Effects of curcumin on ion channels and pumps: a review

Jamshid Tabeshpour[1], Sara Banaeeyeh[1], Farhad Eisvand[1], Mahmoud Hashemzaei[2], Amirhossein Sahebkar[3,4,5]

[1]Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

[2]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Zabol University of Medical Sciences, Zabol, Iran

[3]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

[4]Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

[5]School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence: Amirhossein Sahebkar, Department of Medical Biotechnology, Mashhad University of Medical Sciences, Iran. Email: sahebkara@mums.ac.ir

Running title: Modulation of ion channels and pumps by curcumin

Abstract

Curcumin, an orange-yellow lipophilic polyphenolic molecule, is the active component of *Curcuma longa* which is extensively used as a spice in most of the Asian countries. This natural compound is able to interact with a large number of molecular structures like proteins, enzymes, lipids, DNA, RNA, transporter molecules and ion channels. It has been reported to possess several biological effects such as antioxidant, anti-inflammatory, wound-healing, antimicrobial, anticancer, antiangiogenic, anti-mutagenic and antiplatelet aggregation properties. These beneficial effects of curcumin are because of its extraordinary chemical interactions such as extensive hydrogen and covalent bonding, metal chelation, etc. Therefore, the aim of this review was to outline the evidence in which curcumin could affect different types of ion channels and ion channel-related diseases and also to elucidate basic molecular mechanisms behind it.

Keywords: curcumin, *Curcuma longa*, ion channels, cystic fibrosis transmembrane regulator, NMDA receptor

Introduction

Ion channels, membrane protein complexes of different sizes, are formed in the endoplasmic reticulum and located in the lipid bilayer (33). As evidenced by many mechanistic-based studies, ion channels and pumps via exchanging ions between the intra- and extracellular spaces play very important roles to maintain cell homeostasis, are essential players in signal transductions, regulate membrane potential, influence cell proliferation, migration, apoptosis and differentiation (57, 82). In fact, they act as a communication bridge among different types of cells in a living organism (82). Therefore, any xenobiotic which is able to affect the normal function of ion channels and pumps can lead to ion channel-related diseases.

As the most active ingredient of the plant *Curcuma longa* (*C. longa*), curcumin is a lipophilic polyphenol substance that has been reported to have several pharmacological actions including wound-healing, anti-inflammatory, anti-microbial, antioxidant, immunomodulatory, lipid-modifying, anti-tumor, anti-platelet aggregation and anti-angiogenic effects (39, 41, 80, 87, 81, 21, 84, 68, 78, 83, 28, 53). It can also be used as an encouraging treatment for multiple sclerosis, cancer, diabetes, metabolic, autoimmune, Alzheimer's, human immunodeficiency virus (HIV), cardiovascular, neurological, and liver and lung diseases (73, 74, 49).

Curcumin is reported to have an impact on ion channels and pumps. As far as we know there is no organized and comprehensive review paper that investigates the effect of curcumin on various ion channels in a systematic way. Hence, we have performed a comprehensive review on this subject to clarify the basic molecular mechanisms of health-beneficial properties of curcumin.

1- Classified ion channels

1-1- Voltage-gated Ion Channels

1-1-1- Voltage-gated Calcium Channels (VGCCs)

VGCCs drive calcium ions into cells after depolarization of membrane (98). They play a vital role in biological events including the release of neurotransmitters, neuronal migration and contraction of muscles (94).

Curcumin inhibits stimulated glutamate release from rat prefrontal cortical synaptosomes via the inhibition of presynaptic voltage-gated N-type Ca^{2+} ($Ca_v2.2$) and $Ca_v2.1$ channel. This effect was comparable with the antidepressant fluoxetine potentially by preventing glutamate release from the nerve terminals (56). Curcumin also inhibited L-type Ca^{2+} channel in the hippocampus. In a concentration-dependent way in rat hippocampal neurons, curcumin blocked high voltage-gated Ca^{2+} channel currents via protein kinase-theta isoform-dependent pathway, demonstrating its neuroprotective effects (58).

Curcuma longa (C. longa) extract and cyclocurcumin inhibit the contraction of vascular smooth muscle by the suppression of myosin-light-chain phosphorylation and calcium influx via the L-type calcium channels. This suggests that the extract of *C. longa* may possibly be used as a therapeutic agent and a novel anti-vasoconstrictive natural product (45). Moreover, it has been shown that synthetic curcumin mimics were able to function as dual antagonist scaffold of L-type Ca^{2+} channel and endothelin β2 adrenergic receptor in vascular smooth muscle cells suggesting these agents could have a therapeutic role in the management of hypertension and related cardiovascular diseases (79).

