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Anti-proliferative Efficacy of Xanthorrhizol on Cancer Cells via Activation of hTAS2R38 among 25 Human Bitter Taste Receptors

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Abstract

Human bitter taste-sensing type 2 receptors (hTAS2Rs) are expressed in various human tissues and may be associated with various cell signaling pathways, cell progression, and cell physiology in each tissue. hTAS2Rs can be a potential drug target because it is also expressed in some cancer cells. Xanthorrhizol (XNT) has various biological activities, such as anti-cancer, antimicrobial, anti-inflammatory, and antioxidant. XNT produces a bitter taste, but the specific hTAS2R activated is unknown, and the hTAS2R-mediated effect of XNT on cancer cells has not been studied. This study discovered the target receptor of XNT among 25 hTAS2Rs and confirmed the possibility of the hTAS2R-mediated inhibition of cancer cell proliferation. XNT activated only one receptor, hTAS2R38 (EC_{50}=1.606±0.021 μg/mL), and its activity was inhibited by probenecid, a hTAS2R38 antagonist. When HepG2 and MCF-7 cells were treated with XNT or phenylthiocarbamide (PTC), a known hTAS2R38 agonist, both chemicals inhibited cancer cell proliferation. XNT targets the human bitter taste receptor TAS2R38 and inhibits the proliferation of HepG2 and MCF-7 cells mediated by TAS2R38. This suggests that TAS2R38 may be a new target for disease treatment and a potential new factor for drug development.

Key Words : Xanthorrhizol, bitter taste receptor, TAS2R38, TAS2Rs

I. Introduction

The perception of bitterness is a conserved chemical sensation in mammals, playing a crucial role in detecting and avoiding potentially toxic substances. This sensation is particularly important as many toxic compounds often have a bitter taste (Breslin 2013). Bitter taste receptors (TAS2Rs), which belong to the GPCR (G-protein-coupled receptor) superfamily, sense the bitter taste of chemicals, including plant-based compounds (Andres-Barquin & Conte 2004). This GPCR family is characterized by notable diversity, encompassing approximately 25 distinct TAS2R genes in humans. Each gene encodes a specific TAS2R, each uniquely attached to detect various bitter compounds (Breslin 2013; Janssen & Depoortere 2013), and combinations of TAS2Rs allow the identification and discrimination of a wide range of bitter tastings. The structural and functional diversity of these receptors is a key aspect of the human gustatory physiology, enabling their detection and response to a multitude of bitter tastings found in the natural environment. This diverse receptor repertoire highlights the evolutionary significance of bitter taste perception as a critical mechanism for survival, guiding dietary choices and food intake behaviors.

TAS2R was initially thought to exist only on the tongue. Therefore, it was hypothesized that bitter taste perception originates on the tongue and serves as a pivotal warning signal for potential toxin ingestion (Tuzim & Korolczuk 2021). However, recent research has shown the expression of TAS2Rs in extraoral tissues such as the human bronchi in lower airways (Grassin-Delyle et al. 2013), vasoconstriction in the vasculature (Upadhyaya et al. 2014), nutrient sensing in the heart (Foster et al. 2013), spermatogenesis in the testis (Li & Zhou 2012), antiinflammatory and immune systems (Maurer et al. 2015), and keratinocyte differentiation in the skin (Wolfle et al. 2015). TAS2Rs expressed in the intestine can sense luminal content and GI hormones (Wu et al. 2002). Further, genetic variations in TAS2Rs are associated with various human disorders (Lu et al. 2017). These findings suggest that TAS2Rs play physiological roles beyond taste perception, underlining their potential as therapeutic targets for disease treatment and drug development.

