A nettle (Urtica dioica) extract shows in vitro inhibition of several key inflammatory events that cause the symptoms of seasonal allergies. These include the antagonist and negative agonist activity against the Histamine-1 (H(1)) receptor and the inhibition of mast cell tryptase preventing degranulation and release of a host of pro-inflammatory mediators that cause the symptoms of hay fevers. The nettle extract also inhibits prostaglandin formation through inhibition of Cyclooxygenase-1 (COX-1), Cyclooxygenase-2 (COX-2), and Hematopoietic Prostaglandin D(2) synthase (HPGDS), central enzymes in pro-inflammatory pathways. The IC(50) value for histamine receptor antagonist activity was 251 (+/-13) microg mL(-1) and for the histamine receptor negative agonist activity was 193 (+/-71) microg mL(-1). The IC(50) values for inhibition of mast cell tryptase was 172 (+/-28) microg mL(-1), for COX-1 was 160 (+/-47) microg mL(-1), for COX-2 was 275 (+/-9) microg mL(-1), and for HPGDS was 295 (+/-51) microg mL(-1). Through the use of DART TOF-MS, which yields exact masses and relative abundances of compounds present in complex mixtures, bioactives have been identified in nettle that contribute to the inhibition of pro-inflammatory pathways related to allergic rhinitis. These results provide for the first time, a mechanistic understanding of the role of nettle extracts in reducing allergic and other inflammatory responses in vitro.