Another study demonstrated that the vasorelaxant effect of hexahydrocurcumin was elicited mainly by the endothelium-independent pathway. This could be potentially by blocking extracellular Ca^{2+} influx via voltage-operated Ca^{2+} channels and receptor-operated Ca^{2+} channels, by inhibiting Ca^{2+} mobilization from intracellular stores, as well as by suppressing protein kinase C-mediated Ca^{2+}-independent contraction (69).

1-1-2- Voltage-gated Potassium Channels

These are homotetrameric channels, with each subunit having a voltage sensor and contributing to the central pore (101).

It was shown that curcumin was able to block human ether-á-go-go-related gene (hERG) K^+ channel (Kv11.1) in HEK-293 cells overexpressed with hERG via alteration in gating and blocking the pore (14). This suggests that the inactivation, deactivation and the recovery time from inactivation of hERG channels were altered by curcumin (35). Curcumin, dose-dependently, elevated large conductance Ca^{2+}-activated potassium channels currents in HEK293 and A7r5 smooth muscle cells (11).

Moreover, curcumin potently inhibited Kv11.1 activity and the proliferation of THP-1 cells. Blockade of ionic currents carried by Kv11.1 led to depolarization of cell membrane potential (5). In another study, curcumin was capable of preventing proliferation and pro-inflammatory cytokine secretion of effector memory T cells possibly via blockade of human Kv1.3 channels. This mechanism could be attributed to curcumin's therapeutic role in autoimmune diseases (54). It also blocked potassium channel subtype Kv1.3 which are predominantly expressed in T cells which has a crucial role in psoriasis. Secretion of inflammatory factors was remarkably inhibited both by curcumin *in vivo* and *in vitro*. Consequently, curcumin could be used as a novel drug candidate to manage psoriasis (42). In this regard, another study revealed that curcumin suppressed the Kv2.1 channel through modulating the inactivation gating, which in turn could affect cellular physiology (1).

Curcumin potentially has an anti-inflammatory effect by blocking major ion channels including store-operated Ca^{2+} entry and Ca^{2+} release-activated Ca^{2+} channel, voltage-gated K^+ channel, intermediate-conductance Ca^{2+}-activated K^+ channel in lymphocytes (89). Curcumin also inhibits vascular voltage-gated K^+ channels (34).

1-1-3- Voltage-gated Sodium channels

Voltage-gated sodium channels are accountable for the rising phase of the membranes action potential in neurons as well as other excitable cells (10). Curcumin was able to improve diabetes mellitus and its complications such as diabetic neuropathic pain through voltage-gated sodium channels and by increasing sodium content in dorsal root ganglion neurons (67).

1-1-4- Voltage-gated Chloride Channels (CICs)

They exist in the plasma membranes and the membranes of intracellular organelles and has important functions such as synaptic transmission and cellular excitability (59).

Curcumin has been shown to have a toxic effect on MCF-7 cells and could activate the chloride ion current on their membrane. In fact, ClC-3 chloride channel was involved in the regulation of curcumin-mediated cell apoptosis in these cells suggesting this channel could be a therapeutic target for curcumin in oncological disorders (37).

1-1-5- Two-pore-domain Potassium Channels

The K+-selective mechanosensitive currents consist of voltage-gated K^+-selective channels and two-pore domain K^+-selective (K2P) channels. TRAAK, TREK1, and TREK2 are three types of mechanosensitive K2P channels which are activated by membrane tension (18).

Results of one study suggest that curcumin was able to strongly block bTREK1 K^+ channels and trigger secretion of cortisol from bovine adrenal zona fasciculata cells. Because TREK1 K^+ channels are extensively expressed some of the curcumin's therapeutic effects could be mediated via blockade of these channels (26).

1-1-6- Inwardly Rectifying Potassium Channels

These channels exist in all organisms and regulate the resting membrane potential, K^+ homeostasis, and membrane excitability (91). Curcumin, dose-dependently resulted in mitochondrial membrane potential loss in SGC-7901 cells and elevated the rate of apoptosis. Finally, it was concluded that impaired mitochondrial adenosine triphosphate (ATP)-sensitive Kir opening was the main reason for this loss, and was involved in curcumin-mediated apoptosis in gastric cancer (60). Curcumin has been shown to have a gastroprotective effect via activating nitric oxide/cyclic guanosine monophosphate (cGMP)/ATP-sensitive potassium (K_{ATP}) channels pathway (22). Similarly, Dash et al. indicated that in goat ruminal artery, curcumin directly activated soluble guanylyl cyclase/cGMP pathway and opened the K^+ ion channel (16).

