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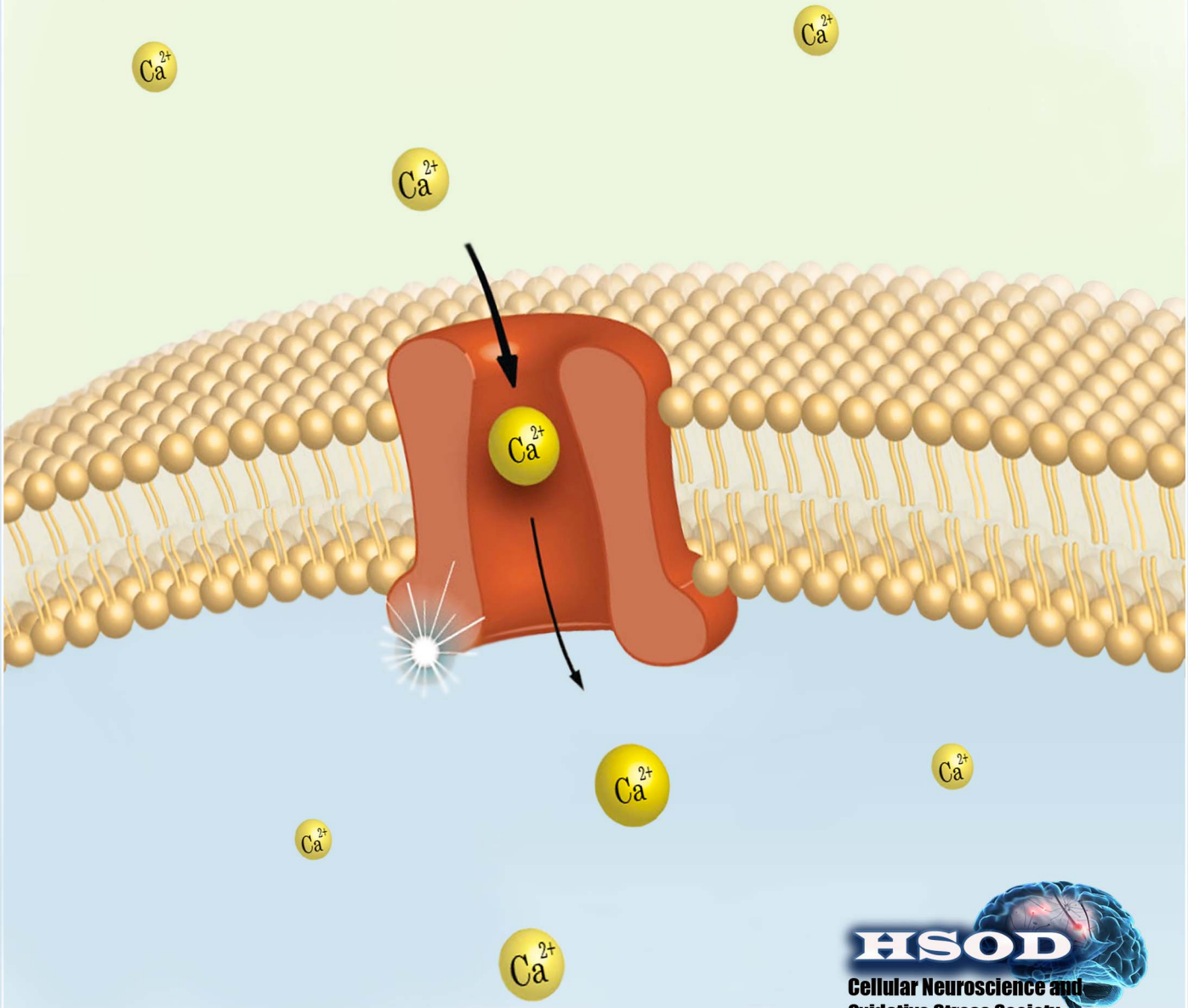

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AIM AND SCOPES

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.

