Volume 19, No 3 | International Journal of Radiation Research, July 2021

The non-thermal biological effects and mechanisms of microwave exposure

X. Zhao, G. Dong, C. Wang*

Department of Experimental Pathology, Beijing Institute of Radiation Medicine, Beijing, P. R. China

► ***Review article***

Corresponding authors:
Changzhen Wang, Ph.D.,
E-mail:
wangcz2002@aliyun.com

Revised: April 2020
Accepted: June 2020

Int. J. Radiat. Res., July 2021; 19(3): 483-494

DOI: 10.29252/ijrr.19.2.483

ABSTRACT

The purpose of this article was to present a brief review of pertinent information regarding the effects of microwave radiation on biological systems. Researchers have been intrigued by the interaction of electromagnetic fields (EMFs) and various life processes since the 18th century. Microwaves refer to the oscillation of an EMF with a wavelength of 1 mm to 1 m, which penetrates matter to varying degrees. With the widespread and ever-increasing use of microwaves, such as cellular telephones and other wireless technologies, great attention and research has been paid to the potential adverse biological effects. It is well recognized that microwaves affect the biological functions of living organisms at both the cellular and molecular levels, and can lead to the appearance of toxicity, genotoxicity and transformation. However, until now no satisfactory mechanism has been proposed to explain the biological effects of these fields. Therefore, increasing attention should be focused on the biological effects of microwaves in the future, especially since microwaves have extensive applications in various fields.

Keywords: *Microwaves, biological effects, mechanism, thermal, non-thermal.*

INTRODUCTION

Microwave radiation is considered a type of non-ionizing electromagnetic field (EMF) and it is present in the environment due to its ever-increasing applications, such as in microwave ovens, radio/television (TV) transmission, cellular phones and in occupational use (e.g. radar operators), as well as through medical exposure via diathermy. Much has been published supporting the notion that microwaves have both thermal and non-thermal effects, which can be identified in terms of their manifestations on cell physiology. Many studies have shown that microwaves cause different biological effects depending upon the field strength, frequency, wave form, modulation and duration of exposure [1]. These effects have mainly been attributed to microwave heating , but the non-thermal effects of microwaves on cells or animals have been documented over the last three decades [2]. Although the exact mechanism underlying the biological effects of microwaves has not been specified, there is a hypothesis that microwaves either cause ions to accelerate and collide with other molecules or cause dipoles to rotate and line up rapidly with an alternating electric field [3].

In previous investigations it was found that microwave exposure was able to induce several changes at the cellular and molecular levels of cells, including increasing the permeability of the blood–brain barrier, causing the death of single-cell organisms, inhibiting cell proliferation, increasing DNA single and double strand breaks, altering gene expression in different cell types, inducing micronuclei, altering protein conformation and inducing oxidative stress [4]. However, identifying and evaluating the biological effects of microwaves is complex and controversial because the

[DOI: 10.52547/ijrr.19.3.483]

mechanisms by which microwaves exert their biological effects remain poorly characterized. Consequently, there is still a great need for elucidation of the real targets and mechanisms of action of pulsed microwaves. Thus, in order to familiarize the reader with pertinent information regarding the non-thermal effects of microwave irradiation, this systematic review had covered the original articles in the biological effects and mechanisms of microwave exposure, such as the ions or electrons of molecules, the characteristics of ion channels, energy metabolism, reactive oxygen species (ROS) and response of biological cells. Moreover, the possible protective measure against the biological effects of microwave radiation were also discussed in this review.

The mechanism of biological effects

The mechanism of the biological effects of microwave radiation is still unknown because of inadequate equipment and techniques, which have left most data open to question. However, many hypotheses have developed, which will now be discussed (figure 1). The biological effects of organisms caused by microwave radiation are complex, possible mechanism of action of biological systems were included in this review (figure 2).

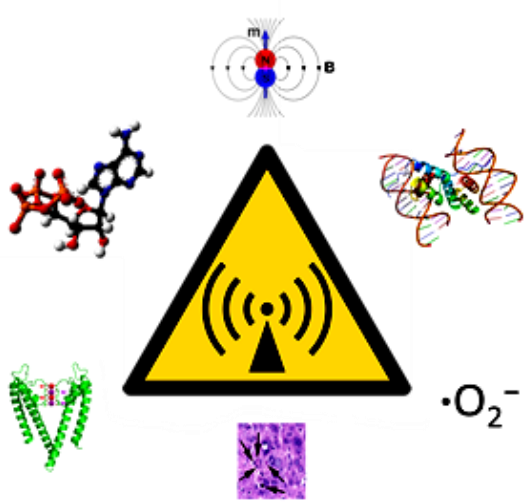

Figure 1. Possible adverse biological effects of microwave radiation.

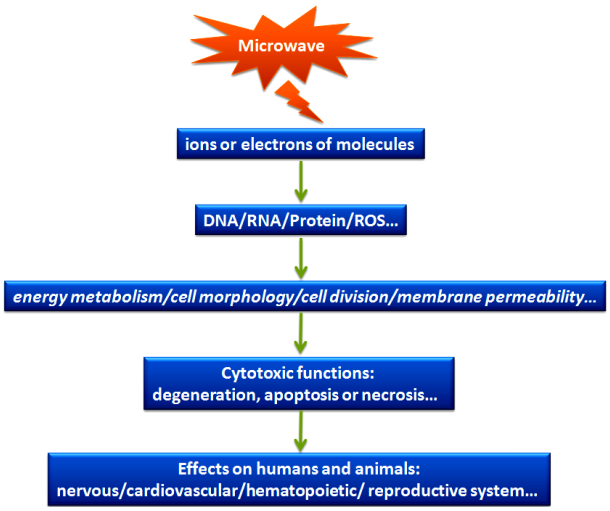

Figure 2. Possible mechanism of action of microwave on biological systems.