Curcumin was able to prevent α-synuclein gene overexpression or mutation mediated α-synuclein oligomers formation. Mitochondrial K_{ATP} channel opening could be the protective mechanism of apoptosis mediated by wild-type overexpression or mutation of α-synuclein. Curcumin might reverse cytotoxicity via further opening this channel (12).

1-1-7- Transient Receptor Potential Channels

These channels play important roles in signal transduction processes in excitable and non-excitable cells (73, 24). Curcumin was capable of decreasing dinitrobenzene sulphonic acid-mediated colitis in mice. In fact, it functioned as a transient receptor potential vanilloid 1 (TRPV1) agonist. Curcumin was also able to produce its protective effect in colitis *in vitro* (in rat Xenopus oocytes) (63, 96). In addition, some researchers came to the conclusion that curcumin had gastroprotective and hyperemic effects against experimental stress-mediated gastric lesions by involving endogenous prostaglandins, nitric oxide, neuropeptides release from capsaicin-sensitive afferent nerves and the activation of TRPV1 receptors located on these nerves (15).

Curcumin prevented visceral nociception by antagonizing TRPV1 and could be a novel therapeutic choice to manage gastrointestinal disorders (109). When the antinociceptive properties of KMS4034, the most favorable derivative of curcumin, was studied, it blocked TRPV1 ion channels in HEK293 cells and mice. These results suggest that KMS4034 could be an effective antinociceptive for different pain conditions (52). Moreover, the data obtained from another experiment showed that curcumin inhibited capsaicin-mediated TRPV1 activation and prevented TRPV1-induced pain hypersensitivity (102). In a dextran sulfate sodium-mediated colitis model, rats receiving oral curcumin showed relief in hyperalgesia. The mechanism behind this effect could be via decreasing the colonic expression and phosphorylation of TRPV1 on the afferent fibers of nociceptive neurons of dorsal root ganglion (100). Another study indicated that curcumin activated and desensitized native and recombinant transient receptor potential ankyrin 1 (TRPA1) ion channels of multiple mammalian species. (51).

In another study, curcumin had an effect on the pathophysiology of Alzheimer's disease, in part, attributed to the expression levels of phosphatidylinositol 3,5-bisphosphate and transient receptor potential mucolipin-1 (106). Another study demonstrated the important role of transient receptor potential melastatin 2 (TRPM2) channels in hepatocellular damage mediated by oxidative stress and could be a therapeutic agent in a range of liver disorders (44). Curcumin had modulatory effects on TRPM2-mediated Ca^{2+} influx caused by ROS and caspase 3 and 9 processes in SH-SY5Y neuroblastoma cells suggesting its therapeutic potential in neurodegenerative disorders (76).

An *in vitro* study showed no direct connection between the effect of elevated concentrations of curcumin and inhibition or activation of Ca^{2+} signaling (through TRPM2 and TRPM8 channels) in DBTRG cells. Nevertheless, the intracellular Ca^{2+} concentration was lower in 5 μM group in comparison with the control group. But curcumin had a key role in attenuating ROS generation and mitochondrial membrane potential in the cells (77).

1-2- Ligand-gated Ion Channels

1-2-1- Acid-sensing (proton-gated) ion channels

It is known that acid-sensing ion channels (ASICs) become activated by a reduction in extracellular pH and are involved in nociception. Curcumin was able to decrease the amplitude of ASICs currents in a dose-dependent fashion in trigeminal ganglion neurons. Therefore, curcumin was able to diminish formalin-mediated ASICs activation and prevent ASICs-mediated inflammatory pain hypersensitivity (99).

1-2-2- GABA$_A$ Receptor

Zhao et al. in 2014 proved that curcumin normalized the depressive-like behaviors of neuropathic mice. This might be at least in part, due to the involvement of supraspinal serotonergic system and downstream gamma-aminobutyric acid-A (GABA$_A$) receptor and might be independent of the concurrent analgesic action (108).

1-2-3- Ionotropic Glutamate Receptors

1-2-3-1. AMPA

Curcumin showed ameliorating effects in a model of streptozotocin-elicited diabetes in rats via N-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. In this matter, curcumin was able to counteract the altered glutathione peroxidases (GPx) gene expression to near control by normalizing GPx expression and glutamate-mediated excitotoxicity through reversing the altered NMDA and AMPA receptors (40).

