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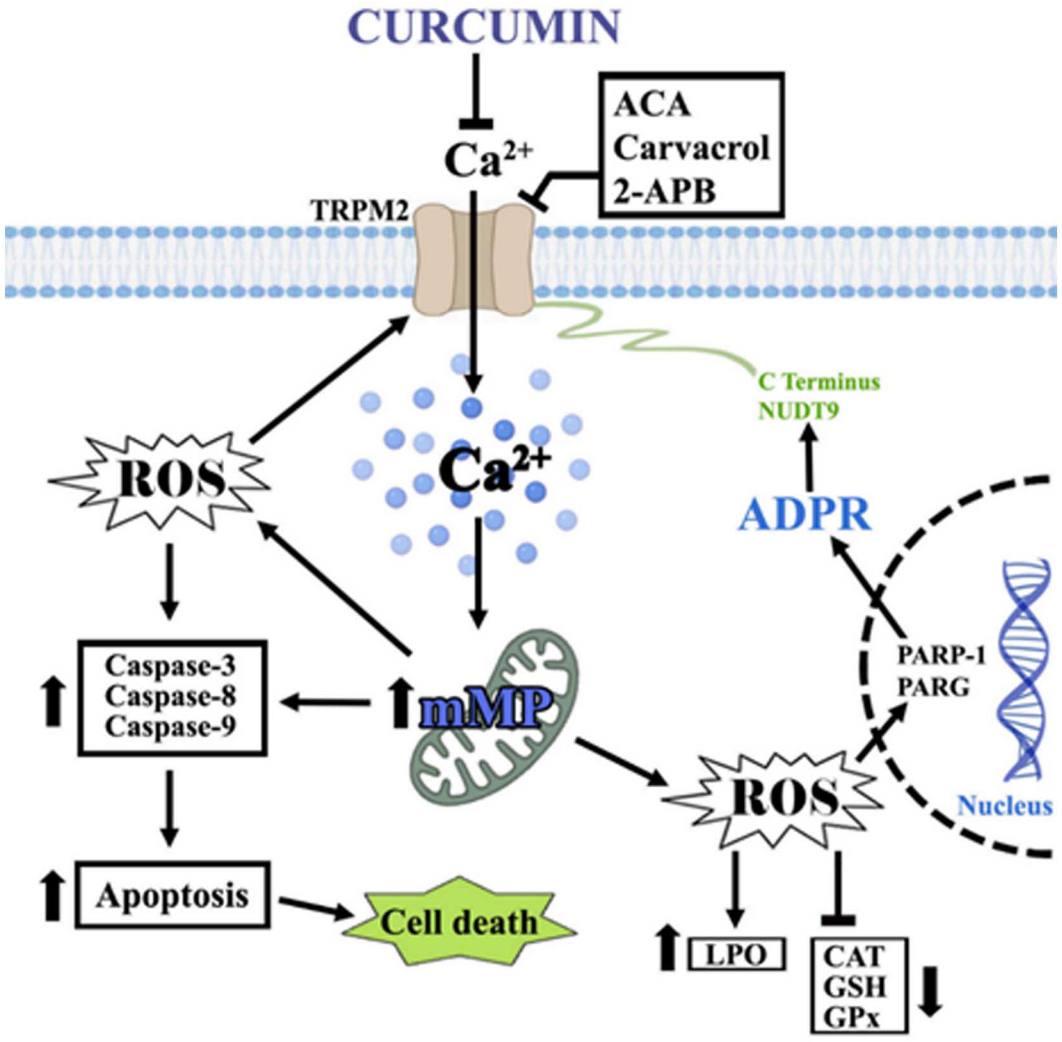

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AIM AND SCOPES
Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

Areas of particular interest are four topics. They are;

A- Ion Channels (Na^+- K^+ Channels, Cl^- channels, Ca^{2+} channels, ADP-Ribose and metabolism of NAD^+, Patch-Clamp applications)

B- Oxidative Stress (Antioxidant vitamins, antioxidant enzymes, metabolism of nitric oxide, oxidative stress, biophysics, biochemistry and physiology of free oxygen radicals)

C- Interaction Between Oxidative Stress and Ion Channels in Neuroscience
(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD^+ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

D- Gene and Oxidative Stress
(Gene abnormalities. Interaction between gene and free radicals. Gene anomalies and iron. Role of radiation and cancer on gene polymorphism)

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Biophysics	Biochemistry
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Ion channels, cell biochemistry, biophysics, calcium signaling, cellular function, cellular physiology, metabolism, apoptosis, lipid peroxidation, nitric oxide, ageing, antioxidants, neuropathy, traumatic brain injury, pain, spinal cord injury, Alzheimer's Disease, Parkinson's Disease.