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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)

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REVIEW ARTICLE

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Is Hypericum perforatum agonist or antagonist of TRPC6 in neurons?

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Abstract

Transient receptor potential canonical 6 (TRPC6) channel is a family of transient receptor superfamily. Hyperforin is an active component of Hypericum species including *Hypericum perforatum* (HPer). In the review paper, the author summarizes the recent information between TRPC6-induced Ca^{2+} entry, HPer and hyperforin to understand the etiology of the neurological diseases and potential therapeutic strategies.

The TRPC6 in several cell types is activated by 4,5 triphosphate (IP_3) and diacylglycerol (DAG) pathways, although it was inhibited in the cells by several non-specific antagonists including Aminoethoxydiphenyl-borane (2-APB), gadolinium and lanthanum. Results of limited studies indicated that hyperforin caused intracellular Ca^{2+} elevations through TRPC6 activation in neurons although the intracellular Ca^{2+} elevation results were not confirmed in the neurons by several recent studies. Release Ca^{2+} from internal stores instead of extracellular Ca^{2+} entry through activation of TRPC6 channel in neurons of brain was also reported. The TRPC6-induced Ca^{2+} influx was inhibited in brain by active components of some antioxidants.

In conclusion, the present literature information shows that interaction between TRPC6-induced Ca^{2+} entry and hyperforin in neurons and cell lines are too complex and it has not been clarified yet.

***Keywords*:** TRPC6, *Hypericum perforatum*, Hyperforin, Calcium ion, Neuron.

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List of Abbreviations;

2-APB, 2-Aminoethoxydiphenylborane; **BDNF**, brain-derived neurotrophic factor; **DAG**, diacylglycerol; **DRG,** dorsal root ganglion; **Gd^{3+},** gadolinium; **HPer,** Hypericum perforatum; **IP_3,** inositol 1,4,5 triphosphate; **La^{3+},** lanthanum; **TRP,** transient receptor potential; **TRPC6,** transient receptor potential canonical 6; **TRPM2,** transient receptor potential melastatin 2; **TRPV1,** transient receptor potential vanilloid 1; **VGCC,** voltage gated calcium channels

Introduction

Transient receptor potential (TRP) superfamily is containing 28 channels in the seven families; TRPA (Ankyrin), TRPC (canonical), TRPM (Melastatin), TRPV (Vanilloid), TRPML (mucolipin), TRPN (NOMPC), and TRPP (polycystin) (Nazıroğlu et al., 2012). The TRPC family can be divided into 4 groups as TRPC1, TRPC2, TRPC4/5, and TRPC3/6/7 according to their amino acid sequences and functional similarities. The Na^+ and Ca^{2+} permeable canonical transient receptor potential (TRPC) channels subfamily are expressed in different tissues including brain synapses (Zhou et al., 2008), dentate gyrus (Kim and Kang, 2015) and dorsal root ganglion (DRG) (Alessandri-Haber et al., 2009). There is growing evidence that transient receptor potential channel 6 (TRPC6) mediates receptor-operated cation entry and is critically involved in numerous physiological processes. Recent studies have provided important insights into the role of TRPC6 in neuronal diseases. For instance, it was demonstrated that TRPC6 channel has also a critical role in promoting neuronal survival against brain injury (Guo et al., 2017).

Hyperforin is a pharmacologically active component of the medicinal plant *Hypericum perforatum* (HPer) (Apaydin et al., 2016). HPer and hyperforin have strong antioxidant and anti-inflammatory effects in treatment of experimental disease models such as inflammatory diseases (Nazıroğlu et al., 2014a and b), peripheral pain (Nazıroğlu et al., 2014c; Özdemir et al., 2016; Uslusoy et al., 2017) and brain disease (Galeotti, 2017).

