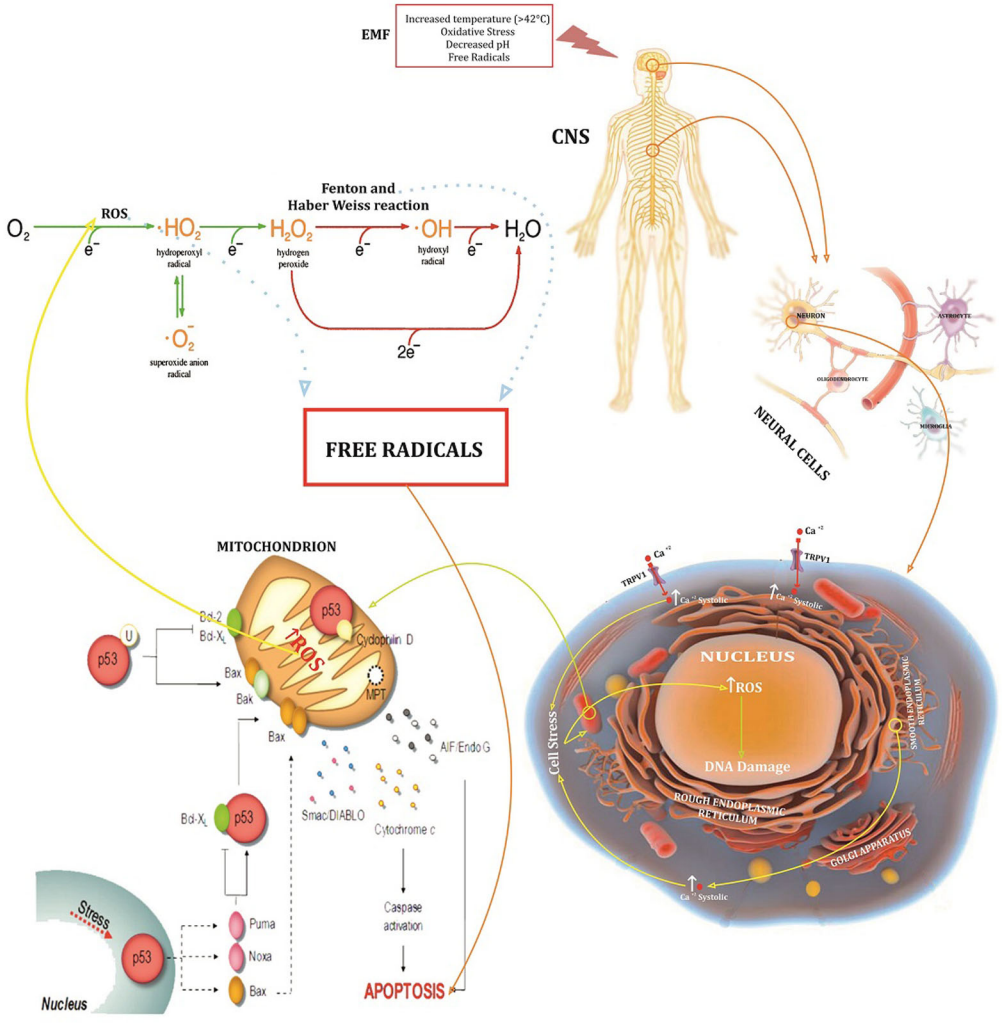
E-ISSN: 2149-7222 (Online)

Journal Cellular Neuroscience and Oxidative Stress



OPEN ACCESS and
NO PUBLICATION FEE

http://dergipark.gov.tr/jcnos

Former name; Cell Membranes and Free Radical Research

Volume 12, Number 2, 2020

Journal of Cellular Neuroscience and Oxidative Stress

http://dergipark.gov.tr/jcnos

BSN Health Analyses, Innovation, Consultancy, Organization, Industry and Trade Limited Company

http://www.bsnsaglik.com.tr/

info@bsnsaglik.com.tr

Formerly known as:

Cell Membranes and Free Radical Research (2008 - 2014)

Volume 12, Number 2, 2020

[CONTENTS]

Volume 12, Number 2, 2020
E-ISSN Number: 2149-7222 (Online)
Indexing: Google Scholar, Index Copernicus, Chemical Abstracts, Scopus (Elsevier),
EBSCOhost Research Database, Citation Index Database,

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)

READERSHIP

Biophysics	Biochemistry
Biology	Biomedical Engineering
Pharmacology	PhysiologyGenetics
Cardiology	Neurology
Oncology	Psychiatry
Neuroscience	Neuropharmacology

Keywords
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.

REVIEW ARTICLE

J Cell Neurosci Oxid Stress 2020;12(2): 937-946.

Cell phone and wireless radiation hazard on TRPV1 channel activation: A Scoping review study

Kiarash SHIRBANDI[1], Amirmohammad Rezaei RASHNOUDI[2], Gholamreza HASSANZADEH[2], Rasoul AKBARI[3], Omid MOBINFAR[4], Fakher RAHIM[5, 6]

[1]International Affairs Department (IAD), Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
[2]Department of Anatomy, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
[3]Department of Clinical Biochemistry, Allied Health Sciences School, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
[4]Department of Radiologic Technology, Faculty of Paramedicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
[5]Research Center of Thalassemia & Hemoglobinopathy, Health research institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
[6]Metabolomics and Genomics Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Received; 13 October 2020; **Accepted;** 24 November 2020

***Address for correspondence:**

Dr. Fakher Rahim,
Research Center of Thalassemia & Hemoglobinopathy, Health research institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
E-mail: Bioinfo2003@gmail.com

List of Abbreviations ;

CPZ, *Capsazepine;* ***CW,*** *Continuous waveform;* ***DRGN,*** *Dorsal root ganglion;* ***HIPPON,*** *Hippocampus;* ***LTE,*** *Long term evolution;* ***MCF-7,*** *Michigan Cancer Foundation-7;* ***MMW,*** *Millimeter waves;* ***NADA,*** *N-arachidonoyl-dopamine;* ***NIR,*** *Non-ionizing radiation;* ***PTZ,*** *Pentylentetrazol;* ***RF-EMF,*** *Radiofrequency electromagnetic field;* ***ROS,*** *Reactive oxygen species;* ***SAR,*** *Specific Absorption Rate;* ***SN,*** *Substantia nigra;* ***TRPV1,*** *Transient receptor potential cation channel subfamily V member 1;* ***UMTS,*** *Universal Mobile Telecommunication Systems;* ***WiMAX,*** *Worldwide Interoperability for Microwave Access.*