REVİEW ARTICLE

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A mini review of curcumin and TRPM2 channel: Focus on oxidative neurotoxicity

Mustafa NAZIROĞLU[1,2]

[1]*Director of Neuroscience Research Center (NOROBAM), Suleyman Demirel University, Isparta, Türkiye*
[2]*Drug Discovery Unit, BSN Health, Analysis and Innovation Ltd. Inc. Teknokent, Isparta, Türkiye*

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***Address for correspondence:**
Prof. Dr. Mustafa NAZIROĞLU,
Head of Department of Biophysics,
Faculty of Medicine, Suleyman Demirel University,
Isparta, TR-32260, Türkiye
Tel: +90 246 2113708
E-mail: mustafanaziroglu@sdu.edu.tr

List of Abbreviations;

2-APB, *2-aminoethyl diphenylborinate;* ***ACA,*** *N-(p-amylcinnamoyl) anthranilic acid;* ***ARPE19,*** *human retinal pigment epithelial 19;* ***Ca^{2+},*** *calcium ion;* ***CAT,*** *catalase;* ***CRV,*** *carvacrol;* ***CURC,*** *curcumin;* ***GPx,*** *glutathione peroxidase;* ***GSH,*** *glutathione;* ***IFNg,*** *interferon gamma;* ***MMP,*** *mitochondrial membrane depolarization;* ***ROS,*** *reactive oxygen species;* ***TRP,*** *transient receptor potential;* ***TRPM2,*** *transient receptor potential melastatin 2*

Abstract

Several neuronal diseases are induced by the induction of apoptosis/cell death and reactive oxygen species (ROS) via the accumulation of excessive free Ca^{2+} into mitochondria. The Na^{+} and Ca^{2+} permeable TRPM2 cation channels are activated by oxidative stress. The TRPM2-mediated Ca^{2+} influx induces excessive generation of mitochondrial ROS, apoptosis, and inflammation. The actions are modulated by the treatment of antioxidant plants. Curcumin (CURC) is a natural yellow antioxidant. Results of recent studies have indicated that CURC acted protective properties through the inhibition of TRPM2 on the hypoxia, anti-tumor, antioxidant, anti-inflammatory actions in tumor, neuronal, retinal, kidney, and hepatocyte cells. However, the treatment of CURC induced oxidant and TRPM2 stimulator actions in tumor cells. The protective actions of CURC via modulation of oxidative stress and TRPM2 channel on the ROS generation, inflammation, and cell death in neuronal cells and mice retina have been recognized.

In conclusion, the present data of TRPM2 demonstrated that the physiologic balance between the neuronal and retinal diseases was arranged in the kidney, neuronal cells and retina by the TRPM2 channels-stimulation mediated Ca^{2+} influx. However, the treatment of CURC induced protective action through the inhibition of TRPM2 on the inflammatory, oxidant, and apoptotic pathways in the cells. Tumor cells were killed through the stimulation of TRPM2 by CURC. It seems that the TRPM2 stimulator and inhibitor actions of CURC are cell specific.

Keywords: Apoptosis; Curcumin; Hypoxia; Neuron; Oxidative stress; TRPM2 channels.

