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A REVIEW: A ROLE OF CAPSAICIN TO REGULATING T2R AND TRPV1 AND ITS ASSOCIATION IN CANCER DEVELOPMENT

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Abstrak

Kanker menjadi salah satu penyebab kematian terbanyak di dunia. Hingga saat ini diperkirakan telah terjadi 10 juta kematian yang disebabkan oleh penyakit ini. Hingga kita dapat mengetaui bahwa kanker merupakan penyakit yang terjadi akibat ketidakseiombangan gen molekul dan reseptor dari sel. Reseptor pengecap rasa pahit (T2R) diketahui diekspresikan diluar organ pengecap dan mempunyai fungsi selain mendeteksi persepsi rasa pahit. Reseptor ini diketahui dapat terlibat dalam mekanisme perkembangan dari sel kanker. capsaicin terlibat dalam berbagai macam gen yang mengatur siklus hidup dan pertumbuhan dari sel kanker. Aktivitas dari capsaicin dalam menghambat pertumbuhan dari sel kanker dapat diamati melalui berbagai macam target gen seperti jalur pensinyalan onkogen dan gen penekan pertumbuhan tumor (tumor-suppressor gene). Pengamatan sistematika pada artikel ini dilakukan dengan menggunakan 4 database elektronik yaitu Google Scholar, PubMed, ResearchGate dan NCBI. Kata kunci yang digunakan adalah “capsaicin” yang digabungkan dengan “T2R”, “T2R8”, “TAS2R”, “TRPV1”, “GPCRs” dan juga “Cancer”, “Cancer cell line”, “Mice”, “Rat”, “Human”. Capsaicin mempengaruhi aktivitas sel normal dan sel kanker melalui jalur TRPV 1 dan T2r. Melalui jalur TRPV1, Capsaicin meningkatkan kalsium intraseluler dan mengganggu integritas matriks mitokondria. Melalui jalur T2r, Capsaicin menyebabkan pelepasan IP3, yang meningkatkan kalsium intraseluler melalui stres retikulum endoplasma.

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***Kata Kunci**: Kanker, Capsaicin, TRPV1, T2R*

Abstract

Cancer is one of the leading causes of death in the world. It is estimated that this disease has caused 10 million deaths. The cause of the development of cells into cancer is still a mystery until we know that cancer is a disease that occurs due to an imbalance of molecular genes and cell receptors. Bitter taste receptors (T2R) are known to be expressed outside the taste buds and detect the perception of a bitter taste. These receptors are known to be involved in the mechanism of cancer cell development. Capsaicin is involved in a wide variety of genes that regulate the life cycle and growth of cancer cells. The activity of Capsaicin in inhibiting cell growth can be observed through various target genes, such as oncogene signaling pathways and tumor-suppressor genes. The systematics in this article is carried out using four electronic databases, namely Google Scholar, PubMed, ResearchGate, and NCBI. The keywords used are "capsaicin" combined with "T2R", "T2R8", "TAS2R", "TRPV1", "GPCRs" and also "Cancer", "Cancer cell line", "Mice", "Rat", "Man". Capsaicin affects the activity of normal cells and cancer cells through the TRPV 1 and T2r pathways. Through the TRPV1 pathway, Capsaicin increases intracellular calcium and disrupts the mitochondrial matrix. Via the T2r pathway, Capsaicin causes IP3, which increases intracellular calcium through endoplasmic reticulum stress.

***Keywords**: Cancer, Capsaicin, TRPV1, T2R*

1. INTRODUCTION

Cancer is one of the leading causes of death in the world. It is estimated that this disease has caused 10 million deaths. The formation of cancer cells is not separated from the division errors that occur in the body's cells. Therefore, cancer can spread throughout the body's tissues. Cancer can be formed due to radiation, chemical compounds, and viruses that can damage genetic material. However, the cause of the development of cells into cancer is still a mystery until we know that cancer is a disease that occurs due to an imbalance of molecular genes and cell receptors (NIH, 2022).

Bitter taste receptors (T2R) are known to be expressed outside the taste buds and have functions other than detecting the perception of a bitter taste. These receptors are known to be involved in the mechanism of the development of cancer cells. Increased expression of T2R mediated by bitter stimuli is known to enhance the anti-cancer effect (Zehentner et al, 2021). The T2R group belongs to G protein-coupled receptors that can be activated through various molecules (Behrens & Meyerhof, 2011). The sensitivity of T2R is known to increase intracellular calcium ions, which causes cells to activate the innate immune response (Lee et al., 2014).