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Various drugs, including xanthorrhizole (XNT), have bitter taste. XNT is a highly active and abundant compound isolated from essential oils of *Curcuma xanthorrhiza Roxb*. rhizome, also known as Java Turmeric (Oon et al. 2015). Curcuma xanthorrhiza exhibits anti-hyperglycemic and anti-inflammatory effects in high-fat diet-induced obese mice (Kim et al. 2014). XNT has anti-bacterial (Bhalodia & Shukla 2011), anticandida (Rukayadi et al. 2006), and anti-fungal activities, which are active against various pathogenic microorganisms (Nariya et al. 2011). Its antibacterial action is particularly noteworthy in the treatment of various diseases in the human body. Additionally, XNT is known for its pharmacological properties, including anticancer effects on various cancers such as skin, colon, and gastric cancers (Saleem et al. 2004; Chung et al. 2007; Oon et al. 2015). The effects of XNT, similar to those of numerous bioactive compounds, are commonly investigated by observing alterations in cellular biomarkers. The process of identifying precise molecular targets or specific cellular components that directly interact with a compound is intricate, necessitating comprehensive biochemical and molecular research. Considering that XNT is known to cause bitter taste, a potential target of XNT could be one or more of these TAS2Rs.

In this study, we explored the interactions between XNT and human TAS2Rs (hTAS2Rs). For this purpose, we transfected HEK293T cells with each of the 25 hTAS2Rs and determined their direct binding to XNT by observing changes in intracellular calcium levels in hTAS2R-expressing cells following XNT treatment in the presence or absence of a TAS2R antagonist. Using XNT and an identified targeted TAS2R agonist, we observed its effects on cell proliferation in two cancer cell lines known for their anticancer efficacy, HepG2 and MCF-7. Our data suggest the potential of hTAS2R agonists as new candidates for drug development, which could lead to the discovery of novel cancer treatment pathways.

II. Materials and Methods

1. Materials

HEK293T, MCF-7, and HepG2 cell lines were purchased from the American Type Culture Collection (ATCC; Manassas, VA, USA). Dulbecco's modified Eagle's medium (DMEM, Gibco), fetal bovine serum (FBS, Gibco), and penicillin/streptomycin were purchased from Gibco (Thermo Fisher Scientific Inc., Waltham, MA, USA). XNT was purchased from Abcam (Cambridge, UK). Resazurin sodium salt and phenylthiocarbamide (PTC, Sigma Aldrich, St. Louis, MO, USA).

2. Cell culture and transfection

The 25 hTAS2Rs (hTAS2R1, 3, 4, 5, 7, 8, 9, 10, 13, 14, 16, 19, 20, 30, 31, 38, 39, 40, 41, 42, 43, 45, 46, 50, and 60) and Gα16gust44 were constructed as described previously (Ammon et al. 2002; Ueda et al. 2003). The hTAS2R plasmids were cotransfected with Gα16gust44 expression plasmid (4:1) into HEK293T cells using Lipofectamine 3000 (Thermo Fisher Scientific, Waltham, MA, USA). The HEK293T, hTAS2R-expressing, HepG2, and MCF-7 cells were maintained in DMEM containing 10% FBS at 37 °C in a humidified atmosphere containing 5% CO_2.

3. Calcium imaging analyses

Human TAS2R-expressing cells were seeded onto black-wall 96-well plates (BD Falcon Labware, Franklin Lakes, NJ, USA) for 24 h prior to use. Cells were washed with assay buffer including 130 mM NaCl, 10 mM glucose, 5 mM KCl, 2 mM $CaCl_2$, 1.2 mM $MgCl_2$, and 10 mM HEPES (pH 7.4) and loaded with 5 μM fura-2, a Ca^{2+} indicator dye (Thermo Fisher Scientific), in assay buffer at 27ºC for 30 min. The cells were then washed with assay buffer and incubated at room temperature for an additional 15 min. Samples were manually administered into the well by adding 100 μL of aliquots of assay buffer supplemented with 2× ligands at the desired concentrations. Fura-2 fluorescence intensities were measured at excitation wavelengths of 340 and 380 nm using an Andor Luca CCD camera (Andor Technology, Belfast, UK) equipped with a fluorescence microscope (IX-71; Olympus, Tokyo, Japan). The images were analyzed using MetaMorph software (Molecular Devices, Sunnyvale, CA, USA). Y axis was performed as $\Delta F/F_0$, where ΔF depicted changes in the fluorescent ratio (340/380 nm) at each time and F_0 was the initial fluorescence intensity.