Introduction

Oxidative stress is induced by the excessive generation of reactive oxygen species (ROS). ROS include several free oxygen radicals such as superoxide radical and hydroxyl radical. There are ROS generations in several physiological functions such as mitochondrial and phagocytic actions. The excessive generations of ROS induce harmful actions on the cellular components such as lipids, nucleic acids, and proteins in cell components (Gutteridge and Halliwell 2018). The produced ROS cannot harm the components of the cell when they are controlled by enzymatic (such as glutathione peroxidase-GPx and catalase-CAT) and non-enzymatic (such as glutathione-GSH and vitamin E) antioxidants (Halliwell 1992). ROS have main roles in the initiation and progression of several neuronal injury conditions such as hypoxia, Alzheimer's disease, and Parkinson's disease (de la Monte et al. 2000; Islam 2017; Yıldızhan and Nazıroğlu 2023).

The activation of numerous cations channels, including voltage gated calcium channels (VGCC) and chemical gated calcium channels, allows the calcium ion (Ca^{2+}) to influx through cell membrane (Kumar et al. 2014). In recent years, new cation channels namely the transient receptor (TRP) superfamily were discovered (Sakaguchi and Mori 2020). In mammalian, the TRP superfamily has 28 members within 6 subgroups. At 2002, Yasuo Mori's group from Kyoto-Japan and Andreas Lückhoff's group from Aachen-Germany independently indicated that TRPM2 channel was activated by oxidative stress (Hara et al. 2002; Wehage et al. 2002). At least 11 TRP channels are activated by ROS. The TRPM2 channel is also activated by DNA damage-induced ADP-ribose (ADPR) production (Perraud et al. 2021). We indicated that TRPM2 is separately activated by ADPR and oxidative stress (Nazıroğlu and Lückhoff 2008). There is no specific inhibitor of TRPM2, although 2-aminoethyl diphenylborinate (2-APB), N-(p-amylcinnamoyl) anthranilic acid (ACA), and carvacrol (CRV) are nonspecific antagonists of TRPM2 (Kraft et al. 2006; Togashi et al. 2008; Nazıroğlu 2022). Curcumin (CURC) is obtained from roots of the turmeric plant, ***Curcuma longa***, *and it* is a natural yellow polyphenol antioxidant (Giordano et al. 2013). The TRPM2 is inhibited by some antioxidants, including the CURC. The modular actions of CURC via TRPM2 channel activity modulation on cancer, cell death, and hypoxia in cell lines were reported. Recent research showed that CURC had modulator qualities that affected the hypoxia, anti-tumor, antioxidant, and anti-inflammatory responses in tumor, neuronal, retinal, kidney, and hepatocyte cells. This was accomplished via inhibiting the TRPM2.

According to my knowledge, there is no enough review report on the CURC and TRPM2 channel in the tumor, neuronal, retinal, kidney, and hepatocyte cells. In the present study, I reviewed recent developments on the CURC and TRPM2 channel in the cells.

Oxidative stress, Ca^{2+} influx, and cellular injury

Oxidative stress includes ROS such as superoxide and hydroxyl radicals (Gutteridge and Halliwell 2018). A main source of ROS is mitochondria. A main target of ROS is polyunsaturated fatty acids (PUFA) in the cell membranes and cellular components. The neuronal cells and brain have low antioxidant levels, but have high oxygen consumption and PUFA content. Hence, the neuronal brain and cells are vulnerable to the excessive ROS production (Halliwell 2006). ROS are scavenged by antioxidants. There are two groups of antioxidants as enzymatic and nonenzymatic. The enzymatic antioxidants include antioxidant enzymes such as CAT and GPx. The non-enzymatic antioxidants include several vitamins and thiol groups such as vitamin E and GSH. The imbalance between the antioxidants and oxidants causes several neuronal injury and neurodegenerative diseases such as hypoxia, Alzheimer's disease, and Parkinson's disease (de la Monte et al. 2000; Islam 2017; Yıldızhan and Nazıroğlu 2023). The imbalance was reported for the induction of cancer, retinal, kidney, and hepatocyte diseases (**Table 1**).

