors have suggested that anting controls ectoparasites; however, direct tests have been surprisingly few[17,31]. Eichler[32] showed that chewing lice in petri dishes are killed when sprayed with 50% formic acid (approximately the concentration produced by ants). Exposure to formic acid vapour also kills lice and feather mites *in vitro* (S. Wilson and N. Hillgarth, unpublished). V.B. Dubinin (in Ref. 33) documented 35% mortality among feather mites removed from meadow pipits (*Anthus pratensis*) observed anting in the field, compared to less than 1% mortality among mites removed from non-anting pipits collected at the same time and location. Although provocative, Dubinin's observations were of only a few birds and no statistical analyses were performed.

A. Bennett and D. Clayton (unpublished) recently tested whether anting reduces the ectoparasite loads of starlings under semi-natural conditions in field enclosures. They compared changes in the ectoparasite loads of anting birds (experimentals) to changes in the loads of birds without access to ants (controls). Their results showed no effect of anting on lice or feather mites, despite extensive anting by experimental birds. This does not rule out the possibility that anting controls other ectoparasites such as bacteria or fungi[18] or possibly even endoparasites[34]. At present, however, the best available evidence goes against the second adaptive hypothesis of self-medication (Table 1). No test of the third hypothesis has been performed.

Non-medicinal functions of anting have also been proposed, further complicating interpretations of this behaviour[17,18,31,35]. For instance, the food-preparation hypothesis suggests that anting merely functions to convert ants into usable food by stimulating them to discharge toxic acid prior to consumption[36]. Wiping ants on the plumage may remove additional acid from the ant's exterior. Recent laboratory experiments show that, when provided with a single acid-containing ant or a mealworm dipped in acid, birds with empty stomachs ant more frequently than birds with food in their stomachs[36]. This result is consistent with food preparation because it suggests that anting is most critical when there is no food in the stomach to dilute ingested acid. (Birds with empty stomachs do not ant more frequently when given acid-free ants or mealworms.)

Birds are also known to 'ant' with items such as fruit peels, flowers, mothballs and other substances, many of which have anti-parasite properties[37]. For example, after observing a common grackle (*Quiscalus quiscula*) anting with a lime for more than a quarter of an hour, D. Clayton and J. Vernon (unpublished) showed that lime oil vapour rapidly kills lice *in vitro*. The effectiveness of anting with such substances has not been tested *in situ*, nor has its effect on host fitness been determined (Table 1).

Discussion

Animals contact medicinal substances in a variety of ways, yet the outcome of such contact has seldom been determined. As this survey shows, unravelling the precise function of medicating behaviour is not always easy. Only the tobacco hornworm study (Table 1) and similar plant–herbivore studies (cited in Felton and Duffey[7]) provide strong evidence for the adaptive function of self-medication. Although several other studies show that medicinal substances kill parasites *in vitro*, this is not equivalent to demonstrating control *in situ*, much less an increase in medicator fitness. The glandular preen oil which birds secrete and spread on their plumage rapidly kills lice *in vitro*; however, surgical removal of the preen gland does not lead to increased louse populations even after several months (D.H. Clayton, unpublished). As in the case of preen oil, the fact that a substance kills parasites *in vitro* does not necessarily mean that it is used for effective defence against parasites.

Although plant–herbivore studies demonstrate that medication can be adaptive, this may not be the case in all systems. Apparent self-medicating behaviour is not necessarily adaptive – in some cases it may be of little consequence to fitness. Potter[25] suggested that birds ant because the thermogenic properties of formic acid soothes their skin during feather moult and replacement. In short, the use of medicinal substances as analgesics or stimulants[1] may be as common in animals as it is in humans.

Adaptive medication may or may not be subject to evolution. Some medicating behaviours, such as ingestion of medicinal compounds by herbivorous insects, are likely to have a heritable basis and evolve. Other examples, such as chimpanzees feeding on *Aspilia* leaves, could be learned behaviour subject only to cultural evolution[5]. Thus, a particular case of self-medication may be an adaptive trait that evolves, a non-evolving adaptive trait, or an adaptively neutral trait. Tests of the adaptive function and evolution of self-medication are needed to determine the frequency and phylogenetic distribution of these different states.

Implications

As already pointed out, self-medication is pertinent to human medicine. It may also be relevant to other established areas of research, as the following examples suggest.

Three-trophic-level interactions

Price *et al.*[26] reviewed the complexities of three trophic level interactions, focusing mainly on relationships between plants, herbivores and their predators or parasitoids. They emphasized the importance of considering all three levels in plant–insect studies. Their comments are equally relevant to self-medication, which involves three (Table 1) or possibly four or more trophic levels; e.g. anting by birds (1) may combat fungi (2) via metapleural gland secretions which ants (3) derive from plant (4) auxins[18]. Ignorance of self-medication can complicate attempts to understand the selective forces at work in interspecific interactions. For example, chemicals produced by plants for defence against herbivores may inadvertently serve a medicinal function allowing those herbivores to escape from parasites that would otherwise serve as 'biological control' agents[27]. In other words, self-medication is a means by which plant chemical defence might actually benefit herbivores more than it harms them! Hence, the production of some chemical defences may be under stabilizing selection, caught between defensive and medicinal functions.

Foraging theory

The immediate goal of foraging may sometimes be the ingestion of medicinal compounds rather than nutrients. This possibility has important ramifications for foraging theory because in cases where medicinal substances offer little or no nutritional value, foraging behaviour may make little sense in energetic terms[28]. Conversely, when nutritional and medicinal benefits coincide, teasing apart their relative selective effects will be difficult. Just recognizing cases of medicinal foraging may be difficult in situations where the primary benefit is one of prevention rather than cure; in such cases parasites may be absent altogether.

Sexual selection

A growing body of evidence suggests that animals choose mates on the basis of parasite-indicative traits in order to acquire 'good-genes' for parasite resistance, protection from parasite transmission, or healthy mates for assistance with parental care[29,30]. It is conceivable that mate choice could also occur on the basis of medicating ability, particularly in cases where parental duties include the medication of offspring, e.g. the nest protection hypothesis. Only male starlings insert green vegetation in the nest. Perhaps females choose males on the basis of this behaviour, as suggested by Fauth *et al.*[24], precisely because of its medicinal importance.

Conservation biology

Medicinal resources should receive consideration in assessing the needs of endangered species. Their potential importance underlines the need to conserve communities, not just particular species. Self-medication may be relevant to captive breeding programs, particularly in cases where cultural information could be lost. In some cases it may be important to maintain the transfer of information about sources of medicine and how to use it, analogous to the maintenance of genetic variation for disease resistance. Data on how endangered species defend themselves against pathogens and other parasites is a critical component of conservation biology.

Acknowledgements

We thank A. Bennett, P. Feeny, B. Hart, P. Harvey, O. Judson, A. Keymer, A. Møller, P. Newton, A. Read and S. Sigstedt for discussion and/or comments on the manuscript.

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