Capsaicin is the most abundant bioactive phytochemical component found in red chili plants. Christian Bucholz first extracted this compound in 1816, and proved to have analgesic activity (Chang et al., 2021). Research from Clark et al. (2016) states that capsaicin is involved in various genes that regulate cancer cells' life cycle and growth. Capsaicin's activity in inhibiting cancer cell growth can be observed through various target genes, such as oncogene signaling pathways and tumor-suppressor genes (Clark et al., 2016). Capsaicin can stimulate the nerves responsible for heat and stimulate the bitter taste receptors. Capsaicin has a function similar to ethanol in increasing the expression of bitter receptors (Nolden et al., 2016). This ability causes capsaicin to be able to enter various balance pathways in the body system (Smail, 2019).

In addition to its function in activating bitter taste buds, the vanilloid content in capsaicin is known to activate the transient Transient receptor potential vanilloid 1 (TRPV1). These receptors can regulate the balance of intracellular calcium ions. Sensitization and activation of TRPV1 can affect several functions of organelles in producing bioactive components involved in the inflammatory response in cells (Clark & Lee, 2016). Activating these two receptors, T2R and TRPV1 can regulate the cell life cycle, such as its ability to divide and carcinogenesis. This review article will focus on the ability of capsaicin to activate these two receptors and their relationship to preventing the development of cancer cells.

This review aims to observe the activity of Capsaicin with membrane receptors on normal cells and cancer cells. The review will focus on the expression of TRPV1 and T2R as the primary receptors for Capsaicin and the intracellular mechanisms involved.

2. RESEARCH METHOD

2.1 Searching Criteria

This systematic review includes studies focusing on the ability of Capsaicin to increase the expression of T2R and TRPV1, which are involved in the development of cancer cells observed from various perspectives. This article aims to summarize the current knowledge regarding the relationship between capsaicin and cancer cells directly or mediated by T2R and TRPV1, related to gene expression, and protein interactions at the molecular level in each compound affected by T2R and TRPV1. The scientific literature on the effect of Capsaicin on cells observed through the link between T2R and TRPV1 is still widely available, so this article is expected to provide a comprehensive overview and encourage further research.

2.2 Journal Search Strategy

The systematics in this article is carried out using four electronic databases, namely Google Scholar, PubMed, ResearchGate, and NCBI. The keywords used are "capsaicin" combined with "T2R", "T2R8", "TAS2R", "TRPV1", "GPCRs" and also "Cancer", "Cancer cell line", "Mice", "Rat", "Man". The articles used are articles that at least meet the two main criteria above—later articles as a database for writing this article. The effect of Capsaicin on taste receptors was carried out by a literature study with inclusion criteria, namely 1) research conducted on humans and experimental animals and 2) observation of bitter receptors found on the tongue, respiratory tract, and digestive tract. Pre-proof journals and review journals are included in the exclusion criteria used.

3. RESULTS AND DISCUSSION

Table 1. Effects and roles of Capsaicin on Taste receptors and TRPV

Object	Cell	Receptor	Function	reference
Kultur sel	Cell line	T2rs	Anti-osteosarcoma agent	Bao *et al, 2019*
Kultur sel	fibroblast cell line	Sitotoksisitas	Induces cytotoxic effects	Lavorgna *et al, 2019*
Kultur sel	MCF-7, T47D, BT-474, SKBR-3 dan MDA-MB231	EGF	Suppressing the growth of breast cancer cells is good	Thoennissen *et al, 2019*
Mencit	t24 cell (bladder cell line)	T2rs	ROS activation and apoptosis induction	Yang *et al*, 2010
Mencit	Fungiform, foliata, circumvallata	TRPV1	Regulates the passage of stimuli to nerves	Zhang *et al*, 2010
Mencit	Brain call	TRPV1	Ca2+ . ion gate	Zhang *et al*, 2010
Tikus	pulmonary neurons	T2rs, TRPV1	Detection of toxic components	Gu *et al*, 2017
Tikus	Fungiform, foliata, circumvallata	T1rs - T2rs	Taste bitter taste via vanilloid receptor (VR1)	Moon *et al, 2010*
Tikus	Epithelial cell	T2rs	somatosensory system	Roper, 2014
Tikus	ciliated respiratory epithelial cells	TRPV1	trpv1 activation via T2rs	Qihai *et al*, 2017
Tikus	Sel epitelial	TRPV1	Circulation, mucus secretion and homeostasis	Holzer *et al*, 2011
human	Fungiform, foliata, circumvallata	TAS2R3/4/5	Bitter taste	Nolden *et al*, 2011
human	Circumvallata	T2r, TRPV1	Peer signal on taste receptors	Jahng *et al*, 2010
Rabit	Dorsal root ganglia	TRPV1	Influx of Ca . ions	Bujak *et al*, 2019
Rabit	HEK293 cells	TRPV2	Influx of Ca . ions	Bujak *et al*, 2019

Based on table 1, it can be observed that Capsaicin has a comprehensive function in the digestive, respiratory and nervous organs. It can be said that Capsaicin can affect the bitter receptor and transient receptor potential vanilloid 1 (TRPV1), which are spread in the body. The effect given by Capsaicin by activating these two channels can extend from Ca2+ ion intake, Chemesthesis, excitatory pathways to nerves, to cell balance and apoptosis.