Although the extracellular Ca^{2+} concentration is approximately 1.2 mM (1-3 mM), the cytosolic free Ca^{2+} concentration ranges from 50 to 100 nM. There is limited Ca^{2+} in the mitochondria. The physiologic Ca^{2+} concentration induces several physiological functions. However, accumulation of Ca^{2+} into mitochondria stimulates the excessive ROS generations (Baev et al. 2022). In mitochondrial ROS-mediated neuronal cells, antioxidant level is inversely correlated with neuronal cell damage (Halliwell 2006; Rajasekar et al. 2013; Islam et al. 2022). However, the antioxidant's ability to protect cells depends on how they influence Ca^{2+} influx in neural cell (Akyuva and Nazıroğlu 2020). It has been demonstrated that excessive ROS production in mitochondria is linked to an increase in mitochondrial membrane depolarization

($\Delta\Psi m$) in neuronal cells, which results in a lack of cellular homeostasis (Bao et al. 2016; Deveci et al. 2019; Akyuva and Nazıroğlu 2020). Furthermore, results of recent studies indicated that the excessive Ca^{2+} influx can induce ROS-dependent apoptosis in the tumor, neuronal, retinal, kidney, and hepatocyte cells. However, the excessive Ca^{2+} influx-induced ROS generation and apoptosis induction were decreased via inhibition of the TRP channels in the neuronal cells by antioxidant treatments such as alpha lipoic acid (Deveci et al. 2019), resveratrol (Akyuva and Nazıroğlu 2020), and CURC (Armağan and Nazıroğlu 2021).

Curcumin and antioxidant system

CURC is produced from the roots of the turmeric plant *Curcuma longa*, and it is a natural yellow antioxidant polyphenol (Giordano et al. 2013). CURC is an effective polyphenol anti-hypoxic, anti-tumor, and against the cellular injury agent, and it exerts several positives effects including anti-hypoxic (Giordano et al. 2013; Wu et al. 2020) and anti-apoptotic actions (Zhou et al. 2020) in several cells, although a conflicting report has also presented (Hollborn et al. 2013).

The antioxidant properties of the CURC molecule are responsible for several of these beneficial activities of CURC (Giordano et al. 2013; Wu et al. 2020). Three highly reactive functional chemical groups are primarily responsible for CURC's biological effects, and they are two phenolic moieties, the central diketone moiety, and complexes of CURC with Cu^{2+} or Mn^{2+} (Teymouri et al. 2017; Ali et al. 2021). Two phenolic moieties and the central diketone moiety in the structure of CURC are responsible for scavenging the ROS of proteins, DNA, and metal ions, although the complexes of CURC with Cu^{2+} or Mn^{2+} scavenge the superoxide radical (Teymouri et al. 2017; Ali et al. 2021). By using CURC to modify proteins and enzymes non-enzymatically, for as by covalently altering cysteine residues, the target enzyme may be inhibited or activated (Hahn et al. 2018).

TRP superfamily

The first members of TRP channel superfamily were discovered in the drosophila flayers' eye cells. In mammalian, there are now 28 members of the TRP superfamily. Canonical (TRPC), no mechanoreceptor potential (TRPN or NOMPC), vanilloid (TRPV), ankyrin

Material	Experimental Model	Pathways	Action of CURC	Reference
ARPE19 retina cells	CURC incubation	Oxidant	Cytotoxic	Hollborn et al. (2013)
SH-SY5Y cells	H_2O_2 and transfection	Antioxidant	Protective	Öz and Çelik (2016)
Renal collecting duct cells	Proteinuria (albumin)	Antioxidant, anti-apoptotic, and anti-inflammatory	Protective	Nazıroğlu et al. (2019)
Human laryngeal squamous cancer cell	Cisplatin	Oxidant, apoptotic, and anti-inflammatory	Antitumor	Gökçe Kütük et al. (2019)
Mouse retina and SH-SY5Y cells	Cisplatin	Antioxidant and anti-apoptotic	Protective	Özkaya and Nazıroğlu (2020)
SH-SY5Y cells	Hypoxia	Antioxidant, anti-apoptotic, and anti-inflammatory	Protective	Armağan and Nazıroğlu (2021)
SH-SY5Y cells	Interferon gamma-induced inflammation	Antioxidant, anti-apoptotic, and anti-inflammatory	Protective	Güzel et al. (2021)
Rat hepatocytes	H_2O_2 or acetaminophen-induced activation of TRPM2	Antioxidant	Protective	Ali et al. (2021)
ARPE19 retina cells	Hydroxychloroquine - induced injury	Antioxidant and anti-apoptotic	Protective	Ertuğrul et al. (2023)

