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REVIEW

Canonical transient receptor potential channels and their modulators: biology, pharmacology and therapeutic potentials

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Abstract Canonical transient receptor potential channels (TRPCs) are nonselective, high calcium permeability cationic channels. The TRPCs family includes TRPC1, TRPC2, TRPC3, TRPC4, TRPC5, TRPC6, and TRPC7. These channels are widely expressed in the cardiovascular and nervous systems and exist in many other human tissues and cell types, playing several crucial roles in the human physiological and pathological processes. Hence, the emergence of TRPCs modulators can help investigate these channels' applications in health and disease. It is worth noting that the TRPCs subfamilies have structural and functional similarities, which presents a significant difficulty in screening and discovering of TRPCs modulators. In the past few years, only a limited number of selective modulators of TRPCs were detected; thus, additional research on more potent and more selective TRPCs modulators is needed. The present review focuses on the striking desired therapeutic effects of TRPCs modulators, which provides intel on the structural modification of TRPCs modulators and further pharmacological research. Importantly, TRPCs modulators can significantly facilitate future studies of TRPCs and TRPCs related diseases.

Keywords Canonical transient receptor potential channels modulators · Calcium ion · High-resolution structures · Drug discovery · Therapeutic potentials

Introduction

The primary Transient Receptor Potential (TRP) protein was initially discovered in the experiment of aberrant visual transduction of *Drosophila melanogaster* (Cosens and Manning 1969). TRP channels (TRPs) feasibly form tetramers, a six-transmembrane domain structure with a cation-permeable pore loop between the fifth and sixth transmembrane domains (Hofmann et al. 2017). It is worth noting that there are differential expressions of TRPs in many tissues and cells and that TRPs show functional diversity and different pathological characters (Zhu et al. 2011). So far, the TRPs superfamily in mammalian is composed of 28 nonselective cation channels, and consists of several subfamilies: TRPC (canonical), TRPM (melastatin), TRPA (ankyrin), TRPV (vanilloid), TRPML (mucolipin), and TRPP (polycystin) (Zhu et al. 2011; Zheng 2013; Minard et al. 2018). The TRPC channels (TRPCs) family is the closest homolog to *Drosophila* TRP channels (Zheng 2013; Li 2017).

TRPCs are nonselective (Ca^{2+}, K^+, Na^+) and high calcium permeability cationic channels. They are extensively expressed in many cells and tissues, including the lung, heart, brain, placenta, adrenal gland, retinal endothelial, testis, and kidney; they play crucial roles in many human physiological and pathological processes and are involved in various pathogenesis (Tai et al. 2017; Li et al. 2019b). TRPCs are activated by various chemical and physical stimuli through the phospholipase C (PLC) signaling pathway. For instance, TRPC1/4/5 homotetramers and heterotetramers channels are activated by Gq protein-coupled PLC and

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phosphatidylinositol 4,5-bi-sphosphate (PIP2) hydrolysis. This process generates inositol triphosphate (IP3) that binds to the endoplasmic reticulum IP3 receptor increasing extracellular Ca^{2+} entry called store-operated calcium entry (SOCE). Also, TRPC3/6/7 channels are unique in being directly activated by diacylglycerol (DAG), a degradation product of PIP2, which is known as receptor-operated calcium entry (ROCE) (Minke and Cook 2002; Jeon et al. 2012; Zheng 2013; Li et al. 2019b).

The present review focuses on the classification, structures, and function of TRPCs, as well as TRPCs modulators and their desired therapeutic effects, highlighting examples and opportunities for the application of TRPCs modulators in the pathology of various diseases.

Classification of TRPCs

TRPs were discovered in 1969 when the founding member of this superfamily was studying the *D. melanogaster* visual nerve transduction system (Cosens and Manning 1969). However, it was not until 1975 that the channels were named (Minke et al. 1975). Since the detection of TRPs, TRPC1 was the first human homolog of TRPs reported in 1995, but no further study for its functionality had been conducted yet (Wes et al. 1995). Over the following 3 years, five more novel related mammalian homologs (TRPC2-6) were detected, in addition to the functional expression of TRPC1 and TRPC3 and the cloning and function of TRPC5 on the store- or receptor-operated Ca^{2+} entry (Zhu et al. 1996; Boulay et al. 1997; Okada et al. 1998). Additionally, another novel Ca^{2+} channel protein, TRPC7, was reported (Nagamine et al. 1998). At present, and considering the sequence homology, the seven mammalian TRPC subfamily members are subdivided into three subgroups: TRPC1/4/5, TRPC2, and TRPC3/6/7 (Zhu et al. 1995). Since human TRPC2 is most likely a pseudogene (Wissenbach et al. 1998), this review focuses on investigating TRPC1/4/5 and TRPC3/6/7 channels.

Structure of TRPCs

Ions channels modulate the flow of ions through the plasma membrane through temperature, chemical signals, electrical signals, or mechanical signals. Determining the channels' structure is crucial to understanding their molecular mechanisms (Moiseenkova-Bell and Wensel 2011). Along with the tremendous advancement of the electron cryo-microscopy (cryo-EM) technology, high-resolution structures have become an increasingly dominant method for determining the structure of many receptor complexes (Egelman 2016). This technological advancement has resulted in a revolution in the mammalian respiratory complex I structure (Agip et al. 2019). In the last few decades, the atomic models of macromolecular complexes were determined by X-ray crystallography (Egelman 2016). It was not until 2018 that the high-resolution structure of TRPCs was revealed (Li et al. 2019a). Compared with classical X-ray crystallography, cryo-EM technology does not need to crystallize or diffract the protein/protein complex, and only uses a small number of samples. Owing to this advancing technology, membrane proteins' structure determination has become convenient, particularly for various ion channels (Li et al. 2019a; Wang et al. 2020a).

The current TRPCs structures reported had TRPC3, TRPC4, TRPC5, and TRPC6 channels (Fan et al. 2018; Duan et al. 2018, 2019; Azumaya et al. 2018; Vinayagam et al. 2018; Tang et al. 2018). The overall resolution of TRPCs in these reports is exceptionally similar, and they all showed that TRPCs are tetramer structures composed of homologous or heterologous monomers that contain six transmembrane spanning domains (Duan et al. 2018, 2019).

Many experiments showed that TRPC5 was closely related to TRPC4, with a 65% sequence identity (Duan et al. 2018). Mice TRPC4 and TRPC5 carry out protein purification (pH 7.5); then, they are used for the single-particle cryo-EM analysis of the overall resolution of 3.3 Å and 2.8 Å in its unliganded (apo) state, respectively. TRPC4 poor densities are due to disordered regions; it consists of 4 residues in the S1-S2 loop, 2 residues in the S3-S4 loop, 27 residues in the distal N terminus, and 28 residues in the truncated distal C terminus, whereas TRPC5 is composed of 7 residues in the S1-S2 loop, 28 residues in the distal N terminus, and 3 residues in the truncated distal C terminus (Duan et al. 2018, 2019). The TRPC4 and TRPC5 structures are formed by a four-fold symmetric homotetramer with dimensions of 100 Å by 100 Å by 120 Å. Each of the four monomers consists of a unique compact cytosolic domain and a transmembrane domain (TMD), distinguishing it from other TRPs. The cytosolic domain is divided into two subdomains: the N terminus region with four ankyrin repeats domain of AR1 to AR4 and seven α-helices domains of H1 to H7 and the C terminus region with a connecting helix and a coiled-coil domain. The TMD is composed of six helices (S1 to S6), a TRP domain, and several small helices (Duan et al. 2018, 2019). In the TRPC4 and TRPC5 channels, the extracellular third transmembrane helix S3 region is made up of four helical turns, limiting potential extracellular interactions (Duan et al. 2019).