Microwaves can affect the ions or electrons of molecules

Microwaves can cause ions or electrons to become misplaced, vibrate or collide with other molecules, and it can cause a change in the direction of a polar molecule's dipole moment, which may explain the mechanism of action with regards to the physiological reactions in cells at the molecular level, whereby biochemical consequences, changes in metabolism and alteration of the proliferation of living cells have been noted [3].

Microwaves can affect the characteristics of ion channels

Microwaves can affect the characteristics of many ion channels, such as the Ca^{2+} channel, and the transfer of Na^+ and K^+ across the plasma membrane. Pall [4] found that the EMF activation of voltage-gated calcium channels (VGCCs) led to rapid elevation of intracellular Ca^{2+}, nitric oxide and, in some cases at least, peroxynitrite, resulting in pathophysiological effects mediated through the Ca^{2+}/nitric oxide/peroxynitrite pathway.

Microwaves can affect reactive oxygen species

In biological systems affected by electromagnetic radiation (EMR), the

[DOI: 10.52547/ijrr.19.3.483]

mechanisms of tissue damage are thought to involve ROS. Excessive ROS can damage membrane structures and large cellular molecules, such as lipids, proteins and nucleic acids; they may also account for failure of the nuclear DNA chain structure following EMR exposure. Moustafa *et al.* [6] found that microwave exposure could increase the levels of free radicals and detrimentally impact antioxidant mechanisms in the body.

Microwaves can impact energy metabolism

Microwave radiation can result in disordered cell energy metabolism, which can affect the function of cells. Srivastava *et al.* [7] found that microwave irradiation decreased adenosine triphosphate (ATP) and increased free Mg^{2+} ions, impacting ATP hydrolysis and the release of Mg^{2+} ions into intracellular spaces. Following exposure of the brain to microwaves, the equilibrium constants of certain metabolic reactions were grossly distorted, affecting determination of the cytosolic phosphorylation potential.

Response of biological cells to microwave irradiation

Effect of microwaves on cells

Microwave radiation may alter cell morphology, disrupt cell division and change cell membrane permeability [8] resulting in degeneration, apoptosis or necrosis in cells at different stages and the details of these results were listed in table 1. One current theory suggests that these effects may be mainly attributed to microwave heating, but other reports have shown or suggested that non-thermal microwaves are able to produce molecular transformations and alterations [3]. For example, it has been reported that the cell cycle is altered in Chinese hamster ovary (CHO) cells by 27 MHz microwave exposure [9]. Furthermore, human amnion cells exposed to 960 MHz show a decreased cell growth rate with increased exposure time. Wu *et al.* [10] found that cytokines produced by microwave-radiated Sertoli cells induced apoptosis and lipid peroxidation in the membranes of germ cells. In addition, germ cell apoptosis was associated with the up-regulation of Bcl-2 Assaciated X/B-cell lymphoma-2 (Bax/Bcl-2) and caspase-3. Song *et al.* [11] observed that the rate of early stage apoptosis in A549 human lung carcinoma cells reached 6.10–17.98% and the rate of advanced stage apoptosis and the necrosis rate reached 8.04–44.06% after 6 hours of continuous microwave radiation. Furthermore, the down-regulation of Bcl-2 expression reached its lowest level and the up-regulation of tumor protein 53 (P53) expression peaked at about 3 hours. This study showed that cell damage, apoptosis and protein expression differed depending on the radiation intensity and duration. Recently, Zhao *et al.* [12] also showed that microwave dose-dependently induced cellular apoptosis, cell cycle arrest and decreased cytotoxic activity in Natural killer cells 92 (NK-92), possibly through extracellular regulated protein kinases (ERK)-mediated regulation of apoptosis and perforin expression. Additionally, Zhang *et al.* [13] demonstrated that continuous microwave radiation once a day for up to 7 days efficiently induced Lewis lung carcinoma (LLC) tumor cell apoptosis in mice even at the low intensity of 10 mW/cm^2 for 5 min each time, and revealed that non-thermal effect played a critical role in the induction of tumor cell apoptosis *in- vivo*.

Many studies have shown that biological systems exposed to extremely high frequency microwaves may suffer significant effects via non-thermal mechanisms primarily involving the interaction of microwaves with phospholipid membrane structures. Biological membranes are likely to be highly sensitive to frequencies in the 1–80 GHz range [14]. Zhadobov *et al.* [15] found that membrane system exposure at 60 GHz significantly increased the lateral pressure of phospholipid monolayer films at power densities as low as 9 $\mu W/cm^2$, although there was no statistically significant phospholipid microdomain reorganization. Furthermore, the ionic transmembrane current has been found to be involved. For example, Geletyuk *et al.* [16] observed significant alterations in the transport of Ca^{2+} ions across a single Ca^{2+}-activated K^+ channel in kidney cells when exposed to 42.25 GHz radiation. In addition, Rougier *et al.* [17] and

[DOI: 10.52547/ijrr.19.3.483]

Zeng *et al.* [18] respectively observed that 2.45 GHz microwave exposure induced membrane modifications to increase cellular permeability to ions and molecules in Escherichia coli and Yeast.

Table 1. Effect of microwaves on cells.