4. Cell viability

HepG2 and MCF-7 cells, seeded in 96-well plates, were pretreated with XNT (10, 50, 100, and 500 μg/mL) or PTC (0.1, 1, 10, and 50 μM). After incubation for 24 h, the cells were incubated with 0.025 mg/mL resazurin solution for 2 h at 37ºC in a humidified atmosphere containing 5% CO_2. Living cells reduced resazurin to fluorescent resorufin. The absorbance was measured at 570 nm using a microplate

reader (Molecular Devices, CA, USA). Data were normalized based on the control.

5. Statistical analysis

All data were analyzed using GraphPad Prism 10.0 (Inc., La Jolla, CA, USA). Data are presented as means±standard error. Data underwent analysis via one-way analysis of variance, subsequently followed by the Tukey's honest significant difference test for further examination.

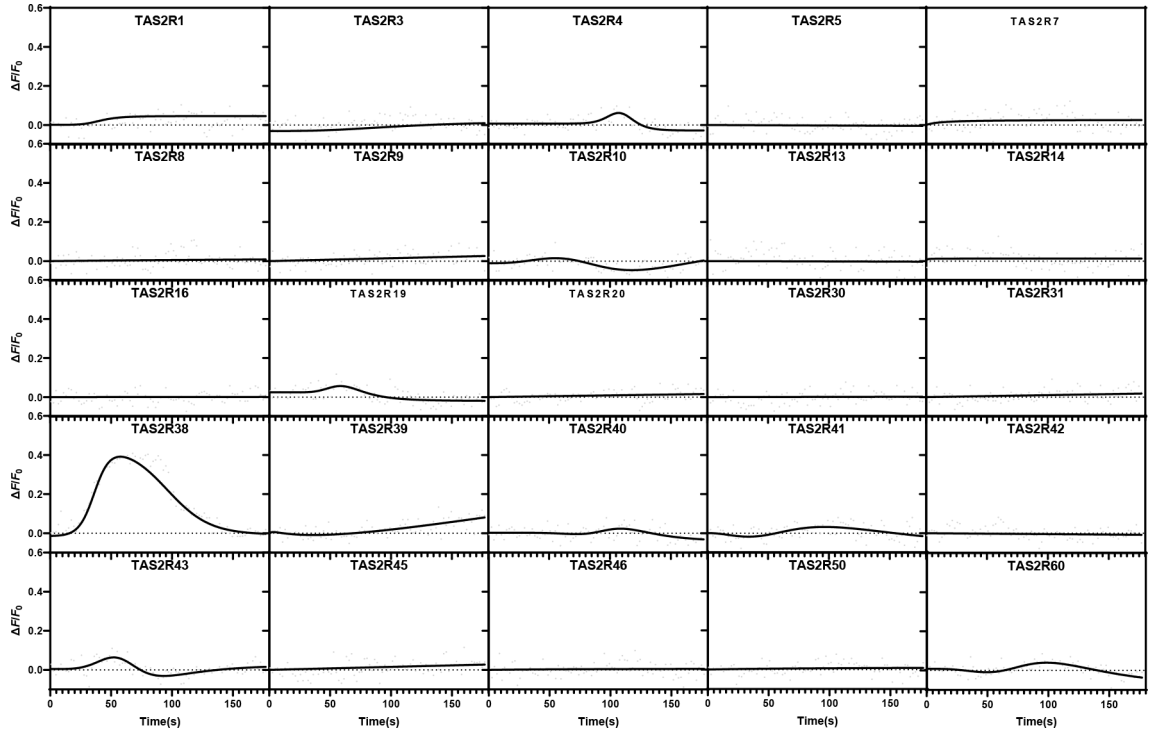
III. Results

1. XNT activates only a single receptor hTAS2R38

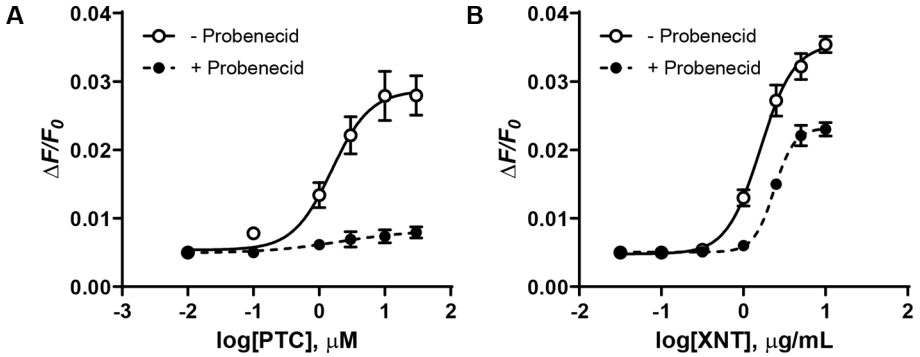
Since XNT is known to have a bitter taste, we investigated whether this taste was related to TAS2Rs. In humans, bitter taste perception is mediated by 25 functional bitter taste receptors (TAS2R1, 3, 4, 5, 7, 8, 9, 10, 13, 14, 16, 19, 20, 30, 31, 38, 39, 40, 41, 42, 43, 45, 46, 50, and 60) located in the taste cells of tongue (Foster et al. 2013). We transfected each of the 25 TAS2R families on HEK 293T cells and performed