Compared with TRPC4 and TRPC5 channels, the extracellular S3 region in the TRPC3 and TRPC6 channels is a unique transmembrane domain that is remarkably long, constituting an extracellular region that can be used as a sensor of external stimuli (Fan et al. 2018; Duan et al. 2019). In the stable closed state, single-particle cryo-EM analyses

revealed human TRPC6 (hTRPC6) channel with a newly identified high-affinity inhibitor [2-(benzo[d] [1, 3] dioxol-5-ylamino) thiazol-4-yl] [(3S, 5R)-3, 5-dimethylpiperidin-1-yl] methanone (BTDM), which has an overall resolution of 3.8 Å; it also revealed human TRPC3 (hTRPC3) channel with a lipid-activator OAG of 4.4 Å resolution. The hTRPC3 and hTRPC6 channels tetramer possesses dimensions of 75 by 75 by 150 $Å^3$. The TRPC3 channel has four elbow-like membranes prior to the first transmembrane helix, while the TRPC6 channel has only three. The TRP helix is perpendicular to the pore-lining S6, and the hTRPC6 intracellular cytoplasmic domain presents an inverted bell shape whose top is below the ion channel pore of TMD (Fan et al. 2018; Tang et al. 2018). The truncation of the N terminus 71 amino acids is dispensable for the hTRPC6 assembly and gating, and the amino acids of TRPC6 cytoplasmic C terminus fold into two long helices (Tang et al. 2018). Novel electron cryo-EM technology provides a structural basis for the function and gating mechanisms of TRPCs.

TRPCs and diseases

TRPCs are expressed in many cells and tissues and have been reported to be involved in the development and progression of various diseases, including cancers, kidney diseases, cardiovascular and nervous system diseases (Hwang et al. 2013; Sukumaran et al. 2017; Dryer et al. 2019; Falcon et al. 2020).

Cardiovascular diseases

Ca^{2+} plays a crucial role in maintaining physiological functions in the cardiovascular system, including diastolic cardiac function, cardiac contractility, and hemodynamic change (Tai et al. 2017; Wu et al. 2019). Several studies showed that TRPCs participate in cardiovascular system disease progression (Kitajima et al. 2016; Zhang et al. 2018b; Falcon et al. 2020). Wu et al. found that Ca^{2+} influx is increased in the hypertrophic myocytes of adult wild-type mice, while this phenomenon is not observed in the myocytes of dominant-negative (dn) TRPC3/4/6 adult mice (Wu et al. 2010). Additionally, the activity of the calcineurin-nuclear factor of activated T cells (NFAT) significantly decreases in dnTRPC3/4/6 mice (Wu et al. 2010). Over-expression of TRPCs could stimulate the activation of NFAT, which accelerates TRPCs expression through a positive feedback mechanism. The activation of this mechanism could contribute to the development of cardiac hypertrophy and hypertension (Watanabe et al. 2008; Wu et al. 2010). A previous study found that TRPC3 can form a complex with A2R and PDE1C, and PDE1C is activated by TRPC3-invoked Ca^{2+}, thereby facilitating cardiomyocyte apoptosis (Zhang et al. 2018b). Remarkably, a background Ca^{2+} entry pathway mediated by TRPC1/C4 can regulate Ca^{2+} cycling in cardiomyocytes. However, the pathological cardiac remodeling development is attenuated in transverse aortic constriction-induced TRPC1/4 double knockout mice (Camacho Londoño et al. 2015).

Cancers

TRPCs play a relevant role in the progression of different types of cancers, such as colorectal cancer, lung cancer, breast carcinoma, gastric cancer, renal cell carcinoma, hepatocellular carcinoma, and more (Wang et al. 2015b, 2018a; Jardin et al. 2018). Multiple studies provided evidence that the homeostasis of intracellular Ca^{2+} is disrupted in cancer cells and that the turbulence of Ca^{2+} signaling is concerned with tumor proliferation, migration, and invasion contributing to the overall tumor progression (Yang et al. 2009; Wang et al. 2015b; Jardin et al. 2018). One study reported that Trpc5-siRNA inhibits the Wnt/β-catenin signal pathway, reduces ABCA1 induction, and causes a prominent reversal resistance of 5-fluorouracil in human colorectal cancer cells (Wang et al. 2015b). However, the role of TRPCs is still controversial in breast cancer. On the one hand, hyperforin depresses the breast cancer's cell growth and viability in MDA-MB-231 cells, which may be due to over-activation of TRPC6, which disrupts Ca^{2+} signaling, thereby affecting cell proliferation (Aydar et al. 2009). On the other hand, TRPC6 knockdown by shTrpc6 significantly attenuates MCF7 and MDA-MB-231 cell proliferation (Jardin et al. 2018). Liang Wen et al. demonstrated that calcium dependence is an essential mechanism for regulating multi-drug resistance via the TRPC6/calcium/STAT3 signal pathway, and silencing TRPC6 elevates the efficacy of doxorubicin in hepatocellular carcinoma cells (Wen et al. 2016). Hong-Ni Jiang et al. found that overexpressing TRPC1 and TRPC6 increases the proliferation of the A549 lung cancer cell (Jiang et al. 2013). Notably, the TRPC6-NFAT pathway is activated by WNK1 promoting clear-cell renal-cell carcinoma cell proliferation and migration (Kim et al. 2019).

Kidney diseases

TRPC6 can accelerate the progression of many acquired glomerular diseases, such as glomerulosclerosis associated with autoimmune glomerulonephritis, primary and secondary focal and segmental glomerulosclerosis (FSGS), and type-1 diabetes (Dryer et al. 2019; Polat et al. 2019). Over-activation of the TRPC6 channel and Trpc6 gene mutations result in glomeruli injury (Dryer et al. 2019; Staruschenko

et al. 2019). It is worth noting that reactive oxygen species and angiotensin II (AngII) are the two major factors that provoke dramatic increases of TRPC6-mediated Ca^{2+} influx in diabetic kidney disease, resulting in hypertrophy and the death of podocytes (Ilatovskaya et al. 2015; Ma et al. 2016; Staruschenko et al. 2019). TRPC6 antagonist, BTP2, attenuates renal fibrosis and glomerulosclerosis in TRPC6-knockout mice (Wu et al. 2017a). However, Wang et al. revealed that TRPC6 knockout reduces proteinuria and decreases tubule injury but increases mesangial expansion and promotes insulin resistance, causing exacerbation of diabetic kidney disease in Akita mice (Wang et al. 2019c). AngII and endothelin-1-induced mesangial contraction are significantly decreased with the downregulation of TRPC1 in TRPC1 antibody-treated rats. Hence, TRPC1 could play a specific role in regulating mesangial cell contractility (Woudenberg-Vrenken et al. 2009). Studies have indicated that TRPC5 blocker, AC1903, could successfully protect podocytes injury in vitro and the kidney filter function in vivo; thus, TRPC5 could be a potential therapeutic target for FSGS (Pablo and Greka 2019).

Nervous system diseases

TRPCs participate in the formation of synapses and the modulation of neurotransmitter release; this involvement of TRPCs plays a vital role in the neurological system's functions, such as memory, movement, cognition, anxiety, and fear (Riccio et al. 2014; Hong et al. 2015). TRPCs are primarily expressed in the brain, which is susceptible to oxidative stress. The TRPC5-like current activated by oxidized glutathione increases Ca^{2+}, which ultimately induces striatal neuronal cell death. TRPC5 inhibition by ML204 predominantly attenuates oxidation-provoked striatal neuronal cell death and improves motor and rearing behavior in Huntington's disease transgenic mice (Hong et al. 2015). Many factors contribute to Parkinson's disease, such as excitotoxicity, mitochondrial dysfunction, endoplasmic reticulum stress, reactive oxide species, and inflammation; almost all of them depend directly or indirectly on Ca^{2+} signaling (Sukumaran et al. 2017). Reduction in apoptosis and Ca^{2+} influx provides neuroprotection via activation of TRPC1 (Thapak et al. 2020). Studies have shown that TRPC6 specifically inhibits its cleavage by γ-secretase of amyloid precursor protein (APP) and reduces β-amyloid formation by preventing APP from interacting with presenilin 1, which could be a novel strategy for treating Alzheimer's disease (Wang et al. 2015a). At the same time, neurotoxic TRPC6-mediated Ca^{2+} entry is mediated by presenilin 2. Activation of TRPC6 increases adult hippocampal neurogenesis and long-term spatial memory but reduces Aβ accumulation due to increased cerebrovascular P-glycoprotein (Thapak et al. 2020). Antonio Riccio et al. reported that $TRPC4^{-/-}$ mice displays decreased anxiety-like behavior and Gq/11-dependent responses (Riccio et al. 2014). Similarly, TRPC1/4/5 blocker, HC-070, alleviates anxiety and depression in mice (Just et al. 2018). Inhibition of TRPC6 degradation by calpain inhibitors prevents ischemic neuronal death, improves behavioral performance, and provides neuroprotection through the Ras/MEK/ERK/CREB pathway (Thapak et al. 2020).