1-2-3-2. NMDA

Curcumin has neuroprotective effects against NMDA-induced excitotoxicity via elevating the GluN2A subunit (a subunit of NMDA receptor) activity. Curcumin also regulated Ca^{2+}/calmodulin-dependent protein kinase II and/or serine/threonine phosphatases activities which could be the potential mechanism involved in neuroprotection against excitotoxicity (62). Another study demonstrated that the neuroprotective activity of curcumin against NMDA toxicity was feasibly associated with an elevated level of NR2A (NMDAR subunit type 2A) (65). The effect of curcumin was evaluated in a model of aluminum- and lead-evoked neurotoxicity. Overall, metal exposure affected NR2A concentrations more than NR2B concentrations. Treatment with curcumin increased these receptor protein concentrations (93). Besides, curcumin prevented amyloid-β-mediated neuronal damage and cell death involving the prevention from intracellular Ca^{2+} increase induced by the NMDA receptor (36).

The data obtained from a study suggested that curcumin possessed antidepressant-like effects in mice and the activation of GluN2B-containing NMDARs played an important role in this beneficial effect. Hence, the antidepressant-like effect of curcumin could be mediated partially via the glutamatergic system (107). Furthermore, Kaur et al. demonstrated that curcumin afforded considerable protection against ischemia reperfusion-mediated acute kidney injury in rats. They concluded that the NMDA receptor antagonism substantially contributed to curcumin-evoked protection against this condition (43). Treatment of rat retinal cultures with curcumin decreased NMDA-induced excitotoxic cell damage via a reduction in cell viability and elevation in apoptosis (66).

1-2-4- Nicotinic Acetylcholine Receptors

Curcumin has been shown to inhibit of adrenocorticotropic hormone- and cortisol secretion stimulated by angiotensin II by the inhibition of $Ca_v3.2$ currents (27). It potentiated the activity of the α_7-nACh receptor expressed in SH-EP1 cells (72).

1-3- Other Ion Channels

1-3-1- Aquaporins

Aquaporins (AQPs) are small and integral membrane proteins which transport water across the plasma membranes of cells in response to osmotic gradients (95). Curcumin could potentially modulate CSF secretion in a variety of states such as severe hyponatremia, hypertension, hydrocephalus, and a variety of neurological conditions since it dose-dependently reduced aquaporin-1 expression in rat choroid epithelium cells (71).

1-3-2- Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

They are found in the epithelial cells of the reproductive, digestive and respiratory system. It is a chloride channel protein and the mutations of its gene lead to cystic fibrosis. (75).

The exposure of Chinese hamster ovary cells to curcumin prevented endoplasmic reticulum chaperone expression calreticulin and elevated wild-type CFTR. This suggests that the beneficial effect of curcumin on CFTR expression was via downregulation of CRT which is a negative regulator of CFTR (31). As it is known, a common reason for cystic fibrosis (CF) is a G551D mutation in the CFTR. Yu et al. showed that curcumin potentiated G551D-CFTR in a high concentration range which resulted in additive effect and had a substantial synergistic impact in their minimum concentration ranges (103). Curcumin was reported to restore function to ΔF508 allele, which is the most frequent allele suggesting its potential as CF management (17). Other studies have shown that curcumin was able to open CFTR channels by phosphorylation of the regulatory domain of these channels (97). An investigation also suggested that curcumin might directly trigger CFTR chloride channels because curcumin elevated CFTR channel activity in excised, inside-out membrane patches via decreasing channel closed time and extending the time duration channels remained open (7). It has also been shown that when homozygous mice were treated with curcumin, it might be effective in correcting defects related to the homozygous expression of ΔF508 CFTR (25).

However, curcumin did not have a significant impact on CFTR-initiated chloride transport in airway epithelial cells (23). There was also no significant impact of curcumin in the functional correction of defective ΔF508-CFTR processing in transfected cells (90). The results from another study suggested caution about the secondary effects of curcumin in the management of CF since it irreversibly activated CFTR channels. They surmised that cyclic curcumin derivatives could be more promising in this regard (8).