Abstract

TRPV1 channel is activated with pH changes, increasing temperature, free radicals, and oxidative stress, and it may be a good measure for detecting the effect of microwave non-ionizing radiation on cellular and molecular responses. The scoping review study aims to survey the influence of mobile and wireless radiation on the TRPV1 channel mechanism. We systematically considered international databases to recognize related studies, including PubMed, Scopus, Cochrane Library, CINAHL, ISI Web of Science, Science Direct from the start, PROSPERO and EMBASE use headings for scientific topics (Mesh). The hunt covered the period from 1980 until 2019. A total of seven studies comprising 137 cases, three in vitro tests on breast cancer cell line Michigan Cancer Foundation-7 (MCF-7), embryonic kidney HEK293 cells and Rabbit polyclonal anti-TRPV1, and four in vivo experimental studies comprising 21 male

and 24 female Wistar Albino rats, were included. Two studies indicated cell phones induced mitochondrial ROS, oxidative stress-induced in the hippocampus, mitochondrial apoptosis via activation of TRPV1 in hippocampus and dorsal root ganglion neurons. The cytosolic Ca^{2+} induced by TRPV1 induced oxidative overactions and apoptosis at a distance of 10 cm from the source of the cells. Our review shows that cell phone and wireless radiation have a possible effect on Ca^{2+} signaling by TRPV1 channel activation. This reaction may induce ROS, Fenton and Haber-Weiss reaction which increase free radicals' level in the mitochondria.

Keywords: Neurobiology; Non-Ionizing Radiation; Wireless Technology; Cell Phone; Oxidative Stress; TRPV1 protein; Calcium Signaling.

Introduction

The use of modern technologies, such as cell phone and wireless, has grown in the present century, in a way that life without these technologies can be somewhat disturbed (Demirhan et al. 2016). The range of frequency microwave cell phone non-ionizing radiation (NIR) is from 450 to 3800 megahertz (MHz) and for wireless is from 9 kilohertz (kHz) to 300 gigahertz (GHz) (Banik et al. 2003). Until now, no reliable information has been reported over the adverse effects of non-ionizing radiation on cellular and molecular function. This could be due to the low energy of non-ionizing particles which affect tissues in a way that just cause a little change on free radical production level and increase tissue temperature partly (Havas, 2017). NIR theorists are divided into two groups who favor the effects of these waves and the harmful effects of NIR on health. From 2002 to 2016, several statements have been reported from institutions of health and welfare regulatory (ICNIRP 2016; Authority 2002; Canada 2010; Environment 2008, FCC 2010, Health Protection Agency 2012; National Cancer Institute 2016; WHO 2014).

Some statements indicate no harmful effects on health or cancer that are caused by the use of cell phone and wireless radiations, only have pointed to an increase in tissue temperature (Authority 2002; Canada 2010; Environment 2008; FCC 2010; Health Protection Agency 2012; National Cancer Institute 2016; WHO 2014), while, the only report of International Commission on Non-Ionizing Radiation Protection (ICNIRP) 2016 emphasizes the harmful impact of high-frequency on health community (ICNIRP 2016); however, various studies have been conducted to clear this secret. Transient receptor potential cation channel subfamily V member 1 (TRPV1) is a non-selective cationic channel coded by the TRPV1 gene (*OMIM: 602076*) (Caterina et al. 1997; Bevan et al. 2014). This channel is located in different regions of the brain including hypothalamus, cerebrum, cerebellum, striatum, midbrain, olfactory bulb, medulla oblongata, hippocampus, thalamus, and substantia nigra (SN), and in the ganglion, trigeminal nerve, nodose ganglion, and especially concerning the afferent nerve fiber, there is a pain in the spinal cord, the end of the peripheral nerves (Bevan et al. 2014; Marrone et al. 2017), and are activated by stimuli such as increased temperature (>42°C), oxidative stress, decreased pH, capsaicin, lipoxygenase products, resiniferatoxin (RTX), anandamide, ethanol, N-arachidonoyl-dopamine (NADA), free radicals, and isothiocyanate allyl (Caterina et al. 1997; Wu et al. 2015). TRPV1 plays a role in creating a sense of heat, inflammation, and pain that is expressed in neurogenic neurons and mediating chronic pain in non-peptidergic neurons (Takayama et al. 2015). TRPV1 is a series of non-specific cationic channels permeable to calcium (Ca^{2+}); it increases the intracellular Ca^{2+} (Fenwick et al. 2017). Also, increasing Ca^{2+} through various pathways affects incitement toxicity in neurons, such as increasing glutamate, activation of proteases and lipases, which damage the cell membrane (Nita et al. 2016).

Since the TRPV1 channel is activated with pH changes, increasing temperature, free radicals, and oxidative stress, it may be a favorable measure for detecting the effect of microwave non-ionizing radiation on cellular and molecular responses, so the goal of this scoping review study is to determine the impact of mobile and wireless radiation on the TRPV1 channel mechanism, oxidative stress, apoptosis and reactive oxygen species (ROS).

Methods

This study is based on the checklist and description of Preferred Reporting Items for Systematic reviews and the application of meta-analysis for Scoping Reviews (PRISMA-ScR) checklist and explanation (Tricco et al. 2018)

