Unraveling amarogentin's potential: A journey from *in silico* screening to *in vitro* and *in vivo* studies of bitter taste receptor (TAS2R)-mediated effects in asthma model

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Bitter taste receptors (TAS2Rs) have roles beyond taste perception, beyond others in modulating inflammation in chronic respiratory disorders. Amarogentin, a secoiridoid glycoside, showed potential to stimulate multiple TAS2Rs, with in silico analysis identifying TAS2R14 as the most suitable target, confirmed on LUVA mast cells. Functional studies revealed amarogentin's dose-dependent inhibition of histamine secretion and intracellular calcium release, reversed by TAS2R14 antagonism. amarogentin also demonstrated cellular uptake and modulation of kinases and transcription factors, indicating intracellular effects beyond receptor activation. In vivo, amarogentin was tested in an ovalbumin-induced asthma model in guinea pigs. Oral administration in three different doses showed a dose-dependent reduction in bronchial hyperreactivity and improved mucociliary clearance without impairing the cough reflex. Immune profiling revealed decreased Th2 cytokines and lymphocyte counts, alongside reduced MUC5AC expression in histological analyses. However, no significant effects were observed on airway remodeling markers such as SMA, TGF-β, EGFR, or collagen V. These findings highlight amarogentin’s potent anti-inflammatory effects, suggesting it as a promising therapeutic candidate for respiratory inflammation. However, its lack of impact on airway remodeling underscores the need for further investigation to define its full therapeutic potential.

Key words: amarogentin, inflammation, bitter taste receptors, remodelling

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