Result of a study indicated TRPC6 activator role of HPer and hyperforin in neurons (Leuner et al., 2007), although results of some studies did not confirm the idea (Friedland and Harteneck, 2015). Contrary, some antioxidants inhibited Ca^{2+} influx through inhibition of TRPC6 blocker in brain of mice (Guo et al., 2017). There are also some reports on hyperforin-induced intracellular Ca^{2+} release from brain mitochondria without activation of TRPC6 (Tu et al., 2010).

I provide an overview on current knowledge regarding the interaction between TRPC6-induced Ca^{2+} entry and hyperforin to understand the etiology of the neurological diseases and potential therapeutic strategies.

Role of TRPC6 in neuron

TRPC family members including TRPC6 have inositol 1,4,5 triphosphate (IP_3) receptor binding sites in the C-tail of the channels, and calmodulin binds to this peptide sequence in a Ca^{2+} dependent manner (Winn et al., 2006). G protein-dependent molecular signaling mechanisms such as diacylglycerol (DAG) and Ca^{2+} store depletion have also activator role on TRPC6. Therefore, intracellular Ca^{2+} concentration has important role on the activation of TRPC6 in neurons (Pfister et al., 2015). Intracellular 1-oleoyl-2-acetyl-sn-glycerol and 1,2-dioctanoylglycerol organic chemicals which were produced in cells from DAG species have TRPC6 activator role in neurons. Result of a recent study was indicated TRPC6 activator role small molecules larixol in HEK293 cells (Urban et al., 2016).

There are non-specific TRPC6 channel inhibitor chemicals. In addition to inhibition of IP3 receptors, 2-Aminoethoxydiphenylborane (2-APB) is an antagonist of TRPC6 in neurons (Sekaran et al., 2007). Lanthanides such as lanthanum (La^{3+}) and gadolinium (Gd^{3+}) are commonly used blockers of nonselective calcium channels and the TRPC6 channel is also inhibited by La^{3+} and Gd^{3+} (Jung et al., 2003).

Accumulating evidence indicates that TRPC6 plays a critical role in neuronal development and most of paper on TRPC6 in neuron and brain are related with neuronal development and brain-derived neurotrophic factor (BDNF) formation. For example, the hyperforin treatment induced modification of rat hippocampal pyramidal neurons such as the neurite spine density, numbers of dendritic branch points and dendritic length through activation of TRPC6 channel (Liu et al., 2015). Gene transcription activator role of hyperforin through activation of TRPC6 channel were recently indicated in HEK293 cells (Thiel and Rössler, 2017).

Hypericum perforatum and cations

The medicinal plant HPer is also known as St John's worth which has been used as an antidepressant with few side-effects for a long time (Apaydin et al., 2016; Galeotti, 2017). The main components of HPer are hypericin, pseudohypericin, flavonoids, phloroglucinols, hyperforin, and adhyperforin (Apaydin et al., 2016) and they have strong antioxidants effects in treatment of experimental disease models such as pain

and brain disease (Nazıroğlu et al., 2014a; Özdemir et al., 2016; Uslusoy et al., 2017; Galeotti, 2017).

Inhibitor role of HPer on uptake of aminergic transmitters such as serotonin and noradrenaline into synaptic nerve endings has been known for a long time (Müller, 2003). Neuroprotective action of hyperforin though inhibition of monoamine oxidase was also reported within last decades (Soto-Otero et al., 2001). It has also stimulator role on the intracellular sodium ion concentration through increasing level of extracellular neurotransmitters such as acetylcholine, GABA and glutamate (Kaehler et al., 1999; Kiewert et al., 2004; Treiber et al., 2005). Inhibitor role of hyperforin on voltage gated calcium channels (VGCC) in P-type VGCC of cerebellar Purkinje neurons was also reported (Fisunov et al., 2000).