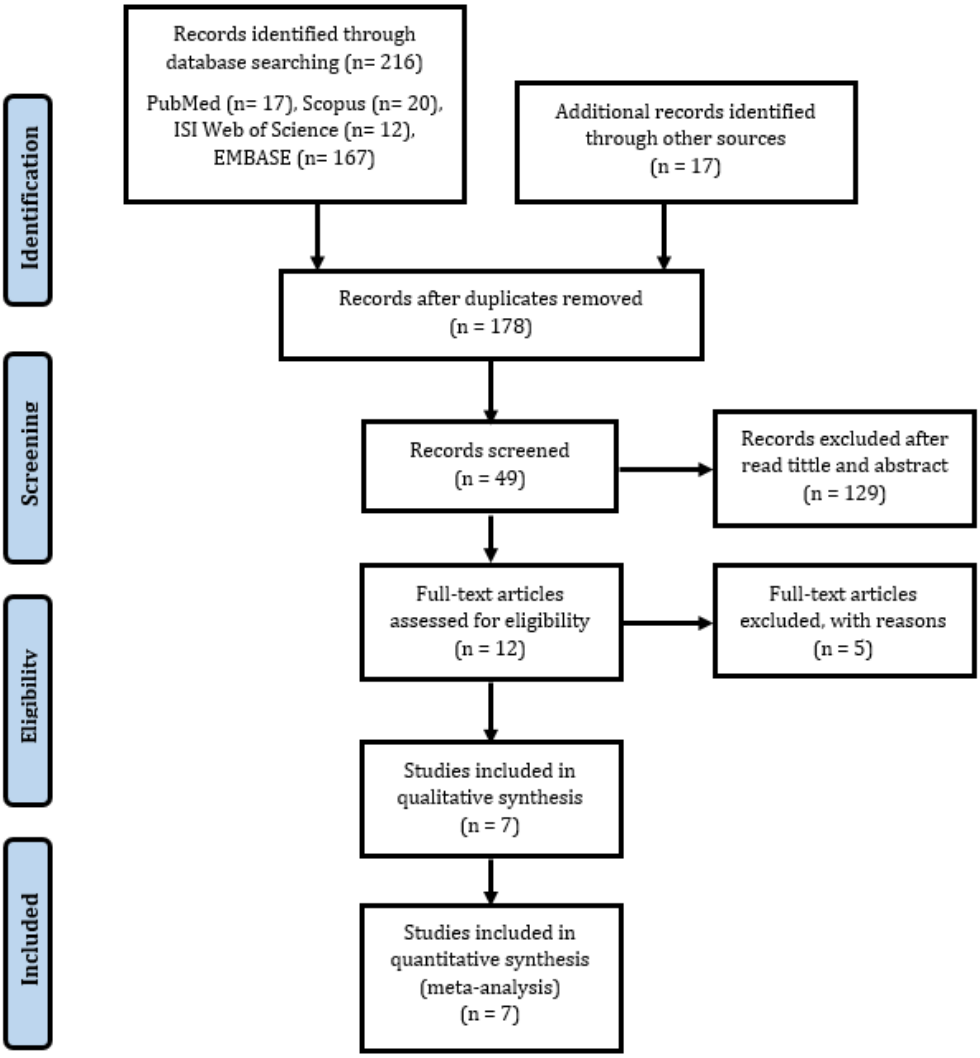


Figure 1. *Study Flow Diagram showing how to extract articles.*

Inclusion and exclusion criteria

Inclusion criteria: All published original articles have reported an association between cell phone and wireless radiation (9 kHz to 300 GHz) with the TRPV1 channel activation. *Exclusion criteria:* Any review studies (Narrative, Systematic review, scoping review, Meta-analysis review, and umbrella review), letters to the editor without original data, commentaries and editorials, Case series, case reports, and other single-arm studies were excluded.

Population

For this scoping analysis, no restriction was considered to the population used in the experiments, and all human samples (female, male) and animal were analyzed.

Outcome

The impact of radiations on TRPV1 channel mechanism activation, oxidative stress, apoptosis, ROS, exposure type, exposure duration, and Specific Absorption Rate (SAR) considered.

Search method

International databases systematically were checked to classify the related studies, including PubMed, Scopus, Cochrane Library, CINAHL, ISI Web of Science, Science Direct from inception, PROSPERO and EMBASE using medical subject headings (Mesh) terms, such as “cell phone,” “mobile phone,” “global system for mobile (GSM),” “radio frequency,” "smartphone," "wireless," "Wi-Fi," "microwave" and were linked with key terms “TRPV1,” “Ca^{2+},” "channel". The search is included in the gap from 1980 until 2019. Also, we have manually

reviewed associated papers through the reference lists of potentially selected studies.

System of data extraction and quality assurance

Two reviewers (K.SH. and F.R.) separately performed screening, taking into account selection criteria; then the data were collected and cross-checked. Any inconsistencies were addressed by consultation with a third reviewer (Gh.H.). The information including author name, publication year, country, target group, the period of exposure (h), and results were obtained. Two researchers have independently carried out quality evaluations of the selected studies using the updated Jadad Scale for randomized controlled trials (Oremus et al. 2001), the methodological index for non-randomized studies (MINORS) tool for non-randomized interventional study (Slim et al. 2003), the Newcastle Ottawa Scale (NOS) tool for observational study (Peterson et al. 2011), and the collaborative approach to meta-analysis and review of evaluation from experimental research (CAMARADES) method for animal study (Macleod et al. 2004).

Results

Eventually, a total of 232 related studies were initially found. After the title–abstract screening, 225 studies were excluded, and seven studies were used for the scope analysis (Cig and Naziroglu 2015; Ertilav et al. 2018; Ghazizadeh and Naziroglu 2014; Naziroglu et al. 2015; Ruigrok et al. 2018; Yuksel et al. 2016; Haas et al. 2016). **Figure 1** shows the search method and the number of researches found and chose during each search process.

The descriptions of the included studies were shown in **Table 1**. Included studies were classified based on the experimental model (in vivo and in vitro). Total of seven studies comprising 137 cases, three studies in vitro comprising breast cancer cell line Michigan cancer foundation-7 (MCF-7), embryonic kidney HEK293T cells and rabbit polyclonal anti-TRPV1. Four in vivo studies comprising 21 male and 24 females Wistar albino rats.

Exposure instrument

The frequency limit used in the trials was 900 MHz-60.4 GHz and the SAR range was 0.52 mW / kg -263.5 W / kg. Researchers have used millimeter waves (MMW), continuous waveform (CW), GSM, universal mobile telecommunication systems (UMTS), long term evolution (LTE), wireless and worldwide interoperability for microwave access (WiMAX) for exposure equipment.

Distance

The distance between the sources and cell or animal was reported in the five studies (Cig and Naziroglu 2015; Ertilav et al. 2018; Ghazizadeh and Naziroglu 2014; Naziroglu et al. 2015; Yuksel et al. 2016). The range of the distance was 0 to 25 centimeters (Cms).

Neural cells

In three studies, the origin cells were derived from the hippocampus (HIPPON) and dorsal root ganglion (DRGN) (Ertilav et al. 2018; Ghazizadeh and Naziroglu, 2014; Naziroglu et al. 2015). Two of these indicated that cell phones induced mitochondrial ROS, oxidative stress-induced in the hippocampus, mitochondrial apoptosis via activation of TRPV1 in HIPPON and DRGN cells (Ertilav et al. 2018; Ghazizadeh and Naziroglu 2014). In contrast M Nazıroğlu et al. 2015 show that apoptosis, caspase-3, caspase-9, ROS, mitochondrial depolarization, and Ca^{2+} influx via TRPV1 channel were enhanced in the hippocampal neurons (Naziroglu et al. 2015).

Cancer cells

One study used a breast cancer cell line (MCF-7) (Cig and Naziroglu 2015). In this in vitro study, human breast cancer cell was exposed to cell phone and Wi-Fi (900, 1800 MHz and 2.4 GHz) radiation in different distances. This study showed that in 10 cm distance from the source of the cells, oxidative overactions and apoptosis were induced, and these led to an increase in cytosolic Ca^{2+} level via TRPV1. The use of TRPV1 channel blockers may present a potential therapeutic approach for the mobile and Wi-Fi-induced oxidative stress and apoptosis by Ca^{2+} gathering.

Other cells

In three studies, researchers have used different types of cells. Yüksel et al. (2016) exposed 32 rats and 40 newborn offspring by cell phone (900 and 1800 MHz) and Wi-Fi (2450 MHz) for 260 hours. After exposing they show that cell phone and Wi-Fi-induced electromagnetic radiation (EMR) might be a reason for raised uterine injury in growing rats by changing TRPV1 cation channels activation (Yuksel et al. 2016). In contrast, in two other studies, the impact of EMR was not

Table 1. General characteristics of the included studies.