Other diseases

Some reports have shown that TRPCs are involved in other diseases, such as obesity, type II diabetes, and lung diseases (Yu et al. 2004; Krout et al. 2017). TRPC3/6 expression in the lung tissues and pulmonary artery smooth muscle cells of idiopathic pulmonary arterial hypertension patients was much higher than those normotensive or secondary pulmonary hypertension patients (Yu et al. 2004). It has been reported that hypoxia-inducible factor-1 boosts the expressions of TRPC1 and TRPC6 increasing intracellular Ca^{2+} level in pulmonary artery smooth muscle cells (Wang et al. 2006). Another study suggested that TRPC1 plays a crucial role in adiposity via inducing autophagy and apoptosis; moreover, high-fat diet-induced obesity and type II diabetes were alleviated in TRPC1 knockout mice (Krout et al. 2017).

TRPCs agonists

TRPC5 channel

Methylprednisolone

The glucocorticoid methylprednisolone is a long-acting, reversible TRPC5 agonist with EC_{50} of 12 μM, which is effectively inhibited by clemizole. Methylprednisolone only activates the TRPC5 channel and does not affect other TRPC subfamily members; however, the carbachol-induced TRPC4 channel can also be activated by methylprednisolone. Prednisolone can also act as a weak activator of TRPC5 channels with EC_{50} of 64 μM (Beckmann et al. 2017). One study has demonstrated that local delivery of methylprednisolone succinate in combination with a copolymer of ethylene oxide and propylene oxide facilitates spinal cord sensorimotor circuitry and increases excitability (Baltin et al. 2021). Additionally, methylprednisolone acetate administration intra-articularly or intravenously has shown to improve the lung function of horses and infants with severe asthma and bronchopulmonary dysplasia, respectively (Millares-Ramirez et al. 2021; Billion et al. 2021; Wang et al. 2021a).

AM237

AM237, a xanthine derivative synthesized compound, potently activates the TRPC5:C5 channel with EC_{50} of 15–20 nM in Ca^{2+} assays. AM237 does not activate either the TRPC4-C1, TRPC5-C1, TRPC4:C4, TRPC1:C5, TRPC1:C4 channels, or native TRPC1:C4 channel in A498 cells; instead, it suppresses the activation evoked by (−)-englerin A (Minard et al. 2019).

GW-1929

A rosiglitazone-related peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist, *N*-(2-benzoylphenyl)-*O*-[2-(methyl-2-pyridinylamino)ethyl]-L-tyro-sine (GW-1929), can weakly stimulate the TRPC5 channel (Majeed et al. 2011). GW1929 inhibits TRPC1 and TRPC6 expressions in the pulmonary artery smooth muscle cells through the activation of PPARγ (Lu et al. 2010; Wang et al. 2013).

TRPC6 channel

Hyperforin

Hyperforin is isolated from the leaves, stems, and roots of the dried herb *Hypericum perforatum* L (St John's wort); it has been used for mild to moderate depression, multidrug-resistant *Staphylococcus aureus,* and (other) gram-positive bacteria (Laakmann et al. 1998; Orth et al. 1999; Ebrey 1999; Singer et al. 1999; Szewczyk et al. 2019). Hyperforin is a specific and highly selective activator of the TRPC6 channel without activating TRPC1/4/5 and TRPC3/7 channels (Leuner et al. 2010; Tu et al. 2010). Hyperforin has a neuroprotective effect by reducing aluminum-induced Aβ production and tau phosphorylation against Alzheimer's disease (AD), which could provide a potential AD therapy (Huang et al. 2017; Jiang et al. 2018; Wang et al. 2019a). TRPC6 channel activation can attenuate brain damage (Lin et al. 2013) and substantially improve recurrent moderate hypoglycemia-induced cognitive impairment (He et al. 2020). Hyperforin has also been demonstrated to promote post-stroke neurovascular regeneration and functional recovery via astrocytic IL-6-mediated negative immune regulation (Yao et al. 2019) and improve post-stroke social isolation-induced exaggeration of post-stroke depression and post-stroke anxiety via TGF-β (Zhang et al. 2019). Additionally, hypericum extracts have been reported to have a protective effect on the brain, improve anxiety-like behavior (Sevastre-Berghian et al. 2018) and exhibit an antidepressant-like activity in mice (Pochwat et al. 2018). Besides, as a specific activator for TRPC6, hyperforin usage could reduce the growth and viability of the various human and rat cancer cell lines by apoptosis with IC_{50} between 3 and 15 μM (Schempp et al. 2002; Chen et al. 2018; Liu et al. 2019). The anti-tumor activity of *H. perforatum* L. and hyperforin has been proven to be linked with mediating inflammatory signaling, ROS generation, and proton dynamics, as well as exhibiting anti-proliferative effects (Allegra and Tonacci 2020). Hyperforin causes apoptosis through extrinsic/intrinsic pathways and inhibits NF-κB-mediated invasion, enhancing the survival potential in bladder cancer and non-small cell lung cancer (Chen et al. 2018; Liu et al. 2019); it also inhibits the EGFR/ERK/NF-κB-modulated anti-apoptotic potential in glioblastoma (Hsu et al. 2020). Hyperforin could prevent parental and oxaliplatin-resistant human adenocarcinoma cells' metastasis through anti-adhesion therapy (Šemeláková et al. 2018). TRPC6 activation stimulates the differentiation and proliferation of keratinocytes, playing a significant role in treating atopic dermatitis and psoriasis; therefore, hyperforin presents an innovative therapeutic strategy in skin disorders (Takada et al. 2017). Additionally, TRPC6 gene silencing through ryanodine receptor type 1 can partially ameliorate muscle cation dyshomeostasis and the halothane's response to malignant hyperthermia in a mouse model (Lopez et al. 2020b). Hyperforin also prevents the growth of infection-induced inflammatory responses of glial cells and neurotropic parasite Toxoplasma gondii (Shinjyo et al. 2021).

OAG

Leuner et al. (2010) demonstrated that 2, 4-diaetylphloroglucinol derivative has the pharmacophore of diacylglycerol and hyperforin; it is also TRPC6 selective. Tesfai et al. (2001) revealed that the membrane-permeant analogs of DAG initiate the activation of Ca^{2+} inflow in the adrenal chromaffin cell line (PC12 cell); similarly is the permeant DAG analog 1-oleoyl-2-acetyl-sn-glycerol (OAG) effect (Hofmann et al. 1999; Tesfai et al. 2001; Venkatachalam et al. 2003; Tu et al. 2009; Fuchs et al. 2011). It has been reported that the TRPC6 channel is essential for acute hypoxic pulmonary vasoconstriction (HPV) in mice. Under the condition of repetitive hypoxic ventilation, OAG dose-dependently attenuates the strength of acute HPV by TRPC6 channel activation (Fuchs et al. 2011).

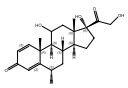
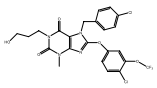
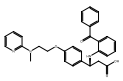
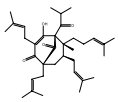
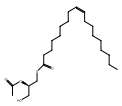
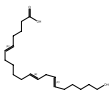
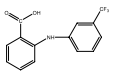
20-HETE

20-hydroxyeicosatetraenoic acid (20-HETE) is an eicosanoid compound that can activate the TRPC6 channel in the HEK293 cell line, Hek-t6.11 with EC_{50} of 0.8 μM (Basora et al. 2003).