Table 1. *Summary of interactions between TRPM2 and curcumin (CURC).*

(TRPA), melastatin (TRPM), polycystin (TRPP), and mucolipin (TRPML) are the six main subgroups (Nazıroğlu 2007; Sakaguchi and Mori 2020). The majority of the time, the TRP proteins act as monovalent and divalent cation channels that are unselective and are activated by a variety of stimuli, such as heat, cold, chemicals, oxidative stress, mechanical stress, and osmotic stress. The number of TRP channels reported in the literature has significantly expanded over the past ten years. The importance of TRP channels in the diseases of eye, kidney, neurodegenerative, and cancer has advanced greatly with the understanding of the TRP channel tissue expression, activation, and inhibitory mechanisms. We are aware that the TRPM subfamily is involved in the migration and proliferation of numerous cancer types, including prostate and glioblastoma, whereas the TRPV1 channels regulate neuropathic pain and changes in body temperature (Nazıroğlu et al. 2023). A limited amount of recent research has suggested that CURC acts modulator action through oxidative stress. In addition, limited recent data indicated that the inhibition of TRPM2 channels involve in the action of CURC (**Table 1**).

TRPM2 subfamily

Through the activation of cell membrane channels, including the TRP channels, ROS-induced excessive Ca^{2+} influx causes excessive mitochondrial ROS production, cell death, and apoptosis in the tumor, neuronal, retinal, kidney, and hepatocyte cells. TRPM2 is a member of the TRP superfamily, and it is Na^{+} and Ca^{2+} permeable a cation channel (Nazıroğlu 2007; Sakaguchi and Mori 2020). The TRPM2 channel is stimulated in the cells by NAD^{+}, ADPR, and ROS. As it was mentioned above, it is inhibited by chemicals, including the 2-APB, ACA, and CRV (Kraft et al. 2006; Togashi et al. 2008; Nazıroğlu 2022). The increase in Ca^{2+} absorption into mitochondria is known to be correlated with an increase in TRPM2 activation. Through an increase in $\Delta\Psi m$, this then causes excessive ROS production, which in turn causes spontaneous apoptosis, cell death, and dysregulation of survival signaling (Aarts and Tymianski 2005; Mai et al. 2020). However, the ROS-evoked cell death and neurodegeneration in the tumor, neuronal, retinal, kidney, and hepatocyte cells were attenuated via inhibition of TRPM2 channel by CURC (**Table 1**).

Curcumin and TRPM2

The treatment of CURC acted TRPM2 antagonist actions in the optic nerve of mice (Özkaya and Nazıroğlu 2020), human laryngeal squamous cancer (Gökçe Kütük et al. 2019), renal collecting ducts (Nazıroğlu et al. 2019), SH-SY5Y neuronal cells (Öz and Çelik 2016; Armağan and Nazıroğlu 2021), and rat hepatocytes (Kheradpezhouh et al. 2016). A reduction in TRPM2 activation, mitochondria ROS, caspase -3, caspase -9, and apoptosis in the cells was induced by the treatment of CURC treatment (**Table 1**).

Kheradpezhouh et al. (2016) looked into liver toxicity brought on by paracetamol and oxidative stress (H_2O_2). They were isolated rat hepatocytes used for the purpose. They also employed kidney (HEK 293T) cells that had been transfected with the TRPM2 gene. CURC, H2O2, and paracetamol were used to treat the hepatocytes and HEK293T cells. The authors noticed TRPM2 activation in the groups of H_2O_2 and paracetamol in the calcium signaling (Fura 2-AM) and electrophysiological (patch-clamp) techniques. However, the activations were decreased in the cells and hepatocytes. The authors concluded that the treatment of CURC (10 μM for 15min) protected the cells via the inhibition of TRPM2 from oxidative stress-induced damage.