calcium imaging experiments using XNT. When hTAS2R-expressing cells were treated with XNT for 15 s, the intracellular calcium response increased only in hTAS2R38-expressing cells within 60 s of injection <Figure 1>. These results indicated that XNT becomes active upon binding to hTAS2R38.

2. PTC and XNT are inactivated by TAS2R38 antagonist

The data shown in <Figure 1> confirmed that XNT reacted only with TAS2R38. PTC is a bitter-tasting synthetic compound that acts as a TAS2R38 agonist. To confirm the generation of XNT through TAS2R38, the activities of XNT and PTC were verified using probenecid, a known TAS2R38 antagonist. As shown in <Figure 2A>, PTC increased the calcium levels in hTAS2R38-expressing cells in a concentration-dependent manner, with an EC_{50} of 1.550± 0.066 μM. Additionally, probenecid completely blocked the PTC-induced calcium increase at concentrations between 0.01 and 30 μM. Similar to PTC, XNT also activated hTAS2R38 with an EC_{50} of 1.606±0.021 μg/mL <Figure 2B>. Upon addition of probenecid to hTAS2R38-expressing cells, the XNT concentration-response curves shifted to the right, indicating an inhibitory response. The shifted EC_{50} value for XNT was 2.360±0.004 μM, and the maximum signal of XNT also reduced from 0.03552 to 0.02320 by TAS2R38 antagonist probenecid. Therefore, we confirmed that XNT and PTC reacted with TAS2R38.