Study ID	Location	Study design	Study model	Number of cases	Origin	Equipment type	SAR (W/kg)	Groups	Exposure duration (h)	Distance (Cm)	Outcomes
Ghazizadeh V, Nazıroğlu M 2014 (Ghazizadeh and Naziroglu, 2014)	Turkey	in vivo	Animal	20 Male Wistar Albino rats	HIPPON and DRGN	Wi-Fi (900, 1800 MHz and 2.4 GHz)	0.52±0.05 mW/kg	Control, PTZ, PTZ + 1-hour Wi-Fi Exposure, PTZ + 1-hour Wi-Fi Exposure + CPZ	1	25	• Epilepsy and Wi-Fi in our experimental model is involved in Ca^{2+} influx. • Oxidative stress-induced hippocampal. • DRGN death through activation of TRPV1 channels. • Negative modulation of this channel activity by CPZ pretreatment.
B Çiğ, M Nazıroğlu 2015 (Cig and Naziroglu, 2015)	Turkey	in vitro	Human cell	--	breast cancer cell line (MCF-7)	Cell phones and Wi-Fi (900, 1800 MHz and 2.4 GHz)	0.36 ± 0.02 mW/kg	Control, 900 MHz, 1800 MHz, 2.4 GHz	1	0, 1, 5, 10, 20, 25	• In 10 cm of the cells induced excessive oxidative responses and apoptosis via TRPV1-induced cytosolic Ca^{2+}. • Use of TRPV1 channel blockers may provide a potential therapeutic approach for the Cell phone and Wi-Fi-induced oxidative stress and apoptosis by calcium accumulation.
M Nazıroğlu et al., 2015 (Naziroglu et al., 2015)	Turkey	in vivo	Animal	21 male Wistar Albino rats	HIPPON	Cell phones (900 MHz)	0.023 ± 0.001 mW/kg	Control, PTZ, PTZ + 1 hour 900 MHz exposure, PTZ + 1 hour 900 MHz exposure + CPZ	1	0.5	• The Cell phone did not change apoptosis, mitochondrial, ROS, and Ca^{2+}. • By Epilepsy induction apoptosis, caspase-3, caspase-9, ROS, and mitochondrial depolarization and Ca^{2+} influx via TRPV1 channel were increased in the hippocampal neurons.
Yüksel M et al., 2016 (Yuksel et al., 2016)	Turkey	in vivo	Animal	32 rats and 40 newborn offspring	Uterus	Cell phone (900 and 1800 MHz) and Wi-Fi (2450 MHz)	0.15 ± 0.10 W/kg	Control, 900, 1800, and 2450 MHz	260	10, 25	• Mobile phone- and Wi-Fi-induced EMR may be one cause of increased oxidative uterine injury in growing rats.
Haas AJ et al., 2016 (Haas et al., 2016)	France	in vitro	Animal	--	Rabbit polyclonal anti-TRPV1	60.4 GHz MMW	263.5	Control, Sham, MMW	24	-	• No impact of MMW exposure on protein expressions of TRPV1.
K Ertilav et al., 2018 (Ertilav et al., 2018)	Turkey	in vivo	Animal	24 female Wistar rats	HIPPON and DRGN	Cell phones (900, 1800 MHz)	0.15 ± 0.10 W/kg	Control, 900 MHz, 900 MHz + CPZ, 1800 MHz, 1800 MHz + CPZ	240	10	• Cell phones Induce mitochondrial ROS production and apoptosis via activation of TRPV1 in HIPPON and DRGN cells.
Ruigrok HJ et al., 2018 (Ruigrok et al., 2018)	France	in vitro	Animal	--	Embryonic kidney HEK293T cells	RF-EMF (1800 MHz) Signals (CW, GSM, UMTS, LTE, Wi-Fi and WiMAX)	between 8 and 32 W/kg	--	--	--	• We found no evidence of such nonthermal mechanism on the activity of the TRPV1 thermoreceptor. • No electronic resonant absorptions, as opposed to the visible range.

Hippocampus **(HIPPON),** Dorsal root ganglion **(DRGN)**, Specific absorption rate **(SAR)**, Pentylentetrazol **(PTZ),** Capsazepine **(CPZ),** Michigan Cancer Foundation-7 **(MCF-7),** Radiofrequency electromagnetic field **(RF-EMF),** Reactive oxygen species **(ROS)**, Continuous waveform **(CW),** Universal Mobile Telecommunication Systems **(UMTS),** Long term evolution **(LTE),** Worldwide Interoperability for Microwave Access **(WiMAX),** Millimeter waves **(MMW)**

observed on expressions of protein TRPV1 (Haas et al. 2016; Ruigrok et al. 2018).

Discussion

Based on our knowledge, it is the first scoping review which is linking cell phones to wireless radiation on TRPV1 channel activation. In the recent century, humans have to make communications, for this stronger electromagnetic radiation is required. So, the new generation of these technologies (up to the 5G network) must be tested for biological compatibility before universal use.

Non-ionizing radiation exists in many sources that were around us. Cell phones and wireless devices are the most equipment that we use. After NIR discovery, some researchers tried to show how this magical harmful radiation for humans (International Commission on Non-Ionizing Radiation 2017). But due to this radiation has not enough energy to dislodge electrons and produce free electron, that would have a direct effect on critical purpose such as deoxyribonucleic acid (DNA) and make it impossible the breaking chemical bonds (Havas 2017).

Important free radicals involved in the disease process are superoxide (O^{-2}), hydroxyl ($^{\bullet}OH$), peroxyl ($RO_2^{\bullet}$), alkoxyl ($RO^{\bullet}$) and hydroperoxyl ($HO_2^{\bullet}$) radicals are produced from molecular oxygen. Some molecules, like hydrogen peroxide (H_2O_2), Hypochlorous acid ($HOCl^{-}$) and single oxygen ($^1O_2$), have the same function as free radicals (Dodd and Ebert 1969; Carrington and Stein 1962). In this mechanism, NIR may lead to anti-oxidants that neutralize free radicals (Phillips et al. 2009). For this evidence has been suggested that the Fenton and Haber Weiss reaction plays a role in free radical generation possibility with NIR (Yakymenko et al. 2016; Lai and Singh 2004).