The original paper of Öz and Çelik (2016) described how transfection procedure and CURC treatment decrease apoptotic and oxidant values via the inhibition of TRPM2 channel in the SH-SY5Y neuronal cells. The authors induced control, CURC, transfected and transfected + curcumin groups. According to the patch-clamp, caspase, channel expression results, they were reported that transfection procedure-induced TRPM2 channel activation, apoptosis, caspase activation, and Ca^{2+} influx were decreased by the treatment of CURC (5 μM for 24h).

Albuminuria induces a proinflammatory response in renal collecting duct cells promoting chronic kidney disease. The incubation of albumin stimulates NF-κB activation, transforming growth factor-β1, profibrotic signaling markers, and ROS. In a recent study (Nazıroğlu et al. 2019), we show that Ca^{2+} signaling is involved in albumin-induced oxidative stress, when calcium enters the cells via TRPM2 channels. The Ca^{2+} influx was reduced via the modulation of TRPM2 by the treatment of CURC (10 μM for 24h). In the cells, the intracellular localization of CURC was also investigated, and its localization was found in membranes of the cells. They concluded that albumin treatment stimulated oxidant, apoptotic,

inflammatory, and Ca^{2+} influx actions via the stimulation of TRPM2, although actions were decreased by the treatment of CURC.

In normal cells, CURC acts antioxidant, anti-inflammatory, and anti-apoptotic actions. However, the treatment of CURC induces antitumor action through inducing tumor apoptosis in the cancer cells. In addition, CURC acted pro-oxidant and calcium channel activator action in lung cancer cells. Gökçe Kütük et al. (2019) investigated that the pro-oxidant action of CURC may enhance CISP efficacy through TRPM2 channel activation for human laryngeal squamous cancer cell management. The apoptotic and oxidant actions of cisplatin via the stimulation of TRPM2 were further increased in the cisplatin+CURC group by the treatment of CURC (10 µM for 24h). However, normal kidney cells (renal collecting duct cells) were protected against to the cisplatin-induced oxidant and apoptotic actions by the treatment of CURC.

Optic nerve adverse reactions are induced by chemotherapy therapies, especially cisplatin treatments. The actions are induced by the stimulation of Ca^{2+} influx-induced apoptosis and oxidative stress. In the mice (60 mg/kg body weight)) and SH-SY5Y (10 µM for 24h) cells, Özkaya and Nazıroğlu (2020) induced four groups as control, CURC, cisplatin, and cisplatin+CURC, and they performed electrophysiology (TRPM2 currents) and laser confocal microscope (Ca^{2+}, ΔΨm, and ROS) analyses in four groups of optic nerve and SH-SY5Y cells. Their results indicated potential neuroprotective molecular mechanisms of CURC against cisplatin-mediated optic nerve oxidative injury and death through the modulation of cisplatin-mediated TRPM2 stimulation.