Hypericum perforatum and TRPC6

As it was mentioned above, the Na^+ and Ca^{2+} permeable TRPC6 channel is belonging to the superfamily of TRP. There is growing evidence that the TRPC6 mediates receptor-operated cation entry and is critically involved in numerous physiological processes (Malczyk et al., 2017). Recent studies have provided important insights into the role of TRPC6 in normal physiology and neuronal diseases.

Role of hyperforin and HPer on TRPC6 was summarized in Table 1. Hyperforin caused intracellular Ca^{2+} elevations through activation of TRPC6 in PC12 cells (Leuner et al., 2007), although other effects of hyperforin are described which might also participate in its pharmacological actions. However, remaining TRPC subfamily members such as TRPC1, TRPC3, TRPC4, TRPC5, and TRPC7 are not affected or activated by the hyperforin (Leuner et al., 2007). Releasing Ca^{2+} and Zn^{2+} from isolated brain mitochondria of C57BL6/J mice embryos were measured by using fluorescein dyes namely Fluo-4 and FluoZin-3, respectively and the hyperforin induced mitochondrial membrane depolarization through releasing both ions from mitochondria (Tu et al., 2010). Contrary, depletion of intracellular Ca^{2+} stores with the thapsigargin (sarco/endoplasmic reticulum Ca^{2+}-ATPase pump inhibitor) did not affect hyperforin-induced intracellular Ca^{2+} transients, although hyperforin increased Ca^{2+} entry through TRPC6 channel activation in the primary hippocampal neurons of mice (Leuner et al., 2013). Decrease of indomethacin-induced Ca^{2+} mobilization in Caco-2 cell line was reported by quercetin as a component of HPer (Carrasco-Pozo et al., 2012). Increase of intracellular Ca^{2+} concentration was indicated in hyperforin treated-cortical neurons by using Ca^{2+} sensitive probe Fluo-4. However, the increase was not decreased by incubation of Gd^{3+} as a potent blocker of TRPC channels (Tu et al., 2009), suggesting that it could release Ca^{2+} from internal stores. Recently it was reported that hyperforin induces TRPC6-independent hydrogen ion currents in HEK-293 cells, cortical microglia, chromaffin cells and lipid bilayers (Sell et al., 2014). No association between hyperforin-induced TRPC6 activation and oxidative stress in neonatal pig glomerular mesangial cell was reported (Soni and Adebiyi, 2016). Contrary, TRPC6 degradation in cortical neuron of cerebral ischemia-induced rat was reduced at 24 hours of cerebral ischemia by hyperforin treatment (Lin et al., 2013). Down-regulated protein expression of TRPC6 was also indicated in depression-induced rats (Liu et al., 2015).

Hyperforin is strong antioxidant component of HPer and expression level of TRPC6 is increased in PC12 cells by the antioxidant hyperforin treatment (Leuner et al., 2007). Calycosin is also antioxidant medicinal plant component and it exerted neuroprotective effects against cerebral ischemia by inhibiting calpain activity and increasing the expressions of TRPC6 level (Guo et al., 2017). Similarly, the some TRP channels such as TRP melastatin 2 (TRPM2) and TRP vanilloid 1 (TRPV1) channels are also inhibited in neurons by the hyperforin and HPer treatments (Nazıroğlu et al., 2014a; Özdemir et al., 2016; Uslusoy et al., 2017; Galeotti, 2017). It seems that the inhibitor roles of HPer and hyperforin are cell specific and they are inhibitor of TRP channels including the TRPC6 instead of activator of TRPC6 in neuronal cells.

Table 1: Effects of Hypericum perforatum (HPer) and hyperforin on Ca^{2+} and TRPC6 in different cells.