The presence of active metals, such as Fe^{+2} and Fe^{+3}, is essential in the production of ROS. ROS as a by-product of the oxidative phosphorylation process in the electron transport chain of mitochondrial complex I (nicotinamide adenine dinucleotide (NADH) - coenzyme Q) and III (coenzyme Q – cytochrome c reductase), released into the matrix space (Vicente-Gutierrez et al. 2019; Bhat et al. 2015). During this reaction, under hydrogen peroxide effect, the iron ions are resuspended and the active hydroxyl radical is produced (Hu et al. 2017; Formanowicz et al. 2018). For increased Ca^{2+} entry, the mitochondrial inner membrane depolarization plays a critical role in excessive ROS production (Espino et al. 2009), caspase 3 and 9 activations in neuronal cells and neurodegenerative diseases (Kovacs et al. 2005; Hong et al. 2008; Granatiero et al. 2017; Paradies et al. 2017).

Some studies show wireless and cell phone radiation can alter the intracellular Ca^{2+} efflux in neuronal cells (Grassi et al. 2004; Manikonda et al. 2007; Ammari et al. 2008; Carballo-Quintas et al. 2011); whereas five studies not reported a significant Ca^{2+} efflux in neuronal cells following wireless and cell phone radiation (Platano et al. 2007; O'Connor et al. 2010, Ghazizadeh and Naziroglu 2014; Naziroglu et al. 2015; Ruigrok et al. 2018).

Some of the extreme Ca^{2+} in the cytosol enters the organelles and increases cell stress (Ca^{2+} release from the smooth endoplasmic reticulum (SER) also increases cytosolic Ca^{2+} levels and thereby enhances cell stress). The resulting cell stress disrupts cell metabolism, including the balance of free radicals and increases the risk of ROS production (Razavi et al. 2006; Iftinca et al. 2016). Following the increase in cytosolic Ca^{2+}, some of the cytosolic Ca^{2+} is entered into the nucleus, which increases the amount of nuclear Ca^{2+} that causes cell stress and subsequently increases the amount of ROS resulting in DNA damage (Fenwick et al. 2017; Iftinca et al. 2016).

Many stimuli can stimulate the TRPV1 channel, the most important of them increase the temperature over 42 ℃ (Sosa-Pagan et al. 2017). By increasing the amount of radiation and then increasing the temperature to the considered level, the TRPV1 channel is activated and opened, resulting in extracellular Ca^{2+} entering the cell and increasing cytosolic Ca^{2+} levels **(Figure 2)** (Fenwick et al. 2017).

Some of the extra cytosolic Ca^{2+} also enters the mitochondria through mechanisms that increase the level of mitochondrial Ca^{2+} (Ghazizadeh and Naziroglu 2014; Manikonda et al. 2007; Platano et al. 2007). In the inner mitochondrial membrane, there is a pore called the permeability transition (PT) pore, which consists of several components including cyclophilin (Cyp)-D, Voltage-dependent anion-selective channel (VDAC) and adenine nucleotide translocase (ANT) that Cyp-D plays a key role in regulating channel opening (Giorgio et al. 2018). These pores open up with increasing mitochondrial Ca^{2+} and cause mitochondrial permeability transition (MPT), which carries ions, antioxidants, free radicals, apoptosis-inducing factor (AIF), Endonuclease G

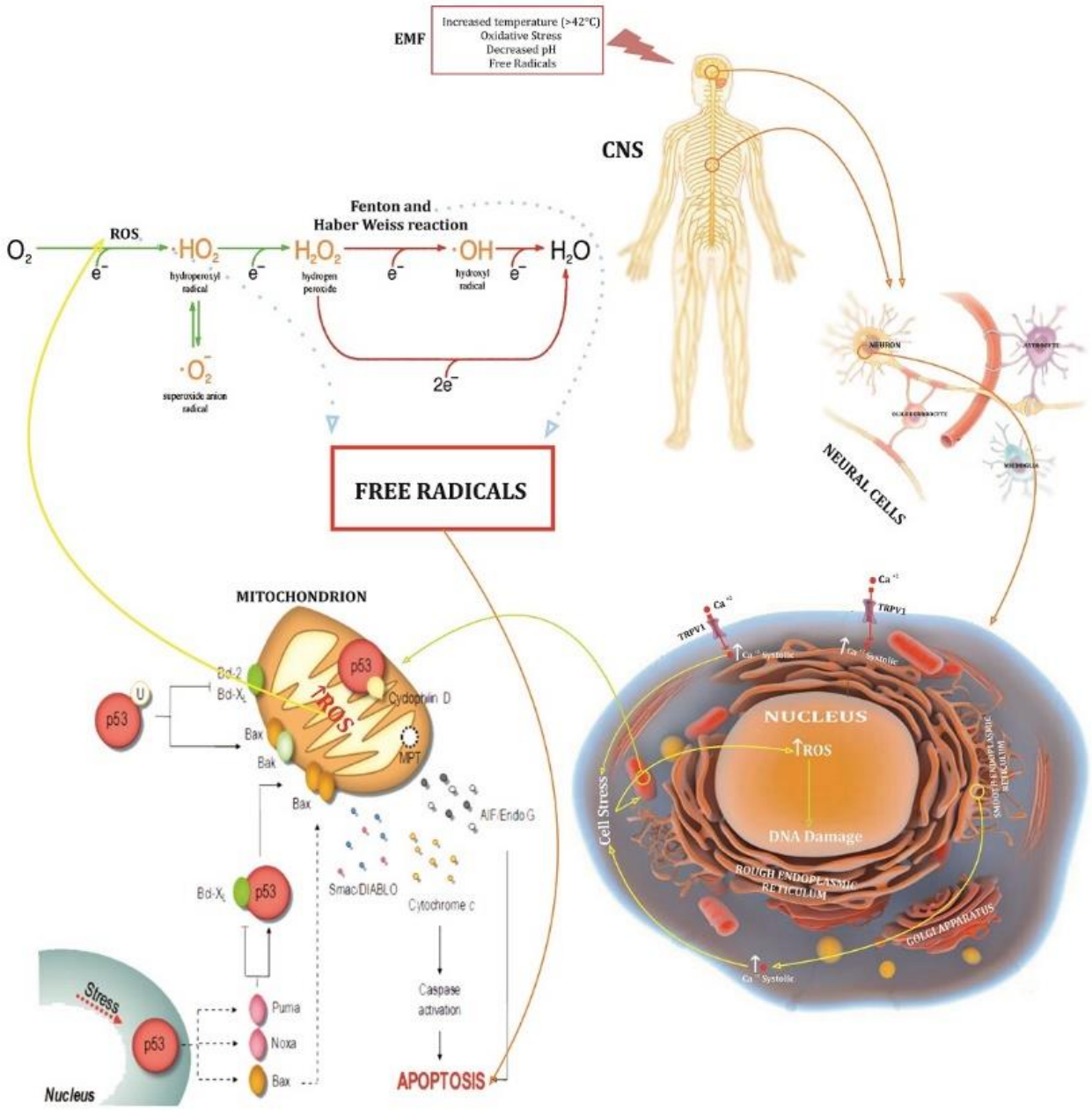


Figure 2. *Possible molecular pathways of cell-phone and wireless radiation on Ca2+ signaling, oxidative stress and apoptosis values through TRPV1 cation channels neuronal cell.*

(ENDOG) into the cytosol (Motloch et al. 2016). AIF and ENDOG also induce chromatin and DNA fragmentation by a translation into the nucleus (Sun et al. 2017).