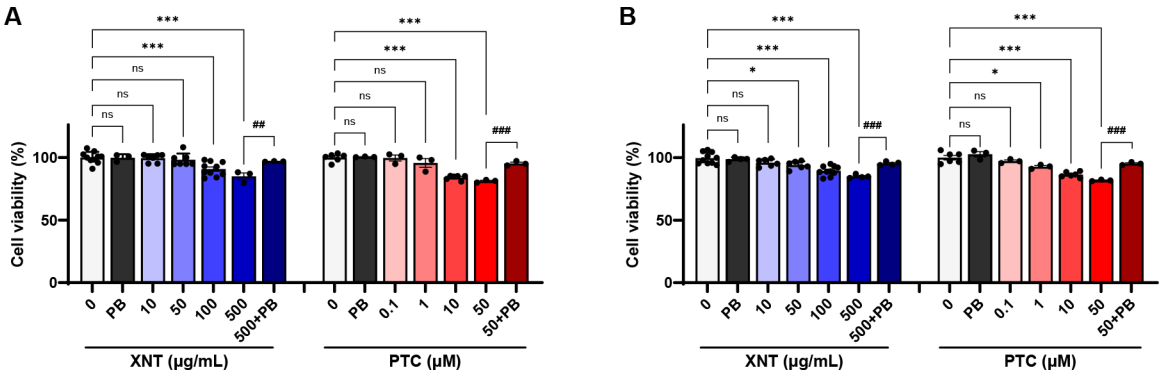


<Figure 1> Intracellular calcium responses of hTAS2R-expressing cells to xanthorrhizol (XNT).
The representative traces showing responses of HEK293T cells co-expressing 25 bitter taste receptors (TAS2Rs) and Gα16gust44 in the presence of XNT in a calcium imaging assay. The data were normalized as percentages of the maximal signals obtained using the ligands.



<Figure 2> Suppression of phenylthiocarbamide (PTC)- and XNT- induced concentration-dependent curves by probenecid, a TAS2R38 antagonist.

Effects of PTC (A) and XNT (B) on hTAS2R38-expressing cells in the presence or absence of probenecid. Cells expressing TAS2R38 were loaded with Fura-2, and the effects of XNT and PTC were quantitatively evaluated using a calcium assay. The concentration-dependent effects of XNT (0.01-30 μg/mL) or PTC (0.1-10 μM) treatments were quantitatively analyzed in the presence or absence of 1 mM probenecid. Each point represents the mean±SEM (n=4). The EC50 values were estimated to be 1.606±0.021 μg/mL for XNT and 1.550±0.066 μM for PTC.



<Figure 3> Regulation of cell proliferation by XNT and PTC in HepG2 and MCF-7 cell lines via TAS2R38-mediated pathway.

HepG2 cells (A) and MCF-7 cells (B) were treated with the XNT or PTC at different concentrations (10, 50, 100, and 500 μg/mL or 0.1, 1, 10, and 50 μM, respectively) and then the high concentration XNT and PTC was treated with 1 mM probenecid (PB). After 24 h incubation, a resazurin assay was performed to determine cell viability. All data were presented as mean±standard deviation (SD) of at least three separate experiments. *p<0.05 and ***p<0.001 vs. control group. $^{\#\#}$p<0.01 and $^{\#\#\#}$p<0.001 vs. 500 μg/mL XNT or 50 μM PTC group.

3. XNT regulates cell proliferation in HepG2 and MCF-7 cell lines via hTAS2R38

XNT increases apoptosis via upregulation of the p53- and Bcl-dependent mitochondrial pathways, as reported in various cancer types such as HepG2 liver cancer (Handayani et al. 2007), HeLa cervical cancer (Ismail et al. 2005), and MCF-7 breast cancer (Cheah et al. 2006). XNT inhibited Akt expression and TPA-induced NF-kB activation in mouse skin cancer. Therefore, we attempted to confirm whether XNT showed anti-proliferative effect through hTAS2R38, and in this case, PTC was also used. HepG2 is a hepatocellular carcinoma cell line, and MCF-7 is a breast cancer cell line. XNT and PTC reduced the viability of HepG2 and MCF-7 cells in a concentration-dependent manner <Figure 3>. Cell viability rescued by TAS2R38 antagonist probenecid in HepG2 and MCF-7 cells with PTC or XNT treatment. Additionally, anticancer effects may be mediated by TAS2R38.

IV. Discussion

Bitter taste is perceived by TAS2Rs on the tongue. It is reported to be expressed in organs with varying functional activities depending on the type of cell or tissue (Wu et al. 2002). However, the factors that target TAS2R and its ligands are yet to be elucidated, and studies on their functions need to be made available. Therefore, we identified a factor, XNT, that targets TAS2R, showing that substances that activate TAS2R can have anti-proliferative effects.