Flufenamic acid

Flufenamic acid is a non-steroidal anti-inflammatory that belongs to the fenamates family and can induce the TRPC6

Table 1 TRPCs agonists (1)

Modulators	Chemical structure	Targeting channels and IC50	Predicted effects	Reference
Methylprednisolone		12 μM (TRPC5:C5)	Activate TRPC5 channel and improve the lung function	Beckmann et al. (2017), Millares-Ramirez et al. (2021)
AM237		15–20 nM (TRPC5:C5)	Suppress activation evoked by (−)-EA	Minard et al. (2019)
GW-1929		TRPC5:C5	a Rosiglitazone-related PPAR-γ agonist	Lu et al. (2010), Majeed et al. (2011)
Hyperforin		3–15 μM (TRPC6)	Mild to moderate depression, inhibit bacteria, Alzheimer's disease, the various human and rat cancer cell lines	Jiang et al. (2018), Liu et al. (2019)
OAG		TRPC3/6/7	The activation of Ca^{2+} inflow, acute HPV in mice	Fuchs et al. (2011)
20-HETE		0.8 μM (TRPC6)	Activate TRPC6 channel in HEK293 cell line, Hek-t6.11	Basora et al. (2003)
Flufenamic acid		TRPC6	Non-steroidal anti-inflammatory	Foster et al. (2009)

expression; it also does not significantly affect TRPC7 expression and reduces TRPC3 expression (Foster et al. 2009). Blocking the TRPC3 channel by flufenamic acid modulates the depolarization of cholinergic interneurons (Xie and Zhou 2014). Increased expression of TRPC6 by flufenamic acid promotes cell proliferation in human megakaryocytes (Ramanathan and Mannhalter 2016) (Table 1).

TRPC1/5 channels

Riluzole

Riluzole is a marketed drug that plays a role in the survivability of amyotrophic lateral sclerosis (ALS) and acts as an antidepressant (Miller et al. 2000; Grant et al. 2010; Minard et al. 2018). Richter et al. (2014b) identified riluzole as a novel TRPC5 channel agonist with EC_{50} of 9.2 μM. Riluzole can activate the heteromeric TRPC1:C5 channel expressed in HEK293 cells and the endogenous TRPC5:C5 channel expressed in the U-87 glioblastoma cell lines. The riluzole-induced TRPC5 activation mechanism is independent of G protein signaling and PLC activity as it differs from the La^{3+}-mediated TRPC5 activation. Finally, the recordings of excised inside-out patches demonstrated that riluzole has a relatively direct effect on TRPC5 activation. Riluzole improves recovery from ischemia in mice through TRPC5 activation in the endothelial cells (Zhu et al. 2019). Additionally, riluzole has neuroprotection and therapeutic application to prevent oxaliplatin-induced neuropathy (Trinh et al. 2021). Riluzole can also treat severe hyponatremia secondary to amyotropic lateral sclerosis (Tambe et al. 2021).

Rosiglitazone

Rosiglitazone, a high-affinity PPAR-γ ligand, can activate TRPC5 with EC_{50} of about 30 μM. The effects of rosiglitazone on TRPC5 occur rapidly and reversibly on washout (Majeed et al. 2011). It has been reported that rosiglitazone also activates the heteromeric TRPC1:C5 channel. Rosiglitazone (as a thiazolidinedione) is an antidiabetic drug that acts as an insulin sensitizer. Rosiglitazone decreases free fatty acids released from adipocytes to ameliorate skeletal muscle insulin resistance. Rosiglitazone can also inhibit angiotensin II-induced proliferation of rats' glomerular mesangial cells via the Gαq/Plcβ4/TRPC signaling pathway (Wei et al. 2017b). Moreover, rosiglitazone ameliorates rat radiation-induced intestinal inflammation by inhibiting NLRP3 inflammasome and TNF-alpha production (Hu et al. 2020a). The development and progression of endometriosis are impacted by rosiglitazone likely by inhibiting angiogenesis and inducing apoptosis (Zhang et al. 2021). Rosiglitazone treatment improves cognitive areas that mainly depend on the dorsal hippocampus (Cortez et al. 2020). However, it has been withdrawn from clinical use in most countries due to its side effects, such as heart attacks and sudden death (Rubaiy 2019; Gong et al. 2020).

TRPC3/6 channels

Artemisinin

Artemisinin has been identified as a well-known TRPC3 channel agonist; it was discovered by screening 2000 bioactive compounds in a Ca^{2+} influx assay (Urban and Schaefer 2020). Artemisinin has a strong stimulatory effect on TRPC3 or heteromeric TRPC3:C6 channels, and it weakly affects the TRPC6 and TRPC7 channels, or these channels lack the response to artemisinin (Urban and Schaefer 2020). Artemisinin is an antimalarial agent isolated from the Chinese medicinal plant *Artemisia annua* L. (Liu et al. 2011; Stringham et al. 2018) and has been used as an effective treatment for malaria (Wang et al. 2021b; van der Pluijm et al. 2021). At the same time, artemisinin, as a novel anti-cancer drug, targets a global cancer pandemic through drug repurposing (Xu et al. 2020; Augustin et al. 2020). Furthermore, Bai et al. (2020) revealed the vital role of pH-dependent molecular rearrangement in the activation and activity of artemisinin against cancer. Interestingly, artemisinin and its derivatives may be valuable in treating obesity and diabetes (Shen et al. 2020; Jiang et al. 2020b). Artemisinin can also ameliorate inflammation by suppressing the process of epithelial-mesenchymal transition and inducing macrophage polarization to the M2 phenotype, which may help treat inflammatory bowel disease in the future (Huai et al. 2020). Zhou et al. (2020) discovered novel artemisinin derivatives through structural optimization of artemisinin that works against liver and ovarian cancers.

GSK1702934A

GSK1702934A is a small 1,3-dihydro-2H-benzo[d]midazole-2-one-based potent agonist that activates TRPC3/6 channels directly with EC_{50} of 0.08 mM and 0.44 mM, respectively. Whole-cell patch-clamp experiments have proven that GSK1702934A can activate the TRPC3/6-currents in HEK293 cells (de la Cruz et al. 2017). Cardiovascular morbidity and mortality are associated with increased blood pressure variability (BPV). Activation of TRPC6 by GSK1702934A exacerbates the systolic and diastolic BPV (Wang et al. 2020d), while TRPC3 activation substantially contributes to cardiac contractility control and arrhythmogenesis (Doleschal et al. 2015).

TRPC1/4/5 channels

Tonantzitlolone

Tonantzitlolone is extracted from the Mexican plant *Stillingia sanguinolenta*; it has been used against fibroblasts cells in mice and certain types of human cancer cells, such as human breast cancer cells and renal cell carcinoma cells (Jasper et al. 2005; Busch et al. 2016; Pfeffer et al. 2016; Rubaiy et al. 2018). In the NCI-60 human tumor cell lines screen, many of the sixty cancer cells were resistant to tonantzitlolone in nanomolar concentrations, indicating that tonantzitlolone could have a beneficial effect on specific subtypes of cancer cells (Rubaiy et al. 2018). Tonantzitlolone works against renal cancer cells through protein kinase C isoform θ- and heat shock factor 1-dependent (Sourbier et al. 2015). Though the profile of tonantzitlolone in this screen is exceptionally parallel to (−)-englerin A, the structures of tonantzitlolone and (−)-englerin A are entirely distinguishable from each other (Rubaiy et al. 2018; Rubaiy 2019).

Rubaiy et al. (2018) revealed that tonantzitlolone is a novel potent agonist for TRPC4, TRPC5, TRPC4-TRPC1, and TRPC5-TRPC1 channels with EC_{50} of 123 nM, 83 nM, 140 nM, and 61 nM, respectively, which could be useful for investigating the function of these ion channels. However, tonantzitlolone could not activate endogenous SOCE in HEK 293 cells and over-expressed the TRPC3, TRPV4, and TRPM2 channels. In whole-cell patch-clamp recordings, tonantzitlolone was washed-out reversibly and inhibited potently by Pico145, a TRPC1/4/5 inhibitor (Rubaiy et al. 2017b). Tonantzitlolone A and its synthetic enantiomer inhibit cell proliferation and kinesin-5 function, and the synthetic enantiomer shows a more potent inhibitory effect; thus, it is possible to enhance the anti-proliferative effect of tonantzitlolon A by chemical modification (Pfeffer et al. 2016).

(−)-englerin A

Similar to tonantzitlolone, (−)-englerin A is a guaian-type sesquiterpene and a natural product that originates from the Tanzanian plant *Phyllanthus engleri*; it is isolated and fractionated from the roots and bark of this plant (Ratnayake et al. 2009). Ratnayake et al. (2009) revealed that (−)-englerin A has 1000-fold selectivity to six of the eight renal cancer cell lines with GI_{50} between 1 and 87 nM. (−)-englerin A can selectively inhibit the growth of renal cancer cell lines in the NCI-60 cytotoxicity screen. However, its use in the pharmaceutical treatment of cancer is limited due to its instability and toxicity (Akbulut et al. 2015; Wu et al. 2017b; Grant et al. 2019; Rubaiy 2019). Although (−)-englerin A has selective cytotoxic to cancer cells, adverse reactions in mice and rats have been reported. One study found that TRPC4 and TRPC5 single knockout mice were partially protected from adverse reactions, and double knockout mice were fully protected (Cheung et al. 2018).

