

## **Exploiting toxins to probe pain pathways**

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Natural plant products have served as tremendously valuable tools for deciphering cellular and molecular mechanisms contributing to somatosensation, nociception, and pain. Notable examples include the use of natural analgesics, such as morphine (from the opium poppy) and salicylate (from willow bark) to discover opioid receptors and cyclooxygenases, respectively. Other important examples include the use of natural irritants, such as capsaicin (from chili peppers) and menthol (from mint leaves) to identify ion channels that detect heat and cold, respectively. Indeed, each of these proteins represents a validated or potential target for pharmacological management of acute or chronic pain.

Plants are not unique in their capacity to produce chemical agents that target sensory neurons or other excitable cells. Indeed, venoms from organisms ranging from crustaceans to mammals represent a vast pharmacopoeia that has great potential to yield novel agents with which to identify or characterize receptors, ion channels, or other signaling molecules that contribute to sensory transduction. With this in mind, we have undertaken screens for novel toxins from spiders and snakes that activate excitatory receptors on somatosensory neurons to produce inflammatory pain - presumably as part of the organism's defensive strategy to ward off predators.

Toxins thusly discovered target two main families of ionotropic receptors, including members of the TRP and ASIC ion channel families. We have exploited these toxins as novel pharmacological and physiological probes for the purpose of (i) analyzing channel gating mechanisms and/or (ii) deciphering roles for these channels *in vivo*, particularly in the context of nociception and pain.