Taste GPCRs are activated by various ligands, such as lipids, sugars, peptides, and proteins in food, and they recruit G proteins to activate cell signaling effectors (Ahmad &

Dalziel 2020). Among two types of GPCRs, type 2 taste GPCRs are represented as bitter taste receptors on bitter taste-sensing cells in type 2 TRC, and 25 TAS2Rs have been reported to be expressed in humans (Andres-Barquin & Conte 2004). TAS2R has been implicated in a variety of chemosensory functions and innate immunity (Gopallawa et al. 2021). For example, TAS2R in nasal epithelial cells binds to bacterial products and activates Ca^{2+}-driven nitric oxide production, which increases ciliary beating and kills bacteria, thus affecting our body's homeostatic regulation (Carey & Lee 2019). Thus, TAS2Rs are sensory receptors are associated with the innate immune responses in the respiratory tract. In particular, the human TAS2R38 receptor encodes a bitter taste receptor that regulates bitter taste perception and differentiation of nutritional compounds ingested in the oral cavity as well as the gastrointestinal tract (Choi et al. 2016). TAS2Rs are present and functionally active in carcinogenic cells (Zehentner et al. 2021). Recent studies have reported differences in TAS2R expression between cancer and normal human cell lines and tissues, highlighting the importance of TAS2R in cancer progress biology (Costa et al. 2023). TAS2R10 and TAS2R38 proteins were detected in over 75% of the human cancer tissue, but not in normal tissue (Singh et al. 2014; Martin et al. 2019; Costa et al. 2023). Moreover, TAS2R38 has been found in tumor-infiltrating leukocytes (Gaida et al. 2016). TAS2R4 is strongly expressed in nearly 70% of breast cancer markers, and functional studies of these cells showed increased intracellular calcium mobilization following application of natural and synthetic bitter agonists (Singh et al. 2014). Therefore, as the role of the ligand that activates TAS2R in anticancer treatment is significant, research to discover this ligand is important.

We found that XNT activated only a single TAS2R38 among 25 hTAS2Rs. This fact highlights a very specific interaction that may be important for targeted therapeutic strategies and provides a clear path for further research into its mechanisms and potential applications in cancer treatment. This fact highlights very specific interactions that may be important for targeted therapeutic strategies and provides a clear path for further research into mechanisms and potential applications in cancer treatment. We then sought to confirm this in HepG2 and MCF-7 cells, where the anticancer efficacy of XNT is known (Cheah et al. 2006; Handayani et al. 2007). In both cancer cell lines, XNT causes cell cycle arrest at the G_2/M phase, significantly reducing cell proliferation, and induces apoptosis by activating caspase-3/7 and -9, leading to mitochondrial-associated cell death. We speculated that this anticancer effect of XNT might be exerted through hTAS2R38. However, although we used commercially available XNT, the anticancer efficacy of XNT observed in this study was unfortunately minimal compared to previously reported results. Consequently, we were only able to observe only its anti-proliferative effects rather than any significant anticancer efficacy. Nevertheless, XNT effectively inhibited the proliferation of cancer cells in a concentration-dependent manner, and its efficacy was found to be effectively inhibited by probenecid, an antagonist of hTAS2R38. In other words, the inhibitory effect of XNT on HepG2 and MCF-7 cell proliferation occurred through hTAS2R38, showing that TAS2R agonists may suggest the potential use of bitter compounds for the prevention and treatment of various human diseases, including many types of cancer.

V. Summary and Conclusion

This study identified a novel target receptor for the bitter compound XNT and confirmed its receptor-mediated anti-proliferative effects. After transfecting each of the 25 types of human bitter taste receptors into HEK293T cells and treating them with XNT, it was found that only the cells transfected with the bitter taste receptor hTAS2R38 showed an increase in intracellular calcium. Furthermore, the reduction in the calcium response by probenecid, an antagonist of hTAS2R38, confirmed that hTAS2R38 is the target bitter taste receptor that binds with XNT. Additionally, treating HepG2 and MCF-7 cells with XNT resulted in a decrease in cell proliferation mediated by hTAS2R38. These results indicate that XNT is detected as bitter through hTAS2R38, and the anti-proliferatie efficacy of XNT in HepG2 and MCF-7 cells is mediated through hTAS2R38. This also suggests that bitter taste receptors could be potential target proteins for cancer drugs.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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