Capsaicin has different effects on the research subjects that have been carried out. At the cell culture level, Capsaicin can stimulate TRPV1 expression, which is continued downstream to enhance the cytotoxic effect of cells (Bao et al., 2019; Lavorgna et al., 2019)). The effect of Capsaicin in increasing the sensitivity of bitter receptors was also observed in mice, rats, and guinea pigs (Holzer et al., 2011). In vitro and in vivo studies using this compound indicate that Capsaicin increases the sensitivity of TRPV and bitter receptors such as Taste 2 receptors (T2rs) (Bao et al., 2019; Yang et al., 2010).

The effect caused by Capsaicin on body functions can be used to observe the homeostatic condition of the body in response to an imbalance. Vanilloid receptor (VR), as the primary receptor of Capsaicin, has a downstream signal that is vital in controlling cell life. Capsaicin will increase

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recognition by TRPV1. The presence of this gate can be used by cells to carry out ion exchange (Ca2+) as an ion balance and response to cell death (Yang et al., 2017).

Increased TRPV1 is also closely related to T2rs. It is known that activation of T2rs is associated with mediating the sensitization of TRPV1 and making it more sensitive to stimuli (gu et al., 2017). Activation of this receptor is also associated with Ca2+ ion intake in Fungiforme, foliate and circumvallate papillae in rats and humans (Park et al., 2003; Green et al., 2003). This gate is highly permeable to calcium ions which are also integrated with the heat sensor (Zhang et al., 2020). The presence of the TRPV1 ion channel and its function in regulating the entry and exit of calcium can mediate the immune response to the presence of cancer cells (Bujak et al., 2019).

The expression of TRPV1 induced by Capsaicin gave the same response as human embryonic kidney (HEK) 293 cells and Dorsal root ganglion (DRG) in receiving heat stimulation (Rosenberger et al., 2020; Nascimento et al., 2018). This activation can also cause a response from NfKb to reduce chemokines and life cytokines from cells (Gavva et al., 2004).

Taste receptors were initially found only on the tongue that functions in taste sensitivity to food but is also involved in chemosensory outside the tongue. The expression of taste receptors has been observed in various organs such as the brain, respiratory, reproductive system, and digestive tract (Kinnamon, 2012). The presence of this receptor outside the tongue has the primary function of detecting taste. It is much more developed to detect toxic components that will or have entered the body (Feng, 2013). The expression of varying taste receptors in human organs can also be closely related to the innate immune response (Lee et al., 2015; Lee et al., 2015)

Taste receptors can be divided into two main classes: ion channels and G protein-coupled receptors (GPCRs). Ion channels maintain the balance of intracellular sodium ions, while GPCRs detect taste perception, one of which is bitter taste (Li, 2013). Ion exchange by the receptor will then be mediated by the epithelial sodium channel (ENaC), which is highly selective for Na+ ions. ENaC belongs to the Degenerin ion channel family, which is expressed on the plasma membrane of cells making up the intestines, kidneys, lungs, and various organs that can be used to exchange Na+ ions (Tushar & Okusa, 2019).

GPCRS was first identified on the tongue's taste 2 receptors (Tas2R). These receptors can then transmit taste and toxic signals to the brain mediated by taste family type 1 (T1R) and taste family type 2 (T2R) receptors. T1R is activated by sweet, salty, and umami tastes, while T2R is activated by bitter tastes (Lee et al., 2015). So far, it is known that there are more than 25 heterodimers of T2R formed by various bitter sensations. Animals use bitter taste recognition as a natural response to detecting the presence of toxins, including alkaloids found in the plants they eat (Li & Zhang, 2015).