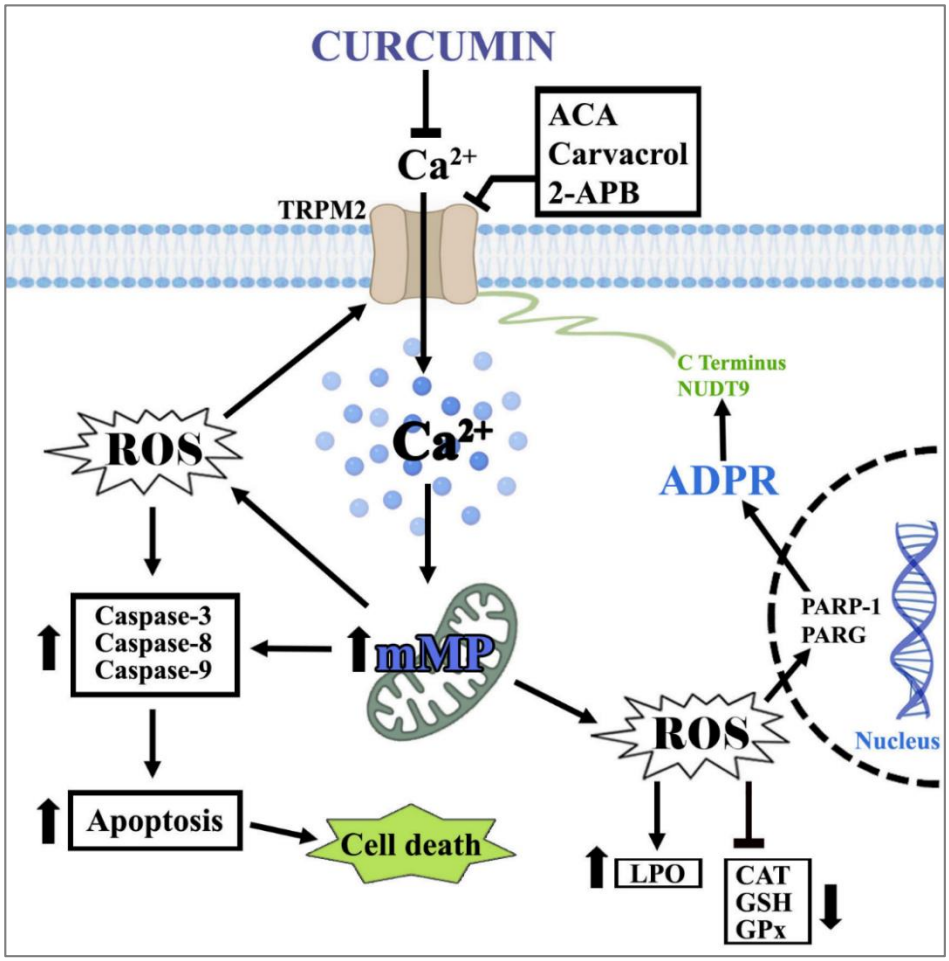

Figure 1. A schematic representation of curcumin on the TRPM2 channels in animal and human cells. *C terminus of TRPM2 has NUDT9 homology (NUDT9) domain. An increase in ROS triggers the activation of poly(ADP-ribose) polymerase-1 (PARP-1) and poly(ADP-ribose) glycohydrolase (PARG) in the nucleus, which in turn triggers the activation of TRPM2. Together with Ca^{2+} ADPR binds to the NUDT9H domain of TRPM2 and opens the channel. ACA, carvacrol, and 2-APB are nonspecific inhibitors of TRPM2. Opening of the TRPM2 channel results in a large entry of Ca^{2+} and Na^{+} into the cytosol. The activation of TRPM2 in lysosomes leads entry of Ca^{2+} into mitochondria via the increase of mitochondrial membrane depolarization (mMP) In turn, it induces increase of apoptosis/cell death and lipid peroxidation (LPO) via the stimulation of caspases (caspase -3, caspase -8, and caspase -9) and ROS via downregulation of catalase (CAT), glutathione peroxidase (GPx), and glutathione (GSH). The adverse actions via the modulation of TRPM2 in the cells are decreased by the treatment of antioxidant curcumin. (↑) Increase. (↓) Decrease.*

The excessive generations of ROS in mitochondria are induced by hypoxic conditions. Hypoxia has an essential action on the initiation and progression of brain and neuronal diseases in human. It is well known that hypoxia-mediated oxidant and apoptotic adverse actions are modulated via the inhibition of TRPM2 channel stimulation in neuronal cells by the treatment of CURC (10 μM for 24h). In a recent study (Armağan and Nazıroğlu 2021), we observed the potential protective actions of CURC on hypoxia-induced increases of TRPM2 channel activation, ROS, apoptosis, cell death, free zinc, and caspases (caspase -3 and caspase -9) in the SH-SY5Y neuronal cells. Finally, we demonstrated that the TRPM2 stimulation-induced Ca^{2+} influx, oxidative stress, apoptosis, and cell death collectively cause the induction of hypoxia in neuronal, although they were attenuated by the treatment of CURC. diseases. The current data suggest a new treatment strategy for preventing hypoxia-mediated oxidative neuronal injury via the modulation of TRPM2 in the SH-SY5Y cells.