Following DNA damage, p53 is activated and expresses genes of the pro-apoptotic family including Bax, Noxa, and Puma (Hafner et al. 2019). This disrupts the release of apoptotic factors like cytochrome (Cyt)-c and the Smac-DIABLO complex (Mastrangelo et al. 2015). Cyt-c connects to apoptotic protease activating factor 1 (APFA1) (an adapter protein) to form an apoptosome complex that induces apoptosis by activating primary and secondary caspases (Ting et al. 2008). The Smac-DIABLO complex also facilitates the activation of caspases by suppressing the inhibitor of apoptosis (IAPs) (Yan et al. 2004).

As a result of increasing Ca^{2+} level, cell stress and consequently mitochondrial ROS, including superoxide radical and H_2O_2, will increase (La Rovere et al. 2016). When H_2O_2 exceeds the normal level, it begins to interact

with Fe, which results in the initiation of the Fenton reaction (Mostofa and Sakugawa 2016). In this reaction, H_2O_2 reacts with Fe^{2+} and results in the production of Fe^{3+} and $^{\bullet}OH$ (Wiegand et al. 2017). Then Fe^{3+} results with H_2O_2 to produce HO_2, hydroxyl radicals are also produced according to the Haber-Wiess reaction from the reaction of O^{2-} and H_2O_2. These chain reactions continue and produce some kind of free radicals which finally lead to inducing apoptosis and cell death (Floyd and Nagy 1984; Schafer et al. 2000).

In conclusion, our review shows that cell phone and wireless radiation have a possible effect on Ca^{2+} signaling by activation TRPV1 channel, and this reaction may induce ROS, Fenton and Haber-Weiss reaction that this reaction increases free radicals' level in the mitochondria.

Conflict of interest: The authors declare that they have no conflict of interest.

Funding source and financial disclosures: No funding.

Contribute: K.SH and F.R: conceived the original idea, designed the scenarios and collected the data, A.R.R, R.A and O.M: carried out the analysis of data, K.SH, F.R and GH.H: approved the final version that was submitted, revised it, K.S.H and A.R.R: drafted the manuscript,

References

Ammari M, Lecomte A, Sakly M, Abdelmelek H, De-Seze R. 2008. Exposure to GSM 900 MHz electromagnetic fields affects cerebral cytochrome c oxidase activity. Toxicology 250**:**70-4.

Authority, SRP. 2002. Epidemiological Studies of Cellular Telephones and cancer Risk e a Review. Swedish Radiation Protection Authority, Stockholm (2002). [Online]. Available: http://w3.iec.csic.es/textos/ssi_rapp_2002_16.pdf. [Accessed].

Banik S, Bandyopadhyay S, Ganguly S. 2003. Bioeffects of microwave--a brief review. Bioresour Technol, 87**:**155-159.

Bevan S, Quallo T, Andersson DA. 2014. TRPV1. Handb Exp Pharmacol, 222**:**207-245.

Bhat AH, Dar KB, Anees S, Zargar MA, Masood A, Sofi MA, Ganie SA. 2015. Oxidative stress, mitochondrial dysfunction and neurodegenerative diseases; a mechanistic insight. Biomed Pharmacother, 74**:** 101-110.

Canada H. 2010. Health Canada, Royal Society of Canada (RSC): Expert Panel Report on Radiofrequency Fields. Recent Advances in Research on Radiofrequency Fields and Health: 2001-2003. [Online]. Available: http://www.hc-sc.gc.ca/ewh-semt/pubs/radiation/radio_guide-lignes_direct-eng.php [Accessed].

Carballo-Quintas M, Martinez-Silva I, Cadarso-Suarez C, Alvarez-Figueiras M, Ares-Pena F. J, Lopez-Martin E. 2011. A study of neurotoxic biomarkers, c-fos and GFAP after acute exposure to GSM radiation at 900 MHz in the picrotoxin model of rat brains. Neurotoxicology, 32**:**478-494.

Carrington, A, Stein, G. 1962. Free radical formation and oxygen effect in irradiated polymethylmethacrylate. Nature, 193**,** 976.

Caterina, M. J, Schumacher, M. A, Tominaga, M, Rosen, T. A, Levine, J. D, Julius, D. 1997. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature, 389**,** 816-24.

Cig, B, Naziroglu, M. 2015. Investigation of the effects of distance from sources on apoptosis, oxidative stress and cytosolic calcium accumulation via TRPV1 channels induced by mobile phones and Wi-Fi in breast cancer cells. Biochim Biophys Acta, 1848**,** 2756-65.

Demirhan, E, Randler, C, Horzum, M. B. 2016. Is problematic mobile phone use explained by chronotype and personality? Chronobiol Int, 33**,** 821-31.

Dodd, N. J, Ebert, M. 1969. Free radical reactions modify cellular damage. Nature, 221**,** 1245-6.

Environment, N.Z. M. F. T. 2008. National Environmental Standards for Telecommunication Facilities. [Online]. Available: http://www.mfe.govt.nz/laws/standards/telecommunication-standards.html. [Accessed].

Ertilav, K, Uslusoy, F, Ataizi, S, Naziroglu, M. 2018. Long term exposure to cell phone frequencies (900 and 1800 MHz) induces apoptosis, mitochondrial oxidative stress and TRPV1 channel activation in the hippocampus and dorsal root ganglion of rats. Metab Brain Dis, 33**,** 753-763.

Espino, J, Mediero, M, Lozano, G. M, Bejarano, I, Ortiz, A, Garcia, J. F, Pariente, J. A, Rodriguez, A. B. 2009. Reduced levels of intracellular calcium releasing in spermatozoa from asthenozoospermic patients. Reprod Biol Endocrinol, 7**,** 11.

FCC. 2010. Federal Communications Commission, How Safe Are Mobile and Portable Phones? [Online]. Available: Http://Www.Fcc.Gov/Oet/Rfsafety/Rf-Faqs.Html. [Accessed].

Fenwick, A. J, Fowler, D. K, Wu, S. W, Shaffer, F. J, Lindberg, J. E. M, Kinch, D. C, Peters, J. H. 2017. Direct Anandamide Activation of TRPV1 Produces Divergent Calcium and Current Responses. Front Mol Neurosci, 10**,** 200.

Floyd, R. A, Nagy, I. 1984. Formation of long-lived hydroxyl free radical adducts of proline and hydroxyproline in a Fenton reaction. Biochim Biophys Acta, 790**,** 94-7.