Moreover, (−)-englerin A directly activates PKCθ to limit the access of tumor cells to glucose, resulting in glucose dependence and insulin resistance in tumor cells through the activation of heat shock transcription factor, HSF1, and insulin receptor substrate 1 (IRS1) (Muraki et al. 2017).

(−)-englerin A is a highly selective and potent activator of both homomeric and heteromeric TRPC1/4/5 channels, which helps study these proteins' pharmacological action (Akbulut et al. 2015; Minard et al. 2018; Rubaiy 2019). (−)-englerin A could activate TRPC1/4/5 channels to influence A498 renal cancer cells (Haque et al. 2017). Acute inflammatory response induced by (−)-englerin A could modulate anti-tumor immunity. Additionally, Batova et al. (2017) revealed that lipid metabolism and ER stress could be targeted vulnerabilities in renal cell carcinoma. However, (−)-englerin B, a (−)-englerin A metabolic product, could not activate TRPC1/4/5 channels to influence A498 renal cancer cells (Wu et al. 2017b). As stated, (−)-englerin A is a potent TRPC4:C4 and TRPC5:C5 channels activator in HEK293 cells with EC_{50} of 11.2 nM and 7.6 nM, respectively (Akbulut et al. 2015). (−)-englerin A may have a similar activating effect on TRPC1:C4 and TRPC4-containing channels, but it does not affect TRPC6, TRPM2, TRPV4 channels, 10 other ion channels, and 59 GPCRs (Akbulut et al. 2015; Minard et al. 2018). Grant et al. (2019) showed that (−)-englerin A-evoked cytotoxicity results in rapid cancer cell death in two different triple-negative breast cancers cancer cells, BT-549 and Hs578T.

BTD

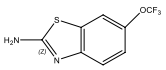
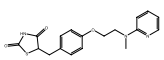
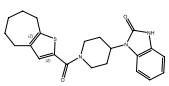
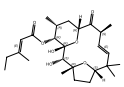
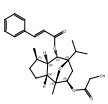
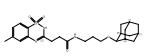
Beckmann et al. identified a novel TRPC5 agonist, which is N-[3-(adamantan-2-yloxy)propyl]-3-(6-methyl-1,1-dioxo-2H-1λ^6,2,4-benzothiadiazin-3-yl)propanamide (BTD) with EC_{50} of 1.4 μM in Ca^{2+} assays and EC_{50} of 1.3 μM in the electrophysiological whole-cell patch-clamp recordings from screening the ChemBioNet compound library (Beckmann et al. 2017). BTD is long-lasting, reversible, and sensitive to clemizole, which is a TRPC5 blocker. Furthermore, BTD displayed selectivity to TRPC1/4/5 channels; it can activate the homomeric TRPC5:C5 channel as well as the heteromeric TRPC1:C5 and TRPC4:C5 channels, and to a less extent, the TRPA1, TRPV1, TRPM3, and TRPM8 channels; however, it does not activate the TRPC4:C4 and TRPC1:C4 channels (Beckmann et al. 2017) (Table 2).

TRPC3/6/7 channels

4m–4p

4m–4p are a series of potent and direct agonists of TRPC3/6/7 channels belonging to pyrazolopyrimidines (Qu et al. 2017). They activate the TRPC3/6/7 channels with a potency order of TRPC3 > C7 > C6. One of the 4n is the most potent with EC_{50} of < 20 nM for TRPC3 channel activation.

Table 2 TRPCs agonists (2)

Modulators	Chemical structure	Targeting channels and IC50	Predicted effects	Reference
Riluzole		9.2 μM (TRPC5:C5) TRPC1:C5	ALS and anti-depressant	Richter et al. (2014b)
Rosiglitazone		~30 μM (TRPC5:C5) TRPC1:C5	An antidiabetic drug and an insulin sensitizer	Majeed et al. (2011)
artemisinin		TRPC3, TRPC3:C6	Antimalarial agent; anti-cancer drug	Urban and Schaefer, (2020), Xu et al. (2020)
GSK1702934A		0.08 mM (TRPC3) 0.44 mM (TRPC6)	Activation of TRPC3/6-currents	de la Cruz et al. (2017)
Tonantzitlolone		123 nM (TRPC4), 83 nM (TRPC5) 140 nM (TRPC4-TRPC1), 61 nM (TRPC5-TRPC1)	Against mouse fibroblasts cells, human breast cancer and renal cell carcinoma cells	Pfeffer et al. (2016), Rubaiy et al. (2018)
(−)-englerin A		11.2 nM (TRPC4:C4) 7.6 nM (TRPC5:C5)	Inhibit growth of various cancer cell lines, breast cancers cancer cells and activate PKCθ	Minard et al. (2018), Ratnayake et al. (2009)
BTD		1.3 μM (TRPC5:C5), TRPC1:C5, TRPC4:C5	Be sensitive to clemizole	Beckmann et al. (2017)

TRPCs antagonists

TRPC3 channel

Pyr3

Ethyl-1-(4-(2,3,3-trichloroacrylamide)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (Pyr3) is a specific and direct inhibitor of TRPC3 channel. Pyr3 ameliorates intracerebral hemorrhage-induced brain injury and could be used as a novel treatment strategy for TRPC3-mediated diseases, including pathological cardiac remodeling and heart failure (Glasnov et al. 2009; Munakata et al. 2013). Moreover, Pyr3 exerts an inhibitory effect on the growth of human glioblastoma cancer cells and triple-negative breast cancer cells in vitro and vivo through inducing apoptosis and inhibiting migration (Chang et al. 2018; Wang et al. 2019d). The inhibitory effect of Pyr3 is dose-dependent in acute lymphoblastic leukemia cell lines (Abdoul-Azize et al. 2016). Pyr3 also inhibits smooth muscle proliferation and alleviates stent implantation-induced arterial injury (Álvarez-Miguel et al. 2017). Exposure to PM2.5 can increase the propensity to cardiac arrhythmias which could be attenuated with TRPC3 inhibition by Pyr3 (Cai et al. 2019). Pyr3 can also significantly decreases intracellular calcium concentrations, normalize resorptive activity and osteoclastic differentiation of TRPC6-deficient cells (Klein et al. 2020; Sato et al. 2020), and promotes systolic blood pressure in hypertensive patients (Hu et al. 2020d).

TRPC5 channel

Galangin

Galangin is a natural flavonoid compound from the ginger family that is used as a novel antidiabetic. It has been screened as a lanthanide-induced Ca^{2+} entry antagonist in overexpressed TRPC5 HEK293 cells with IC_{50} of 0.45 μM through a screen of natural compounds in traditional Chinese medicines (Naylor et al. 2016; Brás et al. 2020). Galangin also inhibits lanthanide-induced TRPC5-mediated current and calcium entry. TRPC5 is less inhibited by other related natural flavonols, such as kaempferol and quercetin, and is not affected by myricetin, luteolin, and apigenin. Galangin can attenuate isoproterenol-induced inflammation, cardiac fibrosis, pulmonary fibrosis and non-alcoholic fatty liver disease (Thangaiyan et al. 2020; Wang et al. 2020c; Zhang et al. 2020). Galangin can also reduce cerebral ischemia–reperfusion injury by inhibiting ferroptosis and activating the SLC7A11/GPX4 axis (Guan et al. 2021). Additionally, galangin improves cardiac remodeling through the MEK1/2-ERK1/2 and PI3K-AKT pathways (Wang et al. 2019b). Differentiation of dendritic cells hows tolerogenic properties in response to lipopolysaccharide stimulation during galangin treatment (Song et al. 2021). Also, galangin has a protective effect on ulcerative colitis induced by dextran sulfate sodium in mice and rats (Sangaraju et al. 2019; Fan et al. 2021). Galangin inhibits cell growth and metastasis of cholangiocarcinoma by downregulating the expression of microRNA-21 (Zou et al. 2020). Besides, galangin inhibits epithelial-mesenchymal transition and angiogenesis of glioma by downregulating CD44 (Chen et al. 2019a). Simultaneously, galangin promotes apoptosis of diverse cancer cells, such as hepatocellular carcinoma cells, ovarian cancer cells and glioblastoma cells (Kong et al. 2019; Fang et al. 2019; Zhong et al. 2020; Huang et al. 2020). One study suggested that galangin, either alone or combined with insulin, can reduce glucose levels and improve skeletal muscle health in patients with diabetes (Kalhotra and Chittepu 2019).