Time	Author	Microwave Parameter	Experimental Cell	Detection Index	Result
1995	Cao *et al.* [9]	27 MHz	CHO cells	Cell cycle	changed
2012	Wu *et al.* [10]	50 Hz	human mesenchymal stem cells	cell apoptosis	the up-regulation of Bax/ Bcl-2 and caspase-3
2011	Song *et al.* [11]	200-600 mW/cm^2	A549 cells	cell apoptosis	the rate of early stage: 6.10–17.98% the rate of advanced stage: 8.04–44.06%
2017	Zhao *et al.* [12]	10, 30, and 50 mW/cm^2	NK-92 cells	Ultrastructural changes, cellular apoptosis and cell cycle regulation	Changed possibly through ERK-mediated regulation of apoptosis and perforin expression
2017	Zhang *et al.* [13]	10 mW/cm 2	LLC cells	cell apoptosis	changed
2006	Zhadobov *et al.* [15]	60 GHz	Artificial Biological Membranes	lateral pressure	increased
1995	Geletyuk *et al.* [16]	42.25 GHz	kidney cells	K+ channel	changed
2014	Rougier et al. [17]	2.45 GHz	Escherichia coli	cellular permeability	increased
2014	Zeng *et al.* [18]	2.45 GHz	Yeast	cellular permeability	increased

Effect of microwaves on free radicals

It is already known that aging, several diseases and exposure to various toxic substances and radiation increase the amount of ROS. The increase of ROS results in the alteration of macromolecules, such as polyunsaturated fatty acids in membrane lipids, vital proteins and DNA. The resulting oxidative stress causes an increase of malondialdehyde (MDA), which causes damage to membrane lipids and a decreased glutathione (GSH) concentration, which plays a central role in defense against different diseases and cell insults. GSH and MDA levels have been evaluated to determine whether microwaves can induce oxidative damage. However, contradictory results regarding the effect of microwaves on the parameters of oxidative stress have been reported and the details of these results were listed in table 2.

Several research groups have found that radiofrequency (RF) radiation has no effect on ROS production at special absorption rate (SAR) values <2.0 W/kg. Ferreira *et al.* [19] found that microwave exposure did not increase the MDA concentration in the brains of rats. In our previous study, we found that electromagnetic pulse (EMP) prevents free radical generation by activating antioxidant enzyme activity and reducing oxygen consumption *in-vitro* [20]. Additionally, our findings indicate that the biological effect of microwave at a SAR of 4 W/kg resulted in instantaneous and recoverability changes *in-vivo* [21]. However, there is evidence that microwaves may stimulate the formation of ROS in exposed cells *in-vivo* and *in-vitro* [22].

Yurekli *et al.* [23] investigated 945 MHz frequency EMFs and the oxidative stress effects on rats. They used a gigahertz transverse electromagnetic (GTEM) cell as the exposure environment. When the EMF was at a power density of 3.67 W/m^2 (SAR of 11.3 mW/kg), which is well below current exposure limits, the MDA level increased and the GSH concentration decreased significantly. Additionally, there was a less significant increase in superoxide dismutase (SOD) activity, demonstrating that oxidative stress resulted from electromagnetic exposure.

[DOI: 10.52547/ijrr.19.3.483]

Esmekaya *et al.* [24] found that MDA levels were increased significantly and GSH levels were significantly lowered in the liver, lung, testis and heart tissues of an exposed group compared to sham and control groups after rats were exposed to 900 MHz pulse-modulated RF radiation at a SAR level of 1.20 W/kg for 20 min/day for 3 weeks. Thus, pulse-modulated RF radiation causes oxidative injury in tissues mediated by lipid peroxidation.

Recently, Narayanan *et al.* [25] reported that exposure to microwave radiation with frequencies ranging from 890-915 MHz at SAR 1.58 W/Kg, for 28 days resulted in oxidative stress as indicated by increased level of thiobarbituric acid-reactive substances (TBARS) in brain. Furthermore, in the study reported by Xing *et al.* [26], it has been shown that 1800MHz microwave activates caspase-3 signaling pathway that leads to cell apoptosis through enhancing ROS production and DNA damage, which is consistent with another study [27] in that microwave induced non-small cell lung cancer (NSCLC) cells apoptosis by increasing the production of ROS *in-vivo*. In addition, Kavindra *et al.* [28] also revealed that exposure of 2.45 GHz microwave frequency adversely affects the whole brain and cause oxidative damage by increased levels of lipid peroxide (LPO) and ROS.

Table 2. Effect of microwaves on free radicals.

Time	Author	Microwave Parameter	Experimental Animal	Detection Index	Result
2006	Ferreira *et al.* [19]	800–1800 MHz	brain of rats	MDA	unchanged
2015	Wang *et al.* [21]	2.856 GHz 4 W/kg	PC12 cells	ROS	instantaneous and recoverability changes
2008	Yao *et al.* [22]	1.8 GHz 2, 3, and 4 W/kg	human lens epithelial cells	ROS	increased
2006	Yurekli *et al.* [23]	945 MHz 11.3 mW/kg	GTEM cells	MDA and GSH	MDA :increased GSH: decreased
2011	Esmekaya *et al.* [24]	900 MHz 1.20 W/kg	liver, lung, testis and heart tissues of rats	MDA and GSH	MDA :increased GSH: decreased
2014	Narayanan *et al.* [25]	890-915 MHz 1.58 W/Kg	discrete brain regions of rats	TBARS	increased
2016	Xing *et al.* [26]	1800MHz 1209 mW/m^2	Mouse NIH/3T3 and human U-87 MG cells	ROS	increased
2018	Zhao *et al.* [27]	433 MHz	NSCLC cells	ROS	increased
2017	Kavindra *et al.* [28]	2.45 GHz 0.2 mW/cm^2	brain of rats	LPO and ROS	increased