Formanowicz, D, Radom, M, Rybarczyk, A, Formanowicz, P. 2018. The role of Fenton reaction in ROS-induced toxicity underlying atherosclerosis - modeled and analyzed using a Petri net-based approach. Biosystems, 165**,** 71-87.

Ghazizadeh, V, Naziroglu, M. 2014. Electromagnetic radiation (Wi-Fi) and epilepsy induce calcium entry and apoptosis through activation of TRPV1 channel in hippocampus and dorsal root ganglion of rats. Metab Brain Dis, 29**,** 787-99.

Giorgio, V, Guo, L, Bassot, C, Petronilli, V, Bernardi, P. 2018. Calcium and regulation of the mitochondrial permeability transition. Cell Calcium, 70**,** 56-63.

Granatiero, V, De Stefani, D, Rizzuto, R. 2017. Mitochondrial Calcium Handling in Physiology and Disease. Adv Exp Med Biol, 982**,** 25-47.

Grassi, C, D'ascenzo, M, Torsello, A, Martinotti, G, Wolf, F, Cittadini, A, Azzena, G. B. 2004. Effects of 50 Hz electromagnetic fields on voltage-gated Ca2+ channels and their role in modulation of

neuroendocrine cell proliferation and death. Cell Calcium, 35**,** 307-15.

Haas, A. J, Le Page, Y, Zhadobov, M, Boriskin, A, Sauleau, R, Le Drean, Y. 2016. Impact of 60-GHz millimeter waves on stress and pain-related protein expression in differentiating neuron-like cells. Bioelectromagnetics, 37**,** 444-54.

Hafner, A, Bulyk, M. L, Jambhekar, A, Lahav, G. 2019. The multiple mechanisms that regulate p53 activity and cell fate. Nat Rev Mol Cell Biol, 20**,** 199-210.

Havas, M. 2017. When theory and observation collide: Can non-ionizing radiation cause cancer? Environ Pollut, 221**,** 501-505.

Health Protection Agency, U. K. 2012. Previously Called the National Radiological Protection Board (NRPB) "Review of the Scientific Evidence for Limiting Exposure to Electromagnetic Fields (0e300 GHz)". [Online]. Available: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947383619. [Accessed].

Hong, S, Agresta, L, Guo, C, Wiley, J. W. 2008. The TRPV1 receptor is associated with preferential stress in large dorsal root ganglion neurons in early diabetic sensory neuropathy. J Neurochem, 105**,** 1212-22.

Hu, P, Wu, T, Fan, W, Chen, L, Liu, Y, Ni, D, Bu, W, Shi, J. 2017. Near infrared-assisted Fenton reaction for tumor-specific and mitochondrial DNA-targeted photochemotherapy. Biomaterials, 141**,** 86-95.

ICNIRP. 2016. International Commission for Non-ionizing Radiation Protection, a Group that Advises Governing Bodies Around the World Including the WHO, Has the Following Statement on Their Website for High Frequency (100 KHze300 GHz) Electromagnetic Radiation. [Online]. Available: http://www.icnirp.org/en/frequencies/highfrequency/index.html [Accessed July 2016].

Iftinca, M, Flynn, R, Basso, L, Melo, H, Aboushousha, R, Taylor, L, Altier, C. 2016. The stress protein heat shock cognate 70 (Hsc70) inhibits the Transient Receptor Potential Vanilloid type 1 (TRPV1) channel. Mol Pain, 12.

International Commission On Non-Ionizing Radiation, P. 2017. ICNIRP Statement on Diagnostic Devices Using Non-ionizing Radiation: Existing Regulations and Potential Health Risks. Health Phys, 112**,** 305-321.

Kovacs, R, Kardos, J, Heinemann, U, Kann, O. 2005. Mitochondrial calcium ion and membrane potential transients follow the pattern of epileptiform discharges in hippocampal slice cultures. J Neurosci, 25**,** 4260-9.

La Rovere, R. M, Roest, G, Bultynck, G, Parys, J. B. 2016. Intracellular Ca(2+) signaling and Ca(2+) microdomains in the control of cell survival, apoptosis and autophagy. Cell Calcium, 60**,** 74-87.

Lai, H, Singh, N. P. 2004. Magnetic-field-induced DNA strand breaks in brain cells of the rat. Environ Health Perspect, 112**,** 687-94.

Macleod, M. R, O'collins, T, Howells, D. W, Donnan, G. A. 2004. Pooling of animal experimental data reveals influence of study design and publication bias. Stroke, 35**,** 1203-8.

Manikonda, P. K, Rajendra, P, Devendranath, D, Gunasekaran, B, Channakeshava, Aradhya, R. S, Sashidhar, R. B, Subramanyam, C. 2007. Influence of extremely low frequency magnetic fields on Ca2+ signaling and NMDA receptor functions in rat hippocampus. Neurosci Lett, 413**,** 145-9.

Marrone, M. C, Morabito, A, Giustizieri, M, Chiurchiu, V, Leuti, A, Mattioli, M, Marinelli, S, Riganti, L, Lombardi, M, Murana, E, Totaro, A, Piomelli, D, Ragozzino, D, Oddi, S, Maccarrone, M, Verderio, C, Marinelli, S. 2017. TRPV1 channels are critical brain inflammation detectors and neuropathic pain biomarkers in mice. Nat Commun, 8**,** 15292.

Mastrangelo, E, Vachette, P, Cossu, F, Malvezzi, F, Bolognesi, M, Milani, M. 2015. The activator of apoptosis Smac-DIABLO acts as a tetramer in solution. Biophys J, 108**,** 714-23.

Mostofa, K. M. G, Sakugawa, H. 2016. Simultaneous photoinduced generation of Fe(2+) and H2O2 in rivers: An indicator for photo-Fenton reaction. J Environ Sci (China), 47**,** 34-38.

Motloch, L. J, Larbig, R, Gebing, T, Reda, S, Schwaiger, A, Leitner, J, Wolny, M, Eckardt, L, Hoppe, U. C. 2016. By Regulating Mitochondrial Ca2+-Uptake UCP2 Modulates Intracellular Ca2+. PLoS One, 11**,** e0148359.

National Cancer Institute, U. S. 2016. Cell Phones and Cancer Risk Fact Sheet updated [Online]. Available: www.cancer.gov/about-cancer/causes-prevention/risk/radiation/cell-phones-fact-sheet. [Accessed May 27, 2016].

Naziroglu, M, Ozkan, F. F, Hapil, S. R, Ghazizadeh, V, Cig, B. 2015. Epilepsy but not mobile phone frequency (900 MHz) induces apoptosis and calcium entry in hippocampus of epileptic rat: involvement of TRPV1 channels. J Membr Biol, 248**,** 83-91.