AC1903

AC1903 is a specific TRPC5 inhibitor synthesized through experimentation. By comparison, AC1903 is nearly equipotent to ML204 in blocking riluzole-activated TRPC5-mediated whole-cell current, but AC1903 fails to inhibit carbachol (CCh)-evoked TRPC4 and OAG-induced TRPC6 currents in whole-cell patch recordings, with a half-maximal inhibitory concentration of 14.7 μM (Zhou et al. 2017). AC1903, as a TRPC5 inhibitor, can provide a therapeutic benefit to podocyte survivability in chronic kidney diseases, such as focal and segmental glomerulosclerosis (Zhou et al. 2017; van der Wijst and Bindels 2018; Sharma et al. 2019; Pablo and Greka 2019).

NU6027

NU6027 is a cyclin-dependent kinase inhibitor that inhibits the basal and zinc-augmented TRPC5 currents in TRPC5 overexpressed HEK293 cells. It has a neuroprotective effect on oxidative neuronal injury in prolonged seizures. NU6027 is considered a potent antagonist of the TRPC5 channel (Park et al. 2019). TRPC5 suppression using NU6027 reduces the neuronal death that may occur after traumatic brain injury (Park et al. 2020).

TRPC6 channel

Ribemansides A and B

Ribemansides A and B are two new acylated β-hydroxynitrile glycosides isolated from the aerial parts of *Ribes manshuricum*. They can inhibit the activity of the TRPC6 channel with IC_{50} of 24.5 and 25.6 μM, respectively. These two compounds can suppress transforming growth factor β1

(TGF-β1)-induced fibrogenesis in HK-2 cells, similar to SAR7334, a TRPC6 inhibitor (Zhou et al. 2018).

Larixyl acetate

Through testing and identifying several preparations from plant extracts, larixol and larixyl acetate were identified as TRPC6 inhibitors of receptor-induced Ca^{2+} entry (Urban et al. 2016). TRPC6 channel is inhibited by larixyl acetate in the DAG-stimulated rat's pulmonary artery smooth muscle cells with IC_{50} of 0.1–0.6 μM. Larixyl acetate can also prevent hypoxia-induced pulmonary vasoconstriction (HPV) (Urban et al. 2016) and improve the endothelial function after traumatic brain injuries in mice (Chen et al. 2019b). TRPC3/7 and TRPC4/5 channels are weakly blocked by larixyl acetate, whereas no significant inhibition occurs in other related TRPV or TRPM channels (Urban et al. 2016). Moreover, larixyl acetate has analgesic and anti-inflammatory effects on neuropathic pain; therefore, it can be a novel therapy for intractable chronic pain (Wang et al. 2020b).

FK506

FK506 (Tacrolimus) is a potent immunosuppressive agent isolated from the filamentous bacteria fermentation broth, a strain of *Streptomyces tsukubaensis* No.9993. FK506 has been generally used in liver and kidney transplantation therapy (Kino et al. 1987; Dumont 2000; Tang et al. 2021). Studies have demonstrated that FK506 could suppress TRPC6 expression to ameliorate podocyte injury in T2DM cells (Chang et al. 2019); it also affects proteinuria and renal damage progression in renal tissues (Wei et al. 2017a; Chen et al. 2021). Down-regulation of TRPC6 by FK506 can also be used to treat overactive bladder (Chang et al. 2019). Besides, FK506-binding protein 52, as a novel interaction partner of TRPC3, improves the hypertrophic growth of cardiomyocyte cultures (Bandleon et al. 2019). Also, FK506 induces the TGF-beta 1/Smad 3 pathway to prevent intervertebral disk degeneration independent of calcineurin inhibition (Ge et al. 2020).

BI 749327

BI 749327 is an orally bioavailable TRPC6 antagonist that has been reported by Lin et al. (2019) with IC_{50} of 13 nM; it can boost cardiac function and ameliorate renal disease fibrosis.

DS88790512

DS88790512 is another orally bioavailable compound that is potent and a selective blocker of the TRPC6 channel; it is a icycle [4.3.0] nonane derivative with IC_{50} of 11 nM. However, there have not been any reports of its efficacy in vivo (Motoyama et al. 2018) (Table 3).

TRPC1/5 channels

Clemizole

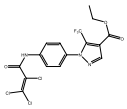
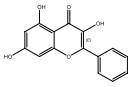
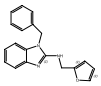
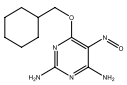
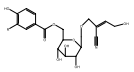
Richter et al. (2014a) identified clemizole as a novel, reversible TRPC5 blocker that can efficiently inhibit TRPC5 currents and Ca^{2+} entry with IC_{50} ranging from 1.0 to 1.3 μM. In excised inside-out membrane patches, clemizole could still block TRPC5 current at single-channel level; it also affected TRPM3 and M8 and weakly impacted the TRPV1, V2, V3, and V4 channels at higher concentrations. Simultaneously, clemizole inhibits the heterologous TRPC1:C5 channel and the native TRPC5-like currents in the U-87 glioblastoma cell line. Studies have also shown that clemizole can have a certain therapeutic effect on Dravet syndrome (Strzelczyk and Schubert-Bast 2020). As a TRPC5 channel inhibitor, clemizole hydrochloride reduces electric field stimulation amplitude, which causes muscarinic receptor-induced contractions impairment of the detrusor and carotid arteries (Griffin et al. 2018; Liang et al. 2019).

TRPC4/5 channels

ML204

Through a cell-based high-throughput fluorescence assay for 305,000 compounds, ML204 has been reported as a novel, potent, and relatively selective antagonist of the TRPC4 and TRPC5 channels with IC_{50} of 13.6 μM (Zhou et al. 2017), as well as weakly inhibiting TRPC6. ML204 has a direct inhibitory effect on TRPC4/5 channels; it also can affect other GPCR-independent receptors (Miller et al. 2011; Alom et al. 2018). ML204 can prevent pseudocyst formation; thus, podocyte numbers can be preserved by treatment with ML204 (Zhou et al. 2017). Also, ML204 reduces carotid arteries endothelium-dependent contractions in mice (Liang et al. 2019). The histamine-induced depolarization is significantly inhibited by ML204, which reduces neuronal excitation (Sato et al. 2020). Although ML204 cannot inhibit pacemaker activity, it modulates the depolarization of the membrane potential (Lee et al. 2020a). Intradermal injections of ML204 in psoriasiform skin significantly reversed chronic pruritus and the inflammation induced by imiquimod (Lee et al. 2020b). Recent studies have reported that ML204, as a selective TRPC4/5 blocker, can completely revert acetylcholine relaxations (Alom et al. 2018; Silva and Ballejo 2019). ML204 can also reduce electric-field stimulation and CCh-evoked contractions in $TRPC4^{-/-}$ detrusor strips mice (Griffin et al. 2018).

