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Drug discovery from edible plants based on GLP-1R disease target

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The glucagon-like peptide-1 receptor (GLP-1R) is expressed in many tissues and has been implicated in diverse physiological functions, such as energy homeostasis and cognition. GLP-1 analogs are approved for treatment of type 2 diabetes and are undergoing clinical trials for other disorders, including neurodegenerative diseases. GLP-1 analog therapies maintain chronically high plasma levels of the analog and can lead to loss of spatiotemporal control of GLP-1R activation. To avoid adverse effects associated with current therapies, we characterized positive modulators of GLP-1R signaling. We screened extracts from edible plants using an intracellular cAMP biosensor and GLP-1R endocytosis assays. Galanal B and a new compound (N55) were isolated from Hedychium coronarium (HC) and Trigonella foenum-graecum (fenugreek) respectively as active principles for modulating glucagon-like-peptide-1 GLP-1 activity. The first total syntheses of both natural products and their analogue were finished for structure elucidation and SAR study. These findings identify a new class of modulators of GLP-1R signaling and suggest that GLP-1 is a viable target for drug discovery.

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