1-3-3- Orai Channels

Orai channels are located in the endoplasmic reticulum and are store-operated Ca^{2+} channels which are gated by a Ca^{2+} sensor known as stromal interaction molecule 1 (104). Two main molecular components of CRAC are Orai and stromal interaction molecule proteins. It has been shown that the electrophilic addition to the Orai1 195Cys was responsible for the inhibitory effect of calcium release-activated channel currents by curcumin and caffeic acid phenethyl ester (88). In another study, Shin et al. declared that the elevation in cytoplasmic Ca^{2+} concentration mediated by the CRAC was an important signal for activating lymphocytes. Curcumin has its anti-inflammatory effects potentially by blocking these channels in lymphocytes (89).

2- Unclassified ion channels

2-1- Effect of Curcumin on Cell Calcium Content

Curcumin mediates the expression of 70 kilodalton heat shock protein gene via the initial depletion of intracellular Ca^{+2} following the repression of p53 gene function in COL0205 colorectal carcinoma cells. It also prevents the growth of HepG2 cell line, alters the cell-surface morphology and stimulates cell apoptosis. (13). In this regard, curcumin could be used as a novel medication for hepatocellular carcinoma management because of its low cytotoxic effect on the healthy cell (103).

Curcumin was able to diminish vincristine-provoked neuropathy. This could be because of its multiple effects such as calcium inhibitory, anti-nociceptive and antioxidant properties (2). This curcuminoid also had protective effects by inhibiting rapid Ca^{2+} influx mediated by interleukin-6 on rat hippocampal neurons (20).

A study shed some light in the beneficial effects of curcumin which caused relaxation in superior mesenteric arterial rings by blockade of Ca^{2+} influx and intracellular Ca^{2+} release, and opening K^{+} channel (105). The results from another study suggested that the crucial factor by which curcumin produced apoptosis was by its action on mitochondrial Ca^{2+} (38).

2-2- P-type ATPase

2-2-1- Na-K ATPase

Results obtained from an investigation showed that curcumin could be a therapeutic agent to lessen hypoxia-induced cerebral edema because it efficiently decreased inflammation along with fluid influx via maintaining the integrity of tight junction with elevated Na^{+}/K^{+}-ATPase expression in hypoxic rat brain (85). Moreover, Mathew and Sagi demonstrated that prophylactic administration of curcumin substantially increased the Na^{+}/K^{+}-ATPase activity. They suggested that the attenuation of oxidative stress caused the activation of NFκB which promoted alveolar fluid clearance and barrier integrity under hypoxic condition (64).

2-2-2- Ca ATPase

One of the studies showed that the structural specificity of curcumin impact on Ca^{2+} accumulation and ATPase activity had similarity in the apparent dissociation constants. This indicated that these effects could be due to the ability of curcumin to bind to a single site on the Ca ATPase (61).

2-3- Mitochondrial Calcium Uniporter

Mitochondria's inner membrane has a mitochondrial Ca^{2+} uniporter which undertakes Ca^{2+} uptake which regulates the rate of energy production and determines the spatio-temporal patterns and amplitude of intracellular Ca^{2+} signals (46).

One study showed that when mitochondrial uniporter was inhibited dose dependently by ruthenium red and it reduced the curcumin-evoked intracellular Ca^{2+} depletion. This shows curcumin stimulates intracellular Ca^{2+} uptake into mitochondria through uniporter pathway and might act as an antiapoptotic agent (3).

2-4- Outwardly Rectifying Chloride Current

Curcumin, dose-dependently, could exert influence on cell survival and cell volume. Curcumin indirectly activated swelling-activated chloride channel (lCl_{swell}) at lower concentrations by inducing apoptosis where as it indirectly blocks the swelling activated chloride current, an arrest of cell cycle in G1-phase and then to cell swelling at higher concentrations (48).

2-5- Effect of Curcumin on Cell Potassium Content

Banerjee et al. suggested that curcumin, at low blood concentrations has antioxidant property in red blood cells (RBCs), which led to its anti-tumor action. They concluded that curcumin in RBCs haemolysis model had both pro-oxidant and antioxidant activities (6).

2-6- Transient Outward Potassium Current

HIV-1 gp120 leads to an elevation in MCP-1, TNF-α and ROS generation in microglia, and promoted apoptosis in cortex via affecting the delayed rectification and transient outward K^+ channel current. Curcumin has shown to protect cortical neurons by reducing inflammatory mediators and ROS probably via prevention of HIV-1 gp120-evoked increase of the delayed rectification and transient outward K^+ current in HIV-1-gp120-stimulated microglia against HIV-1-provoked apoptosis (30).