Genetic effects of microwaves

Numerous experimental reports have shown that RF radiation does not induce genetic effects [29]. However, recent work has pointed to the chromosomes and DNA as targets for resonance interactions between living cells and microwaves and exposure to microwave radiation can damage DNA and gene structures [30] and the details of these results were listed in table 3. Cleary *et al.* [31] found that DNA synthesis was increased in glioma cells and suppressed in lymphocytes after exposure to microwave radiation. In addition, cytogenetic damage has been reported in human lymphocytes from blood samples exposed to a 945 MHz field [32]. Cytogenetic studies of microwave radiation were conducted *in-vitro* and *in-vivo*, and have yielded contradictory and often intriguing experimental results. Garaj-Vrhovac *et al.* [33] found that workers occupationally exposed to pulsed marine radar frequencies (3, 5.5 and 9.4 GHz) have statistically significant differences between the mean tail intensities (0.67 vs. 1.22) and moments (0.08 vs.

[DOI: 10.52547/ijrr.19.3.483]

0.16) assessed via comet assays and micronucleus tests, showing the effects of microwaves on micronuclei, nucleoplasmic bridges and nuclear buds. Additionally, Zhao *et al.* [34] have reported that microwave irradiation at a frequency of 2.45 GHz induced an inactivation of DNA-based hybrid catalyst even at low temperatures (such as 5˚C), and a substantial amount of DNA molecules degraded and lost their characteristic structures. Furthermore, Deshmukh *et al.* [35] have also shown that low level subchronic microwave radiation at frequencies 900, 1800, and 2450 MHz for 2h a day, 5d a week for 90 days might lead to decline in cognitive function on rat brain as evidenced by DNA damage and increased heat shock protein 70 (HSP70) level in hippocampus tissues which could induce hazardous effects in rats. The results suggested that microwaves may cause genetic and cellular alterations.

Trosic *et al.* [36] researched Wistar rats exposed to a power density of 2.4 W/m^2 and a carrier frequency of 915 MHz with Global System Mobile (GSM) signal modulation. They found that repeated 915 MHz radiation could cause DNA breaks in renal and liver cells, but it did not affect the cell genome to a high extent compared to the basal damage. Further investigation is needed on the genotoxic effects of RF radiation, especially to evaluate dependence on the SAR level and to specify possible mechanisms leading to alterations in DNA structure.

Some studies have found that oxidative stress may be one possible mechanism of DNA damage. Luukkonen *et al.* [37] found that human SH-SY5Y neuroblastoma cells exposed to 872 MHz RF radiation at 5 W/kg for 1 h exhibited increased DNA breakage. Furthermore, Kesari *et al.* [38] had 45-day-old male Wistar rats exposed for 2 h a day for 60 d to a mobile phone and found that the ROS content showed a positive linear correlation with DNA damage. Megha *et al.* [39] have also reported that prolonged exposure to low intensity microwave radiation at frequencies 900, 1800 and 2450 MHz might lead to oxidative stress and inflammatory imbalances which subsequently contribute to DNA damage in the rat brain, and revealed that increase in frequency could enhance the severity of effect. The results suggested that RF radiation might enhance chemically induced ROS production and thus cause secondary DNA damage. Any exposure, including RF and microwave exposure, which results in increased free radical production may be considered a plausible biological mechanism for carcinogenesis.

Table 3. Genetic effects of microwaves

Time	Author	Microwave Parameter	Experimental Animal	Detection Index	Result
1992	Cleary *et al.* [31]	27 MHz 25 W/kg	glioma cells and lymphocytes	DNA synthesis	increased
1996	Maes *et al.* [32]	945 MHz 1.5 W/kg	human lymphocytes	cytogenetic	cytogenetic damage
2011	Garaj-Vrhovac *et al.* [33]	3, 5.5 and 9.4 GHz	workers	micronuclei, nucleoplasmic bridges and nuclear buds	changed
2016	Zhao *et al.* [35]	2.45 GHz	salmon testes	DNA	inactivation of DNA-based hybrid catalyst
2016	Deshmukh *et al.* [35]	900, 1800, and 2450 MHz	hippocampus tissues of rats	DNA	DNA damage
2011	Trosic *et al.* [36]	915 MHz 2.4 W/m^2	brain, liver and kidney of rats	DNA	DNA breaks
2009	Luukkonen *et al.* [37]	872 MHz 5 W/kg	SH-SY5Y cells	ROS and DNA	ROS production and DNA damage
2014	Kesari *et al.* [38]	3G mobile phone	brain of rats	ROS and DNA	ROS production and DNA damage
2015	Megha *et al.* [39]	900, 1800 and 2450 MHz	brain of rats	ROS and DNA	ROS production and DNA damage

[DOI: 10.52547/ijrr.19.3.483]

Effect of microwaves on gene and protein expression

If microwave radiation produces any biological effects in animals, this result must imply changes in cell behavior, and gene and protein expression. Microwave radiation can result in thermal damage in association with high rates of energy absorption; it has been shown that the effect of microwaves on gene and protein expression relies on non-thermal effects induced by lower intensities of exposure and the details of these results were listed in table 4. For example, Zhao *et al.* [40] demonstrated that following mice whole body exposure to low level microwaves (2100 MHz), 41 genes (0.45 W/kg group), 29 genes (1.8 W/kg group), and 219 genes (3.6 W/kg group) were differentially expressed, primarily involved in learning and memory processes. Furthermore, after exposure at an average power density of 30 mW/cm 2 for 10 min daily for 3 consecutive days, Zhao *et al.* [41] found that microwave induced differentially expressed miRNAs profiles in rats' hippocampus. Genes known to be stress responsive (heat shock and immediate early genes) have been investigated most frequently since the first publication regarding heat shock gene expression in *Caenorhabditis elegans* after exposure to microwaves at intensities too low to elicit any measurable temperature change [42]. However, a number of studies have failed to show a consistent effect on the expression of either genes or proteins following microwave exposure. Calabrò *et al.* [43] investigated SH-SY5Y human neuroblastoma cells exposed to microwaves for 2 and 4 h at 1800 MHz frequency bands. Under their experimental conditions, neither cell viability, heat shock protein 27 (Hsp27) expression nor caspase-3 activity was significantly changed.