Drug	Material	Value(s) and Effect	Reference
Hyperforin	PC12 cells	Intracellular Ca^{2+} elevations	Leuner et al., (2007)
Hyperforin	Mice cortical neurons	Release Ca^{2+} from internal stores but no TRPC6 activation	Tu et al., (2009)
Hyperforin	Isolated brain mitochondria	Mitochondrial membrane depolarization through releasing zinc and calcium ions from these intracellular organelles.	Tu et al., (2010)
HPer Hyperforin	Cerebellar Purkinje neurons	Inhibition of P-type VGCC currents	Fisunov et al., (2000)
Hyperforin	Primary hippocampal neurons	Depletion of intracellular Ca^{2+} stores did not affect hyperforin-induced Ca^{2+} transients but TRPC6 channel is activated by hyperforin.	Leuner et al., (2013)
Quercetin	Caco-2 cell line	Decrease of indomethacin-induced Ca^{2+} mobilization	Carrasco-Pozo et al., (2012)
Hyperforin	HEK-293 cells, cortical microglia, chromaffin cells and lipid bilayers	TRPC6-independent hydrogen ion currents	Sell et al., (2014)
Hyperforin	Cortical neuron of cerebral ischemia-induced rat	TRPC6 degradation	Lin et al., (2013)
HPer	Rat DRG	Inhibitor role on Ca2+ influx through inhibition of TRPM2	Nazıroğlu et al. (2014c)
Hyperforin	Neonatal pig glomerular mesangial cell	No association between hyperforin-induced TRPC6 activation and oxidative stress	Soni and Adebiyi, (2016)
HPer	Rat DRG	Inhibitor role on Ca2+ influx through inhibition of TRPM2 and TRPV1	Özdemir et al., (2016)
Hper	Rat DRG and sciatic nerve	Inhibitor role on Ca2+ influx through inhibition of TRPM2 and TRPV1	Uslusoy et al., (2017)

In conclusions and future directions

Reports on TRPC6 and intracellular Ca^{2+} concentration are conflicting. According to the conflicting results, the mechanisms of hyperforin on TRPC6 are not fully understood and its effect on the channel seems cell specific and different from antioxidant effect on TRPM2 and TRPV1 in sciatic nerve and DRG neurons. Results of recent studies indicate role of oxidative stress on the activation of TRPC6 in kidney cells (Zhao et al., 2015; Ma et al., 2016), although there is no report on oxidative stress-dependent activation of TRPC6 in brain and neurons. The subject should be clarified by future studies. Therefore, the subject is important to understand the etiopathogenesis of oxidative stress-induced neurological diseases through activation of TRPC6.

Declaration of interest:

There is no conflict interest and financial support in the study

References

Alessandri-Haber N, Dina OA, Chen X, Levine JD. 2009. TRPC1 and TRPC6 channels cooperate with TRPV4 to mediate mechanical hyperalgesia and nociceptor sensitization. J Neurosci. 29(19), 6217-6228.

Apaydin EA, Maher AR, Shanman R, Booth MS, Miles JN, Sorbero ME, Hempel S. 2016. A systematic review of St. John's wort for major depressive disorder. Syst Rev. 5(1), 148.

Carrasco-Pozo C, Castillo RL, Beltrán C, Miranda A, Fuentes J, Gotteland M. 2016. Molecular mechanisms of gastrointestinal protection by quercetin against indomethacin-induced damage: role of NF-κB and Nrf2. J Nutr Biochem. 27, 289-298.

Fisunov A, Lozovaya N, Tsintsadze T, Chatterjee S, Nöldner M, Krishtal O. 2000. Hyperforin modulates gating of P-type Ca2+ current in cerebellar Purkinje neurons. Pflugers Arch, Eur J Physiol. 440:427–434.

Friedland K, Harteneck C. 2015. Hyperforin: To be or not to be an activator of TRPC(6). Rev Physiol Biochem Pharmacol. 169, 1-24.

Galeotti N. 2017. Hypericum perforatum (St John's wort) beyond depression: A therapeutic perspective for pain conditions. J Ethnopharmacol. 200, 136-146.

