The agonistic activity of quercetin and its analogs towards the transient receptor potential ankyrin 1 (TRPA1) has been experimentally investigated. The human TRPA1 was expressed in HEK293T cells using a tetracycline-inducible system. The activation of TRPA1 was evaluated by a fluo-4 fluorescence assay based on calcium sensing. The results of a structure–activity relationship study led to the selection of six flavonoids, all of which activated the TRPA1 channel in a dose-dependent manner. Notably, the activation of TRPA1 by these flavonoid aglycones was completely inhibited by the co-treatment of the HEK293T cells with the TRPA1-specific antagonist, HC-030031. Several flavonoid glycosides and metabolites were also evaluated, but did not activate the TRPA1 except for methylated quercetin. On the other hand, TRPV1 (vanilloid receptor) did not respond to any of the flavonoids evaluated in this study. Therefore, these data suggest that the flavonoids would be promising ligands for the TRPA1.

The activation of TRPA1 was evaluated by fluo-4 fluorescence assay based on calcium sensing. Quercetin and its analogs activated TRPA1 in a dose-dependent manner.