That said, special attention has been given to the investigation of the effects of low power microwave radiation (<10 mW/cm^2) on gene and protein expression. In human lymphocytes, 450 MHz fields at around 1.0 mW/cm^2 affected cyclic adenosine monophosphate- (cAMP-) independent protein kinase activity [44]. Furthermore, Yao *et al.* [45] studied cultured rabbit lens epithelial cells exposed to continuous microwave radiation at a frequency of 2450 MHz, and power densities of 0.10, 0.25, 0.50, 1.00 and 2.00 mW/cm^2 for 8 h. They found that the protein expression of $P27^{Kip1}$ (a cyclin-dependent kinase inhibitor and a potential mediator of extracellular antimitogenic signals) that was available for interaction with cyclin-dependent kinases (CDKs) was markedly increased after microwave radiation. However, the mRNA levels were unchanged. In addition, microwave could result in abnormalities in the N -methyl-D-aspartate receptor-postsynaptic density-95-calcium/calmodulin- dependent protein kinase II (NMDAR-PSD95-CaMKII) pathway; Wang *et al.* [46] have demonstrated that the expression and phosphorylation of synapsin I, which could serve as a link between synaptic transmission and the NMDAR-PSD95-CaMKII pathway, was inhibited and altered in pheochromocytoma-12 (PC12) Cells.

Synapses are important structures for information transmission, and neurotransmitters are released as messengers mainly by Ca^{2+}-dependent synaptic vesicle exocytosis. Qiao *et al.* [47] investigated hippocampal synaptosomes in Wistar rats and differentiated (neuronal) PC12 cells exposed to 2.856 GHz microwave radiation for 5 min at a mean power density of 30 mW/cm^2. They found that the expression of phosphorylated synapsin I (p-Syn I) (Ser-553) and gamma-aminobutyric acid (GABA) release were both attenuated after exposure, suggesting that the abnormal release of neurotransmitters after microwave exposure may cause learning and memory deficits. Additionally, Wang *et al.* [48] have shown that although a stable C-to-T variantat nucleotide position −217 of the N-methyl-D-aspartate receptor-2B (NR2B) promoter sequences, a central synaptic receptor subunit, was not induced by exposure to microwave radiation (30 mW/cm^2) for 5 min, NR2B mRNA and protein expression was decreased in the TT genotype rats but not the CC and CT genotype rats, and caused memory impairment.

[DOI: 10.52547/ijrr.19.3.483]

Table 4. Effect of microwaves on gene and protein expression.

Time	Author	Microwave Parameter	Experimental Animal	Detection Index	Result
2015	Zhao *et al.* [40]	2100 MHz 0.45, 1.8 and 3.6 W/kg	mice	gene expression in learning and memory processes	changed
2014	Zhao *et al.* [41]	30 mW/cm2	hippocampus of rats	miRNAs	differentially expressed miRNAs profiles
1998	Daniells *et al.* [42]	750 MHz	*Caenorhabditis elegans*	heat shock gene expression	changed
2012	Calabrò *et al.* [43]	1800 MHz	SH-SY5Y cells	heat shock gene expression	unchanged
1984	Byus *et al.* [44]	450 MHz 1.0 mW/cm^2	human lymphocytes	cAMP-independent protein expression	changed
2004	Yao *et al.* [45]	2450 MHz 0.10, 0.25, 0.50, 1.00 and 2.00 mW/cm2	rabbit lens epithelial cells	mRNA and P27^{Kip1} expression	mRNA: unchanged P27^{Kip1}: increased
2015	Wang *et al.* [46]	30 mW/cm2	PC12 cells.	NMDAR-PSD95-CaMKII pathway	inhibited
2014	Qiao *et al.* [47]	2.856 GHz 30 mW/cm^2	PC12 cells	p-Syn I expression	decreased
2016	Wang *et al.* [48]	30 mW/cm^2	PC12 cells	NR2B mRNA and protein expression	decreased

Microwave irradiation studies in humans and animals

Exposure to high density microwaves may cause detrimental effects on the testis and eye, and induce significant biological changes involving the central nervous system [49], the cardiovascular system [50], the hematopoietic system [51] and the endocrine system [52]. In addition, it can affect uteroplacental function, and development and behavior of the fetus through its thermal action [53]. Guo *et al.* [54] found that various blood cell parameters of Wistar rats exposed to microwave irradiation changed and the bone marrow smear showed obvious destruction after exposure to 200 mW/cm^2 microwave radiation (The details of each article we referenced in this review were listed in table 5).

Table 5. Microwave irradiation studies in humans and animals.