2-7- Delayed-Rectifier Potassium Current

It has been shown that curcumin prevented hERG tail current density on delayed-rectifier K^+ current in HEK-293 cells transfected with the hERG gene. In these cells, the liposomal curcumin formulation also inhibited drug-evoked delayed-rectifier K^+ current blockade. This blockade by curcumin was attenuated when curcumin was incorporated into a liposome (32). In insulinoma cells, curcumin induced inhibition of delayed-rectifier K^+ current and the increase of current inactivation. Curcumin and curcuminoids (demethoxycurcumin and bisdemethoxycurcumin) depolarized the resting membrane potential and increased the firing of spontaneous action potentials in these cells which could explain their functional activities in insulin-secreting cells (50).

2-8- Mitochondrial Permeability Transition Pore (mtPTP)

It mediates the rapid elevation in permeability of the inner mitochondrial membrane, which is a common feature of apoptosis (47). It has been shown that in the presence of low Ca^{2+} concentrations curcumin could oxidize mitochondrial membrane thiol functions thereby opening of mtPTP. The match between its ability to induce mtPTP and its antioxidant effect possibly direct the cell to die or live. This depends on the nature of the cell and indicates the opposing function of curcumin. This could explain the mechanism behind curcumin's apoptotic activity in tumor cells (70). Another study demonstrated curcumin via reduction of Fe^{3+} to Fe^{2+} enhanced mtPTP opening, increasing hydroxyl radical generation as well as oxidation of thiol groups in the membrane, resulting in pore opening (55).

2-9- Voltage-dependent Anion Channel

MtPTP is consisted of three parts: the voltage-dependent anion channel (VDAC) in the outer membrane, the adenine-nucleotide translocase in the inner membrane and cyclophilin-D in the matrix (4).

It has shown that curcumin-elicited fibroblast apoptosis was completely caspase-independent and was dependent on ROS generation in mitochondria (86). By closing of VDAC in rat liver mitochondria, curcumin accelerated Ca^{2+} mediated mitochondrial PTP and escalated oxidative stress, which are pro-apoptotic factors. Curcumin was able to close VDAC1which explained its well-known pro-apoptotic activity (92).

2-10- Volume-regulated Anion Channel (VRAC)

They are activated in response to hypotonic stress (19). Curcumin has been shown to activate VRAC and stimulate β-cell function which contributed to its anti-hyperglycaemic properties. Curcumin could be a novel drug candidate to manage type 2 diabetes mellitus (9).

Conclusion

This review highlights the possible potential applications of curcumin in the management of a differing ion channel-related conditions such as inflammation, depression, hypertension, diabetes, diabetic neuropathic pain, psoriasis, cancer, colitis, Alzheimer’s and autoimmune diseases. The processes behind such beneficial effects includes inhibition of presynaptic Cav2.2 leading to antidepressant effect, suppression of L-type calcium channels resulting in anti-vasoconstrictive effect, blockade of Kv11.1 activity leading to acute myeloid leukemia treatment, blockade of human Kv1.3 channels resulting in therapy of autoimmune diseases, ClC-3 chloride channel suppression leading to breast cancer treatment, activation of K_{ATP} channels resulting in gastroprotective and anticytotoxic effects, TRPV1 agonist leading to anticolitis effect, inhibition of TRPM2 channels resulting in the treatment of oxidative stress-associated liver disorders, and decrease in ASICs activation preventing inflammatory pain hypersensitivity. Despite such positive effects, no clinical use has been made of this potentially valuable agent. Therefore, further clinical studies are required to precisely assess its efficacy and safety, and its use as a potential therapeutic agent in various disorders.

Conflict of Interests

None.

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Figure legend

Figure 1. Blocking or stimulating effects of curcumin on ion channels (in different cells). Abbreviations: VGCC, voltage-gated calcium channel; VGPC, voltage-gated potassium channels; VGPC, voltage-gated sodium channels; ClCs, voltage-gated chloride channels; TPC, two-pore channel; Kir, inwardly rectifying potassium channels; TRPV, transient receptor potential channels; ASIC, acid-sensing ion channel; GABAA, gamma-aminobutyric acid-A; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-d-aspartate; nAChR, nicotinic acetylcholine receptor; AQP, aquaporin; CFTR, cystic fibrosis transmembrane conductance regulator; SERCA, sarcoplasmic reticulum Ca2+ ATPase; MCU, mitochondrial calcium uniporter; mPTP, mitochondrial permeability transition pore; VDAC, voltage-dependent anion channel.