Nita, Ii, Caspi, Y, Gudes, S, Fishman, D, Lev, S, Hersfinkel, M, Sekler, I, Binshtok, A. M. 2016. Privileged crosstalk between TRPV1 channels and mitochondrial calcium shuttling machinery controls nociception. Biochim Biophys Acta, 1863**,** 2868-2880.

O'connor, R. P, Madison, S. D, Leveque, P, Roderick, H. L, Bootman, M. D. 2010. Exposure to GSM RF fields does not affect calcium homeostasis in human endothelial cells, rat pheocromocytoma cells or rat hippocampal neurons. PLoS One, 5**,** e11828.

Oremus, M, Wolfson, C, Perrault, A, Demers, L, Momoli, F, Moride, Y. 2001. Interrater reliability of the modified Jadad quality scale for systematic reviews of Alzheimer's disease drug trials. Dement Geriatr Cogn Disord, 12**,** 232-6.

Paradies, G, Paradies, V, Ruggiero, F. M, Petrosillo, G. 2017. Mitochondrial bioenergetics decay in aging: beneficial effect of melatonin. Cell Mol Life Sci, 74**,** 3897-3911.

Peterson, J, Welch, V, Losos, M, Tugwell, P. 2011. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute.

Phillips, J. L, Singh, N. P, Lai, H. 2009. Electromagnetic fields and DNA damage. Pathophysiology, 16**,** 79-88.

Platano, D, Mesirca, P, Paffi, A, Pellegrino, M, Liberti, M, Apollonio, F, Bersani, F, Aicardi, G. 2007. Acute exposure to low-level CW and GSM-modulated 900 MHz radiofrequency does not affect Ba 2+ currents through voltage-gated calcium channels in rat cortical neurons. Bioelectromagnetics, 28**,** 599-607.

Razavi, R, Chan, Y, Afifiyan, F. N, Liu, X. J, Wan, X, Yantha, J, Tsui, H, Tang, L, Tsai, S, Santamaria, P, Driver, J. P, Serreze, D, Salter, M. W, Dosch, H. M. 2006. TRPV1+ sensory neurons control beta cell stress and islet inflammation in autoimmune diabetes. Cell, 127**,** 1123-35.

Ruigrok, H. J, Arnaud-Cormos, D, Hurtier, A, Poque, E, De Gannes, F. P, Ruffie, G, Bonnaudin, F, Lagroye, I, Sojic, N, Arbault, S, Leveque, P, Veyret, B, Percherancier, Y. 2018. Activation of the TRPV1 Thermoreceptor Induced by Modulated or Unmodulated

1800 MHz Radiofrequency Field Exposure. Radiat Res, 189**,** 95-103.

Schafer, F. Q, Qian, S. Y, Buettner, G. R. 2000. Iron and free radical oxidations in cell membranes. Cell Mol Biol (Noisy-le-grand), 46**,** 657-62.

Slim, K, Nini, E, Forestier, D, Kwiatkowski, F, Panis, Y, Chipponi, J. 2003. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg, 73**,** 712-6.

Sosa-Pagan, J. O, Iversen, E. S, Grandl, J. 2017. TRPV1 temperature activation is specifically sensitive to strong decreases in amino acid hydrophobicity. Sci Rep, 7**,** 549.

Sun, Y, Gao, W, Zhao, Y, Cao, W, Liu, Z, Cui, G, Tong, L, Lei, F, Tang, B. 2017. Visualization and Inhibition of Mitochondria-Nuclear Translocation of Apoptosis Inducing Factor by a Graphene Oxide-DNA Nanosensor. Anal Chem, 89**,** 4642-4647.

Takayama, Y, Uta, D, Furue, H, Tominaga, M. 2015. Pain-enhancing mechanism through interaction between TRPV1 and anoctamin 1 in sensory neurons. Proc Natl Acad Sci U S A, 112**,** 5213-8.

Ting, J. P, Willingham, S. B, Bergstralh, D. T. 2008. NLRs at the intersection of cell death and immunity. Nat Rev Immunol, 8**,** 372-9.

Tricco, A. C, Lillie, E, Zarin, W, O'brien, K. K, Colquhoun, H, Levac, D, Moher, D, Peters, M. D. J, Horsley, T, Weeks, L, Hempel, S, Akl, E. A, Chang, C, Mcgowan, J, Stewart, L, Hartling, L, Aldcroft, A, Wilson, M. G, Garritty, C, Lewin, S, Godfrey, C. M, Macdonald, M. T, Langlois, E. V, Soares-Weiser, K, Moriarty, J, Clifford, T, Tuncalp, O, Straus, S. E. 2018. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med, 169**,** 467-473.

Vicente-Gutierrez, C, Bonora, N, Bobo-Jimenez, V, Jimenez-Blasco, D, Lopez-Fabuel, I, Fernandez, E, Josephine, C, Bonvento, G, Enriquez, J. A, Almeida, A, Bolaños, J. P. 2019. Astrocytic mitochondrial ROS modulate brain metabolism and mouse behaviour. Nature Metabolism, 1**,** 201-211.

WHO. 2014. Media Centre, fact sheet on “Electromagnetic fields and public health: mobile phones” [Online]. Available: http://www.who.int/mediacentre/factsheets/fs193/en/ [Accessed October 2014].

Wiegand, H. L, Orths, C. T, Kerpen, K, Lutze, H. V, Schmidt, T. C. 2017. Investigation of the Iron-Peroxo Complex in the Fenton Reaction: Kinetic Indication, Decay Kinetics, and Hydroxyl Radical Yields. Environ Sci Technol, 51**,** 14321-14329.

Wu, Z, He, E. Y, Scott, G. I, Ren, J. 2015. alpha,beta-Unsaturated aldehyde pollutant acrolein suppresses cardiomyocyte contractile function: Role of TRPV1 and oxidative stress. Environ Toxicol, 30**,** 638-47.

Yakymenko, I, Tsybulin, O, Sidorik, E, Henshel, D, Kyrylenko, O, Kyrylenko, S. 2016. Oxidative mechanisms of biological activity of low-intensity radiofrequency radiation. Electromagn Biol Med, 35**,** 186-202.

Yan, Y, Mahotka, C, Heikaus, S, Shibata, T, Wethkamp, N, Liebmann, J, Suschek, C. V, Guo, Y, Gabbert, H. E, Gerharz, C. D, Ramp, U. 2004. Disturbed balance of expression between XIAP and Smac/DIABLO during tumour progression in renal cell carcinomas. Br J Cancer, 91**,** 1349-57.

Yuksel, M, Naziroglu, M, Ozkaya, M. O. 2016. Long-term exposure to electromagnetic radiation from mobile phones and Wi-Fi devices decreases plasma prolactin, progesterone, and estrogen levels but increases uterine oxidative stress in pregnant rats and their offspring. Endocrine, 52**,** 352-62.