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Capsaicin: Tailored Chemical Defence Against Unwanted "Frugivores"

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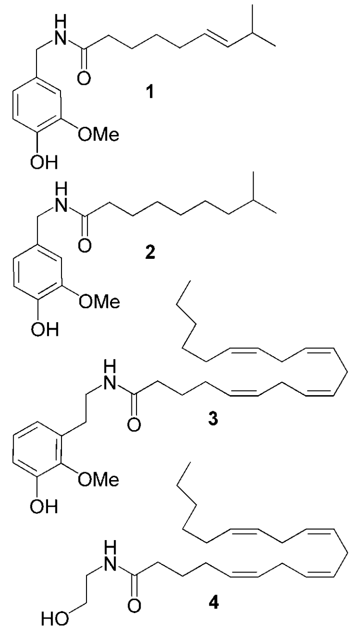
Chilli peppers (*Capsicum* spp.) have been used by humans for centuries, probably initially due to their antimicrobial properties, making them useful for preserving food, and only secondly because of their spiciness.[1] In 1910, Nelson characterised the pungency of chilli peppers as resulting from the presence of vanillyl amides, the major component of which is capsaicin (**1**; Scheme 1).[2] Subsequently the physiological and pharmaceutical properties of capsaicinoid alkaloids—for example, their anti-inflammatory or anticancer activities—have attracted considerable attention.[3]



Scheme 1. Capsaicin (**1**), dihydrocapsaicin (**2**) and the structurally related endogenous *N*-arachidonoyl-dopamine (NADA, **3**) and anandamide (**4**).

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In 1997 Caterina et al. identified the vanilloid receptor (VR1) that is responsible for the recognition of the pungent sensation caused by capsaicinoids in mammals.[4] This receptor reacts not only to capsaicinoids but also to protons and heat. Huang et al. demonstrated that the vanilloid receptor responds to endogenous metabolites such as *N*-arachidonoyldopamine (NADA, **3**) and anandamide (**4**), which are structurally closely related to capsaicin (**1**).[5] Interestingly, whereas mammals are sensitive to capsaicin (**1**), many birds are not.[6] The reason for this is a variation of the VR1.[7]

Despite such detailed knowledge about capsaicinoids, a major question has long remained unanswered: Why are chilli pepper fruits pungent?

In contrast to hot chillies, many fruits rely on sweetness to attract animals (frugivores). By rewarding frugivores with nutritious, delicious fruits, plants ensure that their seeds are dispersed.[8] Interested in the ecology of fruits, Tewksbury et al. addressed the ecological role of capsaicinoids for chillies.

Capsaicinoids are localised particularly in the tissue directly around the seeds; this suggests that they might serve to protect the seeds. The concentration of capsaicin (**1**) in wild peppers can vary enormously, and some plants are not pungent at all. Molecular analysis revealed a genetic basis for this discrepancy.[9] For example, Garcès-Claver et al. identified a single nucleotide polymorphism (SNP) that is associated with pungency.[10] In their studies, Tewksbury et al. discovered a polymorphic wild species (*Capsicum chacoense*) that produces both pungent and nonpungent fruits,[11] thus indicating that capsaicin (**1**) might not be necessary or beneficial under all conditions. In order to study the ecological role of capsaicinoids, Tewksbury et al. conducted a series of field studies using the polymorphic *C. chacoense*, an ideal tool for comparing the effects of pungent and nonpungent fruits.

Monitoring chillies in their natural environment revealed that certain birds (mainly elaenias and thrashers) feed on the fruits and efficiently disperse the seeds. In contrast, mammals such as rats did not feed on pungent chillies. Those mammals were identified as unsuitable seed dispersers, since, as feeding experiments with the nonpungent fruit revealed, the chilli pepper seeds were destroyed during the passage of the seeds through the gut.[12] Tewksbury's field observations perfectly match the structural data for the vanilloid receptors, which showed that many birds were insensitive to capsaicinoids and many mammals highly sensitive.[6,7] Thus capsaicinoids serve chillies by discouraging those consumers that do not disperse the seeds (directed deterrence).[12] The attraction of suitable frugivores and deterrence of unsuitable frugivores by chilli peppers is a good example of how major differences in the perception between organisms induce different behaviour. A fact that is often ignored by humans, being too much focused on their own senses.

However, microbial pathogens, in particular *Fusarium* fungi, are the major threat to chilli pepper seeds. The fungus appears to make its way into the fruit with the help of hemipteran insects (*Acroleucus coxalis*) that poke small holes in the chilli fruit's flesh. But capsaicinoids efficiently protect the seeds against infection by *Fusarium*,[13] as Tewksbury et al. observed for the polymorphic *C. chacoense*. In comparison to nonpungent chillies, those containing capsaicinoids were much less affected by the fungus (41–80%) and thus remained viable.

Why then do nonpungent peppers exist? Nonpungent chillies were found to produce harder seed coats than pungent fruits. Obviously, this constitutes an alternative protection mechanism. As Tewksbury et al. have shown, seeds with harder seed coats are better adapted to withstanding the gut passage of seed-dispensing birds than are less robust seeds.[14] A strong geographical correlation was found: places with high hemipteran/*Fusarium* pressure had more capsaicinoid-producing peppers, whereas sites with a low risk of pathogenic infection had more nonpungent fruits. Seed loss caused by fungal infection was shown to be more severe than seed loss caused during the gut passage because of the less robust seed coats of seeds from pungent fruits.[13] Apparently, the polymorphic *C. chacoense* allocate their resources responding to environmental challenges by investing either in physical protection (seed coat) or in chemical protection (capsaicinoids).

Because Tewksbury's studies attribute diverse biological roles (deterrence of unsuitable frugivores and antimicrobial defence) to capsaicinoids in their natural context, they raise many more questions:

- Why do capsaicinoids occur mainly around the seeds but not in the fruit shell, where they could prevent infections and attack of susceptible insects and microbes at an earlier stage?
- Is there a genetic link between the occurrence of capsaicinoids and the formation of harder seed shells in plants with fewer capsaicinoids? What are the roles of environmental factors or inducible defence traits?
- What is the mode of action of capsaicinoids against *Fusarium*?
- Do insects such as *A. coxalis* actively introduce the fungus? Do the insects benefit from the infection, for example, by an improved acquisition of nutrients?
- How do fungi such as *Fusarium* cope with the challenge from capsaicinoids? Furthermore, do plants react to adaptations on the part of the fungus? Answers to these questions may reveal counterdefence strategies of the fruit–frugivore interactions and constitute a unique example of coevolution.
- Can multifaceted biological roles, such as have been found for capsaicinoids, also be found for secondary metabolites in other fruits? Do common principles exist?

Matching information on the chemistry and physiology of capsaicinoids with that from detailed biological field studies, Tewksbury et al. have revealed exciting details on how capsaicinoids shape a complex ecosystem. Only by considering multiple viewpoints can the sometimes unexpected facets of natural products in their ecological context be discovered.

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