Guo C, Ma Y, Ma S, Mu F, Deng J, Duan J, Xiong L, Yin Y, Wang Y, Xi M, Wen A. 2017. The Role of TRPC6 in the neuroprotection of Calycosin against cerebral ischemic injury. Sci Rep. 7(1), 3039.

Jung S, Mühle A, Schaefer M, Strotmann R, Schultz G, Plant TD. 2003. Lanthanides potentiate TRPC5 currents by an action at extracellular sites close to the pore mouth. J Biol Chem. 278(6), 3562-3571.

Kaehler ST, Sinner C, Chatterjee SS, Philippu A. 1999. Hyperforin enhances the extracellular concentrations of catecholamines, serotonin and glutamate in the rat locus coeruleus. Neurosci Lett. 262, 199-202.

Kiewert C, Buchholzer ML, Hartmann J, Chatterjee SS, Klein J. 2004. Stimulation of hippocampal acetylcholine release by hyperforin, a constituent of St. John's wort. Neurosci Lett. 364:195–198.

Kim YJ, Kang TC. 2015. The role of TRPC6 in seizure susceptibility and seizure-related neuronal damage in the rat dentate gyrus. Neuroscience 307, 215-230.

Leuner K, Kazanski V, Müller M, Essin K, Henke B, Gollasch M, Harteneck C, Müller WE. 2007. Hyperforin--a key constituent of St. John's wort specifically activates TRPC6 channels. FASEB J. 21, 4101-4111.

Leuner K, Li W, Amaral MD, Rudolph S, Calfa G, Schuwald AM, Harteneck C, Inoue T, Pozzo-Miller L. 2013. Hyperforin modulates dendritic spine morphology in hippocampal pyramidal neurons by activating Ca(2+) -permeable TRPC6 channels. Hippocampus 23, 40-52.

Lin Y, Zhang JC, Fu J, Chen F, Wang J, Wu ZL, Yuan SY. 2013. Hyperforin attenuates brain damage induced by transient middle cerebral artery occlusion (MCAO) in rats via inhibition of TRPC6 channels degradation. J Cereb Blood Flow Metab. 33(2), 253-262.

Liu Y, Liu C, Qin X, Zhu M, Yang Z. 2015. The change of spatial cognition ability in depression rat model and the possible association with down-regulated protein expression of TRPC6. Behav Brain Res. 294, 186-193.

Ma R, Chaudhari S, Li W. 2016. Canonical transient receptor potential 6 channel: A new target of reactive oxygen species in renal physiology and pathology. Antioxid Redox Signal. 25(13), 732-748.

Malczyk M, Erb A, Veith C, Ghofrani HA, Schermuly RT, Gudermann T, Dietrich A, Weissmann N, Sydykov A. 2017. The role of transient receptor potential channel 6 channels in the pulmonary vasculature. Front Immunol. 8, 707.

Müller WE. 2003. Current St John's wort research from mode of action to clinical efficacy. Pharmacol. Res. 47, 101-109.

Nazıroğlu M, Dikici DM, Dursun S. 2012. Role of oxidative stress and Ca(2+) signaling on molecular pathways of neuropathic pain in diabetes: Focus on TRP channels. Neurochem Res. 37, 2065-2075.

Nazıroğlu M, Kutluhan S, Ovey IS, Aykur M, Yurekli VA. 2014a. Modulation of oxidative stress, apoptosis, and calcium entry in leukocytes of patients with multiple sclerosis by Hypericum perforatum. Nutr Neurosci. 17(5), 214-221.

Nazıroğlu M, Sahin M, Ciğ B, Aykur M, Erturan I, Ugan Y. 2014b. Hypericum perforatum modulates apoptosis and calcium mobilization through voltage-gated and TRPM2 calcium channels in neutrophil of patients with Behcet's disease. J Membr Biol. 247(3), 253-262.

Nazıroğlu M, Çiğ B, Özgül C. 2014c. Modulation of oxidative stress and Ca(2+) mobilization through TRPM2 channels in rat dorsal root ganglion neuron by Hypericum perforatum. Neuroscience 263, 27-35.