Table 2 Comparison of observations on t2r8 in various organisms

Organism	**Cell**	**Pengamatan**	**Function**	**reference**
Cell line	Acute Myeloid Leukemia (AML)	t2r8	Balance of leukemia cell culture	Salvestrini *et al*, 2020
Caenorhabditis elegans	ASI Neurons	cDNA t2r8	Chemotaxis	Conte *et al*, 2006
Mencit	RAW264.7 Cell line	t2r8	Anti-inflammatory	Coquant *et al*, 2021
Tikus	STC-1 cells	rt2R8	Regulates intracellular Ca concentration	Wu *et al*, 2002
Tikus	foliata	t2r8	Bitter taste	Adler *et al*, 2000
Human	Epithelial Cell	t2rs	Bitter taste	Tarragon *et al*, 2020
Human	Papillary Thyroid Carcinoma (PTC)	TAS2R3/4	Controls thyroid hormone production	Choi *et al*, 2018

Human	Airway Epithelial cells	t2rs	Initiation of innate immune response and apoptosis	Sharma *et al*, 20[illegible]

Increased expression of T2rs occurs in the papillae Fungiformis, foliate and circumvallate and can also increase the expression of T2rs found in the respiratory and digestive tract. T2rs are not only a bitter taster but can also be used to regulate the reception of extracellular signals in the intracellular direction (Zhang et al., 2010). Activation of T2rs is also associated with introducing toxic or toxic substances to cells through vanilloid receptors. So it can be seen that the presence of Capsaicin here can increase mucus excretion in an organ through vanilloid receptors (Green et al., 2003).

Capsaicin can also increase the sensitivity of mucous gland epithelial cells to a substance or chemical compound. This condition can increase the response of somatosensory cells that regulate the work of the sensory nervous system (Roper, 2014). This response is also related to the function of T2rs, which can transmit stimuli as bitter taste buds (Green et al., 2003). Its ability to continue this stimulation can play a role in maintaining homeostatic conditions of the body, so some literature still says that the presence of Capsaicin can increase mucus production from glands and even reduce its activity (Holzer et al., 2011).

In STC-Cells isolated from the duodenum of rats, the presence of the t2r family can be detected, namely t2r2, t2r3, t2r5, t2r6, t2r8, t2r10, and t2r12 (Wu et al., 2018). Furthermore, the presence of t2r8 was found in the intestinal secretin tumor cell line (STC-1), which regulates the concentration of intracellular calcium ions (Wu et al., 2018). t2r8, together with other t2r families, can initiate physiological responses when combined with their receptors. This condition can increase the chance of t2r8 preventing the spread and growth of cancer cells (Seo et al., 2017).

The group of t2r8 in mice includes T2R08; mGR08; mT2R8 PTC; T2R8; HTAS2R8; H T2R4; HTAS2R4 (Andres-Barquin & Conte, 2004). The presence of t2r8 and t2r4 in mice has the same function in detecting bitter taste and calcium ion balance (Wolfgan et al., 2010). Genetic variations on t2r4 in humans can also be used to reduce the severity of thyroid hormone-related Papillary Thyroid Carcinoma (PTC) patients (Choi et al., 2018). In addition, the expression of t2r8 could also be observed at the cell line level of Acute Myeloid Leukemia (AML). The presence of this receptor has a function in regulating the intake of calcium ions into cells (Salvestrini et al., 2020)

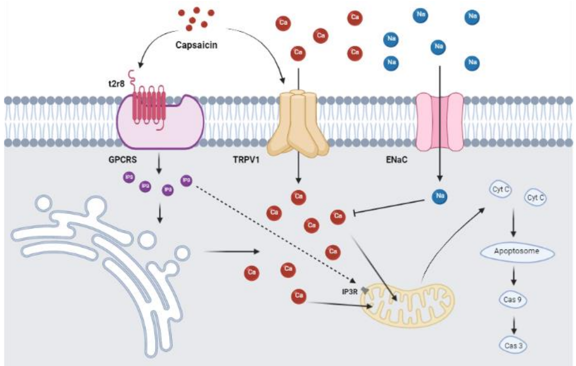

Figure 1 Interaction between Capsaicin with t2r8 and TRPV1 on cancer cell apoptosis

Capsaicin activates the Inositol triphosphate (IP3) signaling pathway via GPCRS-mediated t2r8 (Miura et al., 2007). IP3 can stimulate endoplasmic reticulum stress, which can affect the balance of Ca2+ ions directly in the cytoplasm of pc12 cells (Krizanova et al., 2014). Capsaicin has the same role as resiniferatoxin in increasing the activity of the lipid-dependent kinase in dorsal root ganglion neurons and triggering the activity of protein kinase C, which is also involved in regulating cell division (Harvey et al., 1995). IP3 receptors (IP3R) are also found on the surface of the mitochondrial membrane. This protein also mediates communication between the ER and mitochondria in activating the cell death cascade through apoptosis (Bartok et al., 2019).

4. CONCLUSIONS AND SUGGESTIONS

Capsaicin affects the activity of normal cells and cancer cells through the TRPV 1 and T2r pathways. Through the TRPV1 pathway, Capsaicin increases intracellular calcium and disrupts the integrity of the matrix mitochondrial. Through the T2r pathway, Capsaicin causes the release of IP3, which increases intracellular calcium through endoplasmic reticulum stress.

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