An inflammatory cytokine is interferon gamma (IFNg), and it has an essential role against to the tumor, bacteria, and viruses. The excessive IFNg generation-induced apoptotic and oxidant actions in the central nervous system were diminished by the treatment of natural plant products. It is well-known that CURC has antioxidant and anti-inflammatory actions in neuronal cells, although its anti-inflammatory mechanism has not been clarified yet. Güzel et al. (2021) investigated anti-inflammatory, antiapoptotic, and antioxidant properties via the modulation of the TRPM2 channel in the IFNg treated SH-SY5Y cells. They observed modulator role of CURC (10 μM for 24h) on the properties in the cells. They claimed that CURC inhibited the IFNg-dependent TRPM2 pathway, and the results could be potentially useful for the treatments of inflammatory neuronal diseases.

ROS play crucial roles in the development of both acute and chronic liver disorders. It was discovered that CURC prevented the ADPR-induced activation of TRPM2 in rat hepatocytes. TRPM2 activity was assessed in rat hepatocytes using patch clamp recording and Ca^{2+} imaging in a study by Ali et al. (2021). By using CURC (50 nm for 24h), the H_2O_2 or acetaminophen-induced activation of TRPM2 was likewise inhibited.

On the antioxidant and Ca^{2+} modulator role, there are also conflicting reports. Hollborn et al. (2013) investigated cytotoxic effects of CURC on oxidant and Ca^{2+} influx actions in the human retinal pigment epithelial 19 (ARPE19) cells. While low doses of CURC (0.1–10 M for 24 hours) operated as an antioxidant and a Ca^{2+} influx blocker in the cells, high CRC incubation (50-100 μM for 24h) was discovered to have cytotoxic effects in the cells. The cytotoxic effect of high CURC involved activation of caspase-3 and calpain, cytosolic Ca^{2+} signaling, mitochondrial permeability, ROS, increased phosphorylation of p38 MAPK and decreased phosphorylation of Akt protein.

Hydroxychloroquine is an anti-inflammatory, anti-COVID19, and anti-malarial drug. However, it has adverse action in retina via the excessive generation of ROS. The protective action of CURC (5 μM for 24h), on the hydroxychloroquine-induced oxidative retina injury via the inhibition of TRPM2 in the ARPE19 cells was recently investigated by our group (Ertuğrul et al. 2023). We observed the potential protective actions of CURC on hydroxychloroquine-caused upregulation of TRPM2 channel activation, ROS, apoptosis, cell death, free zinc, and caspases (caspase -3, caspase-8, and caspase -9) in the ARPE19 cells. In the study, we demonstrated that the TRPM2 stimulation-induced Ca^{2+} influx, oxidative stress, apoptosis, and cell death collectively cause the induction of hydroxychloroquine in the retina cells, although they were modulated by the treatment of CURC.

Conclusions

Taken together, the findings of the present studies show that CURC acts as a TRPM2 stimulator in tumor cells (human laryngeal squamous cancer cell), but inhibits Ca^{2+} influx by blocking TRPM2 channels in normal cells like hepatocyte, retina, kidney, and neuronal cells. Although the molecular mechanisms of CURC have not been clarified fully involved, CURC may offer an avenue for the inhibition of TRPM2, and hence inhibition of ROS-initiated normal cell injury and apoptosis. CURC, as a potential natural agent for the clinical treatment of kidney, liver, retina, and neuronal diseases or oxidative injury via inhibition of TRPM2. In turn, its treatment induces third pathways. Firstly, CURC reduces ROS through inhibition of Ca^{2+} entry via TRPM2 channels and reduction of mitochondrial membrane depolarization. Secondly, CURC has an anti-apoptotic action through the inhibition of caspase -3 and caspase -9. Third, CURC through the stimulation of TRPM2 induces tumor cell death and oxidative stress. Hence, the oxidant and apoptotic actions

of CURC indicate that the actions of CURC through the TRPM2 stimulation are cell specific. According to the available research on CURC in various cells, the majority of CURC's actions via TRPM2 stimulation or inhibition have not yet been studied. Further research is needed to investigate the action of CURC via the TRPM2 modulation on several diseases such as Alzheimer's disease and Parkinson's disease. The anticancer action of CURC via the TRPM2 modulation in the cancer cells such as glioblastoma and breast cancer should be clariid by future studies.

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