Özdemir ÜS, Nazıroğlu M, Şenol N, Ghazizadeh V. 2016. Hypericum perforatum attenuates spinal cord injury-induced oxidative stress and apoptosis in the dorsal root ganglion of Rats: Involvement of TRPM2 and TRPV1 Channels. Mol Neurobiol. 53(6), 3540-3551.

Pfister S, Weber T, Härtig W, Schwerdel C, Elsaesser R, Knuesel I, Fritschy JM. 2015. Novel role of cystic fibrosis transmembrane conductance regulator in maintaining adult mouse olfactory neuronal homeostasis. J Comp Neurol. 523(3), 406-430.

Sekaran S, Lall GS, Ralphs KL, Wolstenholme AJ, Lucas RJ, Foster RG, Hankins MW. 2007. 2-Aminoethoxydiphenylborane is an acute inhibitor of directly photosensitive retinal ganglion cell activity in vitro and in vivo. J Neurosci. 27(15), 3981-3986.

Sell TS, Belkacemi T, Flockerzi V, Beck A. 2014. Protonophore properties of hyperforin are essential for its pharmacological activity. Sci Rep. 4,7500.

Soni H, Adebiyi A. 2016. TRPC6 channel activation promotes neonatal glomerular mesangial cell apoptosis via calcineurin/NFAT and FasL/Fas signaling pathways. Sci Rep. 6,29041.

Soto-Otero R, Mendez-Alvarez E, Hermida-Ameijeiras A, Sanchez-Sellero I, Cruz-Landeira A, Lamas M. 2001. Inhibition of brain monoamine oxidase activity by the generation of hydroxyl radicals: potential implications in relation to oxidative stress. Life Sci. 69, 879–889.

Thiel G, Rössler OG. 2017. Hyperforin activates gene transcription involving transient receptor potential C6 channels. Biochem Pharmacol. 129, 96-107.

Treiber K, Singer A, Henke B, Müller WE. 2005. Hyperforin activates nonselective cation channels (NSCCs). Br J Pharmacol. 145, 75-83.

Tu P, Gibon J, Bouron A. 2010. The TRPC6 channel activator hyperforin induces the release of zinc and calcium from mitochondria. J Neurochem. 112, 204-213.

Tu P, Kunert-Keil C, Lucke S, Brinkmeier H, Bouron A. (2009). Diacylglycerol analogues activate second messenger-operated calcium channels exhibiting TRPC-like properties in cortical neurons. J. Neurochem. 108, 126–138.

Urban N, Wang L, Kwiek S, Rademann J, Kuebler WM, Schaefer M. 2016. Identification and validation of larixyl acetate as a potent TRPC6 inhibitor. Mol Pharmacol. 89(1), 197-213.

Uslusoy F, Nazıroğlu M, Çiğ B. 2017. Inhibition of the TRPM2 and TRPV1 Channels through Hypericum perforatum in sciatic nerve injury-induced rats demonstrates their key role in apoptosis and mitochondrial oxidative stress of sciatic nerve and dorsal root ganglion. Front Physiol. 8, 335.

Winn MP, Daskalakis N, Spurney RF, Middleton JP. 2006. Unexpected role of TRPC6 channel in familial nephrotic syndrome: does it have clinical implications? J Am Soc Nephrol. 17(2), 378-87.

Zhao B, Yang H, Zhang R, Sun H, Liao C, Xu J, Meng K, Jiao J. 2015. The role of TRPC6 in oxidative stress-induced podocyte ischemic injury. Biochem Biophys Res Commun. 461(2), 413-420.

Zhou J, Du W, Zhou K, Tai Y, Yao H, Jia Y, Ding Y, Wang Y. 2008. Critical role of TRPC6 channels in the formation of excitatory synapses. Nat Neurosci. 11(7), 741-743.

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