Table 3 TRPCs antagonists (1)

Modulators	Chemical structure	Targeting channels and IC50	Predicted effects	Reference
Pyr3		TRPC3	Ameliorate severity of seizures and cardiac injury, inhibit human glioblastoma cancer and melanoma cells growth	Álvarez-Miguel et al. (2017), Cai et al. (2019)
Galangin		0.45 μM (TRPC5)	Improve ulcerative colitis; apoptosis of diverse cancer cells	Fan et al. (2021), Naylor et al. (2016), Zhong et al. (2020)
AC1903		14.7 μM (TRPC5)	Provide chronic kidney diseases	Zhou et al. (2017)
NU6027		TRPC5	Inhibit TRPC5 currents, and oxidative neuronal injury	Park et al. (2019)
Ribemansides A and B	 A: R = H B:R = OCH_3	24.5 μM (TRPC6, A) 25.6 μM (TRPC6, B)	Suppress TGF-β1-induced fibrogenesis in HK-2 cells	Zhou et al. (2018)
larixyl acetate		0.1–0.6 μM (TRPC6)	Prevent HPV, improved traumatic brain injuries	Urban et al. (2016)
FK-506		TRPC6	Ameliorate liver and renal damage	Chang et al. (2019)
BI 749327		13 nM (TRPC6)	Support cardiac function and renal disease	Lin et al. (2019)
DS88790512		11 nM (TRPC6)	Inhibit TRPC6 channel	Motoyama et al. (2018)

M084

M084 is a 2-aminobenzimidazole derivative similar to ML204 reported to effectively block the TRPC4 and TRPC5 channels with IC_{50} of 10.3 and 8.2 μM, respectively. On the other hand, M084 weakly inhibits TRPC3 and moderately inhibits TRPC6 (Zhu et al. 2015). Research has discovered that M084 also has antidepressant and anti-anxiety effects in mice experiments (Yang et al. 2015). Additionally, Zhu et al. (2015) proved that M084 effectively inhibits the plateau potential induced by TRPC4-containing channels through electrophysiological recording in the lateral septal neurons of mice. Through synthesizing and testing a total of 28 structural analogs of M084, it has been found that the 2-aminobenzimidazol skeleton is an essential requirement for blocking the TRPC4 channel (Zhu et al. 2015).

AM12

Based on structure–activity relationship studies of the stated natural and other synthetic flavonols, 3,5,7-trihydroxy-2-(2-bromophenyl)-4H-chromen-4-one (AM12) was designed. AM12 can directly inhibit the activation of lanthanide-induced and (−)-englerin A -evoked TRPC5 channel with IC_{50} of 0.28 μM. Likewise, it inhibits TRPC4 channels and weakly inhibits the TRPC1-TRPC5 channel (Naylor et al. 2016).

TRPC3/6 channels

Salvianolic acid B

Salvianolic acid B, extracted from the root of *Salvia miltiorrhiza Bunge* (Lamiaceae), is the most abundant bioactive compound that inhibits the expression of TRPC3 and TRPC6 channels. In the cardiovascular system, salvianolic acid B effectively counteracts doxorubicin (DOX)-evoked structural heart abnormalities and apoptotic damage, and inhibits the DOX-induced Ca^{2+} overload and endoplasmic reticulum stress in cardiomyocytes via TRPC3 and TRPC6 inhibition (Chen et al. 2017; Li et al. 2020a). Salvianolic acid B can also alleviate myocardial ischemic injury by inhibiting activation of the NLRP3 inflammasome and promoting mitophagy (Hu et al. 2020c). Regarding its effects

on the hepatic system, salvianolic acid B suppresses hepatic endoplasmic reticulum stress to improve insulin resistance in ob/ob mice (Shi et al. 2020). Salvianolic acid B also blocks the activation of hepatic stellate cells, protects against sepsis-induced liver injury, and prevents and alleviates liver, pulmonary and renal interstitial fibrosis (Su et al. 2020; Ma et al. 2020; Jiang et al. 2020a; Hu et al. 2020b; Tian et al. 2021; Gong et al. 2021). Furthermore, salvianolic acid B prevents high-fat diet-induced obese mice body weight gain and regulates gut microbiota (Li et al. 2020b). Additionally, salvianolic acid B decreases mice interleukin-1 beta-induced colitis recurrence (Feng et al. 2020). Ragarding its effects on the skeletal system, salvianolic acid B promotes new bone formation and protects against oxidative damage (Kayalar et al. 2020; Xiao et al. 2020; Bian and Xiang 2020); it improves atherosclerosis by inhibiting the YAP/TAZ/JNK signaling pathway in endothelial cells and pericytes (Yang et al. 2020). In the nervous system, salvianolic acid B could improve the cognitive impairment of mice infected with *Porphyromonas gingivalis* by inhibiting neuroinflammation and reducing Aβ level (Liu et al. 2020). Salvianolic acid B can also improve chronic mild stress-induced depressive behaviors in rats via the AMPK/SIRT1 signaling pathway (Liao et al. 2020). As an otoprotective agent, salvianolic acid B inhibits ototoxic drug-induced ototoxicity by suppressing the apoptosis pathway (Zheng et al. 2020).

Rox4560

Rox4560 is a TRPC3/6 channel antagonist that could suppress the elevation of thrombin intracellular calcium levels in podocytes (Guan et al. 2017).

TRPC1/6 channels

Sildenafil

Sildenafil inhibits TRPC1 and TRPC6 expressions through PPARγ-dependent mechanisms counteracting podocyte injury and proteinuria (Sonneveld et al. 2017). Sildenafil also has potential cardioprotective effects (Santiago-Vacas et al. 2021).

TRPC1/4/5 channels

Pico145

Pico145 (C31, HC-608) is a xanthine derivative that potently inhibits TRPC1/4/5 channels with IC_{50} of 1.3 nM (TRPC5:C5), 0.349 nM (TRPC4:C4), 0.199 nM (TRPC5:C1, heteromers), and 0.033 nM (TRPC4:C1, heteromers) (Rubaiy et al. 2017b). Pico145 can directly, reversibly, and competitively inhibits the AM237-mediated TRPC5:C5 channel activation (Rubaiy et al. 2017a; Minard et al. 2019; Wright et al. 2020). The potency of Pico145 depends on the concentration of the (−)-englerin A (Rubaiy et al. 2017b). Pico145 was also found to be highly similar to HC-070 (Just et al. 2018). Inhibition of TRPC1 by Pico145 causes group I metabotropic glutamate receptors-induced long-term depression and memory extinction in mice (Yerna et al. 2020). Additionally, Pico145 can prevent adverse reactions of the cancer cell cytotoxic agent (−)-englerin A (Cheung et al. 2018).

HC070

HC070 is a highly potent, small molecule antagonist of TRPC4 and TRPC5 invented by Just et al. (Just et al. 2018). HC070 inhibits the homologous TRPC4:C4 (IC_{50} = 46.0 nM) and TRPC5:C5 (IC_{50} = 0.52 nM) channel, as well as the heterologous TRPC1:C5 (IC_{50} = 1.4 nM, La^{3+}-activated; IC_{50} = 4.4 nM, M1 receptor-activated), and TRPC1:C4 (IC_{50} = 1.3 nM) channel. HC070 also reversibly inhibits the lanthanum-induced mouse TRPC5 current with IC_{50} of 0.55 nM. Additionally, HC070 and Pico145 showed anxiolytic and antidepressant effects on mice (Just et al. 2018; Rubaiy 2019).

TRPC3/6/7 channels

SAR7334

SAR7334 is a novel, highly potent, and bioavailable compound that inhibits TRPC6-, TRPC3-, and TRPC7-induced Ca^{2+} influx with IC_{50} of 9.5, 282, and 226 nM, respectively, whereas it does not affect TRPC4/5 channels (Maier et al. 2015). Furthermore, SAR7334 suppresses TRPC6-dependent acute HPV in the isolated perfused lungs of mice (Maier et al. 2015) and (O-3)-induced airway inflammatory responses (Chen et al. 2020a). SAR7334 can also negate malignant hyperthermia hypersensitivity by blocking TRPC3/6 (Lopez et al. 2020a). There is a strong possibility that SAR7334 improves cognitive deficits (Uryash et al. 2020). As for the cardiovascular system, SAR7334 dose-dependently attenuates systolic and diastolic blood pressure variability (Wang et al. 2020d). Additionally, TRPC6 knockdown by SAR7334 inhibits renal tubular epithelial cells apoptosis upon oxidative stress through autophagy activation (Hou et al. 2018).

Compound 14a

Compound 14a is a novel TRPC6 antagonist that strongly inhibits 4o, TRPC3/6/7 agonist-induced, and receptor-operated activation of the TRPC6 channel. Compound 14a inhibits TRPC3/6/7 (TRPC6 > C7 > C3) with IC_{50} of around

1 μM against gastric cancer cell growth and xenograft tumor formation. Compound 14a weakly affects the TRPC4 channel and doesn't affect other TRP channels (Ding et al. 2018).