Time	Author	Microwave Parameter	Experimental Animal	Detection Index	Result
2010	Wang *et al.* [49]	30 mW/cm^2	cerebral cortex and hippocampus of rats	central nervous system	changed
2015	Zhu *et al.* [50]	100, 150 and 200 mW/cm^2	heart tissue of rabbits	cardiovascular system	changed
2010	Cao *et al.* [51]	900-MHz	hippocampus of mice	hematopoietic system	changed
2012	Wang *et al.* [52]	2.1 W/kg	urine of rats	endocrine system	changed
2015	Zhao *et al.* [53]	9.417-GHz 2.0 W/kg	fetal of mice	uteroplacental function	changed
2011	Guo *et al.* [54]	200 mW/cm^2	hematopoietic system of rats	bone marrow	changed
1985	Nawrot *et al.* [55]	2.45-GHz 30 mW/cm^2	Pregnant CD-1 mice	fetal toxicity and teratogenicity	teratogenic effects
2010	Kesari and Behari [56]	50 GHz	male rats	sperm glutathione peroxidase (GPx), SOD activity and histone kinase	decreased
2014	Shahin *et al.* [57]	2.45-GHz 0.018 W/Kg	male mice	sperm count and sperm viability	decreased
2018	Wu *et al.* (58)	30 mW/cm^2 and 100 mW/cm^2	testis of rats	TLRs signalling	activated

[DOI: 10.52547/ijrr.19.3.483]

However, there is no epidemiologic evidence showing that occupational or daily life exposure to microwaves harm human reproductive processes, although experimental animal studies have suggested that microwaves can produce intrauterine effects, including teratogenic effects [55]. Kesari and Behari [56] investigated the effects of 50 GHz microwave frequency EMFs on the reproductive systems of male Wistar rats. Their results showed a significant decrease in the levels of sperm glutathione peroxidase (GPx), SOD activity and histone kinase after exposure; furthermore, the results also indicated a decrease in the G_2/M transition phase of the cell cycle in the exposed group. Shahin *et al.* [57] have also shown a decrease in sperm count and sperm viability at a non-thermal low-level 2.45-GHz microwave radiation (CW for 2 h/day for 30 days, power density 0.029812 mW/cm 2 and SAR 0.018 W/Kg) in male mice. Furthermore, Wu *et al.* [58] have demonstrated that Toll-like receptors (TLRs) signaling can be activated by microwave radiation in testis, which may provide novel clues into the preventive and therapeutic strategies for the impairment of spermatogenesis and male fertility by microwave radiation. The authors concluded that radiation may have a significant effect on the reproductive system of male rats, which may relate to male infertility.

CONCLUSION

During recent years there has been increasing public concern regarding the biological effects of microwave radiation emissions from wireless communications. The number of reports on the effects induced by microwave radiation in various cellular and molecular systems continues to increase, attracting public attention toward microwave radiation protection. However, until now no satisfactory mechanism has been proposed to explain the biological effects of these fields. The theories and hypotheses that explain some of the local physiological phenomena have limitations, making it difficult to formulate a specific diagnostic criteria and specific methods of prevention and treatment.

Currently, physical protection is the main measure of EMR protection, including protective clothing with metal wires. In addition, medical interventions through the use of antioxidants are also beneficial for protection against EMR, though specific drugs are lacking. Possible medications include melatonin [28], carnitine, caffeic acid phenethyl ester (CAPE) [59], vitamin C [60] and different kinds of Chinese medicines [61].

Whether mobile phones or other wireless technologies are harmful to humans is still controversial, but research increasingly suggests that they are unlikely to cause brain cancers in adults [62] or affect learning and memory processes [63, 64]. In addition, some studies have even found that microwaves emitted from mobile phones can induce adaptive responses that make animals more resistant to ionizing radiation [65]. That said, efforts should be made to minimize microwave radiation exposure by remaining remote from TV towers, radar stations and other strong radiation areas. Furthermore, while mobile phone use has not been linked to brain cancer, long-term use may be harmful to the eyes [66] and brain [67]. Thus, mobile devices should be kept at a safe distance from the head and, if possible, earphones should be used.

Microwave radiation may also be emitted from microwave ovens, which are widely used for food preparation in daily life. A commonly used frequency in such ovens is 2450 MHz [68]. In general, microwave ovens may be considered a safe form of cooking [68]; however, improper use can damage the eyes or even result in scald injuries and burns [69]. As a safety precaution, a safe distance should be maintained from microwave ovens when in use. Thus, some studies suggest that although current literature lacks definitive evidence associating male infertility with cell phone exposure, limitation of exposure to the possible harmful effects of cell phone, laptop, and microwave ovens is recommended [70].

In conclusion, although the biological effects of microwaves are controversial, future studies regarding the non-thermal effects and

[DOI: 10.52547/ijrr.19.3.483]

mechanisms of microwave radiation are likely to progress our understanding, as well as our comprehension of temporary biological effects that may have long-term impacts on microbial cells, animals and humans. An increased number of studies are paying attention to the biological effects of microwaves and they are expected to increase in number in the future since microwaves have extensive applications in various fields.

Conflicts of interest*: *Declared none.