TRPC3/5/6 channels

KB-R7943

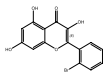
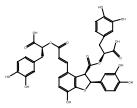
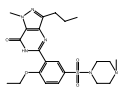
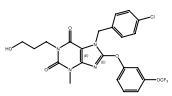
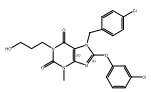
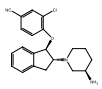
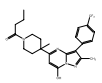
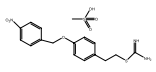
Whole-cell voltage-clamp experiments confirmed that KB-R7943 could potently block TRPC3, TRPC6, and TRPC5 currents with IC_{50} of 0.46, 0.71, 1.38 μM, respectively, and nearly fully suppress the OAG-induced Ca^{2+} entry in HEK293 cells (Kraft 2007) (Table 4).

Nonselective TRPCs

SKF96365

Merritt et al. (1990) originally identified SKF96365 as a novel inhibitor of ROCE, (1-(β-[3-(4-methoxy-phenyl) propoxy]-4-methoxyphen-ethyl)-l H-imidazole hydrochloride), with IC_{50} of around 10 μM. However, SKF96365 was not as potent or selective as desired because it could also block T-type calcium channels (Singh et al. 2010). A previous study indicated that SKF96365 inhibits TRPC channels, arrests the cell cycle in the G2/M phase, and suppresses cell growth in AGS or MKN45 human gastric cancer cell lines

Table 4 TRPCs antagonists (2)

Modulators	Chemical structure	Targeting channels and IC50	Predicted effects	Reference
Clemizole		1.0–1.3 μM (TRPC5) TRPC1:C5	Inhibit TRPC1:C5 channel and TRPC5 currents in the U-87 glioblastoma cell line	Richter et al. (2014a)
ML204		13.6 μM (TRPC4/5)	Block riluzole-activated TRPC5-mediated current; reduce the mouse carotid arteries endothelium-dependent contractions	Liang et al. (2019), Miller et al. (2011), Zhou et al. (2017)
M084		10.3 μM (TRPC4), 8.2 μM (TRPC5)	Antidepressant and anti-anxiety effects	Yang et al. (2015), Zhu et al. (2015)
AM12		0.28 μM (TRPC5) TRPC4	Inhibit the activation TRPC5 channel	Naylor et al. (2016)
Salvianolic acid B		TRPC3, TRPC6	Counteracted DOX-evoked heart abnormalities and tissue injury	Chen et al. (2017), Su et al. (2020)
Rox4560		TRPC3/6	Suppress calcium levels in podocytes	Guan et al. (2017)
Sildenafil		TRPC1/6	Counteracting renal injury; cardioprotective effects	Lu et al. (2010), Santiago-Vacas et al. (2021), Sonneveld et al. (2017)
Pico145		1.3 nM (TRPC5:C5), 0.349 nM (TRPC4:C4) 0.199 nM (TRPC5:C1), 0.033 nM (TRPC4:C1)	Inhibit AM237-mediated TRPC5:C5 channel activation	Minard et al. (2019), Rubaiy et al. (2017a, b)
HC070		46.0 nM (TRPC4:C4), 0.52 nM (TRPC5:C5) 1.4 nM (TRPC1:C5), 1.3 nM (TRPC1:C4)	Anxiolytic and anti-depressant	Just et al. (2018)
SAR7334		9.5 nM (TRPC6), 282 nM (TRPC3) 226 nM (TRPC7)	Suppress acute HPV; attenuate renal injury	Hou et al. (2018), Maier et al. (2015)
Compound 14a		~1 μM (TRPC3/6/7)	Inhibit gastric cancer cell growth	Ding et al. (2018)
KB-R7943		0.46 μM (TRPC3), 0.71 μM (TRPC6) 1.38 μM (TRPC5)	Suppress Ca^{2+} entry	Kraft (2007)

(Ge et al. 2018), as well as arresting the cell cycle in the S and G2 phases in glioblastoma cells (Song et al. 2014). SKF-96365 is proven effective in the therapy of primary thermal and mechanical hyperalgesia and persistent spontaneous nociception (Ding et al. 2011, 2012). As a SOCE inhibitor, SKF-96365 also exhibits potent anti-neoplastic activity in non-small cell lung cancer cells (Wang et al. 2018b). Moreover, recent reports showed evidence that SKF-96365 induces reduction in cardiac conduction (He et al. 2017). Moreover, SKF96365 reduces Ca^{2+} concentration and airway smooth muscle cell viability in asthmatic mice (Zhang et al. 2018a).

2-APB

2-Aminoethoxydiphenyl borate (2-APB) is an inositol 1,4,5-trisphosphate receptors (IP3Rs) antagonist and TRPC channel antagonist that blocks the expression of human TRPC5 and TRPC6 in HEK-293 cells. In the concentration–response curve, 2-APB has IC_{50} of 20 μM (Diver et al. 2001; Xu et al. 2005; Sekaran et al. 2007). 2-APB can act directly on TRPC ion channels in melanopsin-expressing ganglion cells (Sekaran et al. 2007). TRPC1/3/6 inhibition by SKF96365 and 2-APB attenuates TGF-β1-induced epithelial-mesenchymal transition in gastric cancer via the Ras/Raf1/ERK signaling pathway (Ge et al. 2018) (Table 5).

All nonselective TRPCs antagonists have certain inhibitory effects on various cell types and can target a particular channel or disease through structural modification, which presents a novel TRPCs therapeutic target for drug discovery.

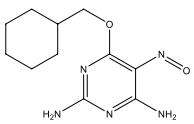
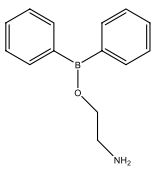
Discussion

TRPCs are associated with the occurrence and development of many diseases. Studies have proved that they are linked with different crucial roles in the pathophysiological process of many diseases; thus, they present a novel target for the intervention and treatment of some diseases. Additionally, the emergence of TRPCs modulators can prompt an understanding of these channels in health and disease.

At present, highly potent and highly selective TRPCs modulators, such as (−)-englerin A, hyperforin, ML204, Pico145, HC070, Pyr3, DS88790512, and AC1903 are still unprecedented opportunities for TRPCs research. However, some obstacles, such as the toxicity and instability of (−)-englerin A in the cardiac and respiratory systems limit their use (Wu et al. 2017b; Minard et al. 2018; Rubaiy 2019). Additionally, hyperforin is also unstable and susceptible to oxygen, heat, and light. Pico145 and HC070 are suitable for in vivo studies, whereas ML204 and DS88790512 were only conducted in vitro studies; thus, there are no reports on their in vivo efficacy. AC1903 could cause a developmental defect in the amygdala. These problems are collectively obstructive to the usage of the current selective TRPCs modulators; thus, the development of new TRPCs modulators drugs that are more potent and more selective is needed.

With the tremendous advancement of science and drug technologies, discovering the means to overcome the mentioned undesired effects becomes possible. In structural biology, high-resolution structures are increasingly becoming the dominant method for determining the structures of many receptor complexes through cryo-EM technology. In recent decades, rich combinatorial compound libraries provide an abundant material basis for high-throughput screening due to their vast quantities and diverse structures that have become a popular approach to discovering and developing new medications, offering possibilities for finding suitable TRPCs modulators. Furthermore, many reports revealed that antisense oligonucleotide therapies and small molecule peptides therapies have increasingly become a novel strategy for treating a variety of diseases (Yamamoto et al. 2016; Beekman and Howell 2016; Mignani et al. 2019; Chen et al. 2020b; Tahirovic et al. 2020). Studying channel domains functions, especially the precise interpretation of modulators' binding sites, helps discover highly selective TRPCs

Table 5 TRPCs antagonists (3)

Modulators	Chemical structure	Targeting channels and IC50	Predicted effects	Reference
SKF96365		TRPC, low-voltage-activated T-type calcium channels 10 μM	suppress growth in human gastric cancer cell lines, glioblastoma cells, non-small cell lung cancer and colorectal cancer cells, primary thermal and mechanical hyperalgesia and persistent spontaneous nociception, induce a reduction in cardiac condition	Ding et al. (2011), Singh et al. (2010), Song et al. (2014), Ge et al. (2018)
2-APB		TRPC, TRPM3 20 μM	Act directly on a TRPC ion channel in melanopsin-expressing ganglion cells, block human TRPC5, TRPC6 and TRPM3 channels	Diver et al. (2001), Ge et al. (2018), Sekaran et al. (2007), Xu et al. (2005)

modulators. These new technologies permit a more comprehensive assessment of the structures and function of TRPCs in physiology and pathophysiology, thereby providing the means to find more potent and selective TRPCs modulators.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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