REFERENCES

1. Rai S, Singh U, Mishra G, Singh S (1994) Effect of water's microwave power density memory on fungal spore germination. *Electromagnetic Biology and Medicine*, ***13(3):*** *247-252*.
2. Williams JM (2016) Biological effects of microwaves: Thermal and nonthermal mechanisms. *Physics,* ***11:*** *49.*
3. Banik S, Bandyopadhyay S, Ganguly S (2003) Bioeffects of microwave--a brief review. *Bioresour Technol*, ***87(2):*** *155-159*.
4. Wang LF, Li X, Gao YB, Wang SM, Zhao L, Dong J, Yao BW, Xu XP, Chang GM, Zhou HM (2015) Activation of VEGF/Flk-1-ERK pathway induced blood-brain barrier injury after microwave exposure. *Molecular Neurobiology*, ***52(1):*** *478-491*.
5. Pall ML (2013) Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. *J Cell Mol Med*, ***17(8):*** *958-965*.
6. Moustafa YM, Moustafa RM, Belacy A, Abou-El-Ela SH, Ali FM (2001) Effects of acute exposure to the radiofrequency fields of cellular phones on plasma lipid peroxide and antioxidase activities in human erythrocytes. *J Pharm Biomed Anal*, **26(4):** 605-608.
7. Shireesh S (2012) Microwave irradiation decreases ATP, increases free [Mg2+], and alters *in-vivo* intracellular reactions in rat brain. *Journal of neurochemistry*, ***5(123):*** *668-75.*
8. Pakhomov AG, Akyel Y, Pakhomova ON, Stuck BE, Murphy MR (1998) Current state and implications of research on biological effects of millimeter waves. *Bioelectromagnetics*, ***19(7):*** *393-413*.
9. Cao G, Liu L-M, Cleary SF (1995) Cell cycle alterations induced by isothermal 27 MHz radio-frequency radiation exposure. *Bioelectrochemistry and Bioenergetics*, ***37(2):*** *131-140*.
10. Luo F, Hou T, Zhang Z, Xie Z, Wu X, Xu J (2012) Effects of pulsed electromagnetic field frequencies on the osteogenic differentiation of human mesenchymal stem cells. *Orthopedics*, ***35(4):*** *e526-531*.
11. Song X-l, Wang C-h, Hu H-y, Y-u C, Bai C (2011) Microwave induces apoptosis in A549 human lung carcinoma cell line. *Chinese Medical Journal-Beijing*, ***124(8):*** *1193*.
12. Zhao L, Li J, Hao YH, Gao YB, Wang SM, Zhang J, Dong J, Zhou HM, Liu SC, Peng RY (2017) Microwave-induced Apoptosis and Cytotoxicity of NK Cells through ERK1/2 Signaling. *Biomedical and Environmental Sciences*, ***30(5):*** *323-332*.
13. Zhang KD, Tong LR, Wang SM, Peng RY, Huang HD, Dong YC, Zhang XX, Li Q, Bai C (2017) Apoptosis of Lewis lung carcinoma cells induced by microwave via p53 and proapoptotic proteins *In-vivo*. *Chinese Medical Journal*, ***130(1):*** *15-22*.
14. Ramundo-Orlando A (2010) Effects of millimeter waves radiation on cell membrane-A brief review. *Journal of Infrared, Millimeter, and Terahertz Waves*, ***31(12):*** *1400-1411*.
15. Zhadobov M, Sauleau R, Vié V, Himdi M, Le Coq L, Thouroude D (2006) Interactions between 60-GHz millimeter waves and artificial biological membranes: dependence on radiation parameters. *Microwave Theory and Techniques, IEEE Transactions on*, ***54(6):*** *2534-2542*.
16. Geletyuk VI, Kazachenko VN, Chemeris NK, Fesenko EE (1995) Dual effects of microwaves on single Ca(2+)-activated K+ channels in cultured kidney cells Vero. *FEBS Lett*, ***359(1):*** *85-88*.
17. Carole R (2014) Thermal and nonthermal effects of discontinuous microwave exposure (2.45 gigahertz) on the cell membrane of Escherichia coli. *Applied and Environmental Microbiology*, ***16(80):*** *4832-41.*
18. Zeng SW, Huang QL, Zhao SM (2014) Effects of microwave irradiation dose and time on Yeast ZSM-001 growth and cell membrane permeability. *Food Control*, ***46:*** *360-367*.
19. Ferreira AR, Bonatto F, de Bittencourt Pasquali MA, Polydoro M, Dal-Pizzol F, Fernández C, De Salles AA, Moreira JC (2006) Oxidative stress effects on the central nervous system of rats after acute exposure to ultra high frequency electromagnetic fields. *Bioelectromagnetics*, ***27(6):*** *487-493*.
20. Wang C, Zhou H, Peng R, Wang L, Su Z, Chen P, Wang S, Wang S, Liu Y, Cong J (2013) Electromagnetic pulse reduces free radical generation in rat liver mitochondria *in-vitro*. *Free Radic Res*, ***47(4):*** *276-282*.
21. Wang C, Zhou H, Wang L, Wang S, Xu X, Chen P, Wu K, Peng R, Hu X (2015) Pulsed microwave exposure real time and dynamically reduces reactive oxygen species in rat pheochromocytoma cells *in-vivo*. *Microwave & Optical Technology Letters*, ***57(10):*** *2395-2400.*
22. Yao K, Wu W, Wang K J, Ni S, Ye P P, Yu Y B, Ye J, Sun L X (2008) Electromagnetic noise inhibits radiofrequency radiation-induced DNA damage and reactive oxygen species increase in human lens epithelial cells. *Molecular Vision*, ***14(112-15):*** *964-969*.
23. Yurekli AI, Ozkan M, Kalkan T, Saybasili H, Tuncel H, Atukeren P, Gumustas K, Seker S (2006) GSM base station elec-

[DOI: 10.52547/ijrr.19.3.483]

tromagnetic radiation and oxidative stress in rats. *Electromagnetic Biology and Medicine*, **25(3):** *177-188*.
24. Esmekaya MA, Ozer C, Seyhan N (2011) 900 MHz pulse-modulated radiofrequency radiation induces oxidative stress on heart, lung, testis and liver tissues. *General Physiology and Biophysics*, **30(1):** *84-89*.
25. Narayanan SN, Kumar RS, Bhat PG, Kedage V, Nalini K, Nayak S (2014) Evaluation of oxidant stress and antioxidant defense in discrete brain regions of rats exposed to 900 MHz radiation. *Bratislavské Lekárske Listy*, **115(5):** *260 -266*.
26. Xing F, Zhan Q, He Y, Cui J, He S, Wang G (2016) 1800MHz microwave induces p53 and p53-mediated caspase-3 activation leading to cell apoptosis *in-vitro*. *Plos One*, **11(9):** *e0163935*.
27. Zhao YY, Wu Q, Wu ZB, Zhang JJ, Zhu LC, Yang Y, Ma SL, Zhang SR (2018) Microwave hyperthermia promotes caspase-3-dependent apoptosis and induces G2/M checkpoint arrest via the ATM pathway in non-small cell lung cancer cells. *International Journal of Oncology*, **53(2):** *539-550.*
28. Kesari KK, Jamal QMS, Sharma A, Chauhan P, Dhasmana A, Siddiqui MH, Sisodia R, Verma HN (2017) LPO and ROS production in rat brain exposed to microwaves: Computational elucidation of melatonin in repair system. *Perspectives in Environmental Toxicology,* **3:** *31-46.*
29. Shahinjafari A, Bayat M, Shahhosseiny MH, Tajik P, Roudbarmohammadi S (2016) Effect of long-term exposure to mobile phone radiation on alpha-Int1 gene sequence of Candida albicans. *Saudi Journal of Biological Sciences*, **23 (3):** *426-433*.
30. Tice RR, Hook GG, Donner M, McRee DI, Guy AW (2002) Genotoxicity of radiofrequency signals. I. Investigation of DNA damage and micronuclei induction in cultured human blood cells. *Bioelectromagnetics*, **23(2):** *113-126*.
31. Cleary S F, LIU L M, Cao G (1992) Effects of RF power absorption in mammalian cells. *Annals of the New York Academy of Sciences*, **649(1):** *166-175*.
32. [32]. Maes A, Collier M, Slaets D, Verschaeve L (1996) 954 MHz microwaves enhance the mutagenic properties of mitomycin C. *Environ Mol Mutagen*, **28(1):** *26-30*.
33. Garaj-Vrhovac V, Gajski G, Pažanin S, Šarolić A, Domijan A-M, Flajs D, Peraica M (2011) Assessment of cytogenetic damage and oxidative stress in personnel occupationally exposed to the pulsed microwave radiation of marine radar equipment. *International Journal of Hygiene and Environmental Health*, **214(1):** *59-65*.
34. Zhao H and Shen K (2016) Microwave-induced inactivation of DNA-based hybrid catalyst in asymmetric catalysis. *International Journal of Biological Macromolecules*, **84:** *367-371*.
35. Deshmukh PS, Megha K, Nasare N, Banerjee BD, Ahmed RS, Abegaonkar MP, Tripathi AK, Mediratta PK (2016) Effect of low level subchronic microwave radiation on rat brain. *Biomedical and Environmental Sciences*, **29(12):** *858 -867*.
36. Trosic I, Pavicic I, Milkovic-Kraus S, Mladinic M, Zeljezic D (2011) Effect of electromagnetic radiofrequency radiation on the rats' brain, liver and kidney cells measured by comet assay. *Coll Antropol*, **35(4):** *1259-1264*.
37. Luukkonen J, Hakulinen P, Mäki-Paakkanen J, Juutilainen J, Naarala J (2009) Enhancement of chemically induced reactive oxygen species production and DNA damage in human SH-SY5Y neuroblastoma cells by 872MHz radiofrequency radiation. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, **662(1):** *54-58*.
38. Kesari KK, Meena R, Nirala J, Kumar J, Verma HN (2014) Effect of 3G cell phone exposure with computer controlled 2-D stepper motor on non-thermal activation of the hsp27/p38MAPK stress pathway in rat brain. *Cell Biochemistry & Biophysics*, **68(2):** *347-358*.
39. Megha K, Deshmukh PS, Banerjee BD, Tripathi AK, Ahmed R, Abegaonkar MP (2015) Low intensity microwave radiation induced oxidative stress, inflammatory response and DNA damage in rat brain. *Neurotoxicology*, **51(***158-165*.
40. Zhao Y, Xian H, Dong, L, Jiang G, Yang Z (2015) The screening of genes sensitive to long-term, low-level microwave exposure and bioinformatic analysis of potential correlations to learning and memory. *Biomedical & Environmental Sciences*, **28(8):** *558-570*.
41. Zhao L, Sun C, Xiong L, Yang Y, Gao Y, Wang L, Zuo H, Xu X, Dong J, Zhou H (2014) MicroRNAs: Novel mechanism involved in the pathogenesis of microwave exposure on Rats' Hippocampus. *Journal of Molecular Neuroscience*, **53 (2):** *222-230*.
42. Daniells C, Duce I, Thomas D, Sewell P, Tattersall J, de Pomerai D (1998) Transgenic nematodes as biomonitors of microwave-induced stress. *Mutation Research/ Fundamental and Molecular Mechanisms of Mutagenesis*, **399(1):** *55-64*.
43. Calabro E, Condello S, Curro M, Ferlazzo N, Caccamo D, Magazu S, Ientile R (2012) Modulation of heat shock protein response in SH-SY5Y by mobile phone microwaves. *World J Biol Chem*, **3(2):** *34-40*.
44. Byus CV, Lundak RL, Fletche RM, Adey WR (1984) Alterations in protein kinase activity following exposure of cultured human lymphocytes to modulated microwave fields. *Bioelectromagnetics*, **5(3):** *341-351*.
45. Yao K, Wang K J, Sun Z H, Tan J, Xu W, Zhu L J, Lu D Q (2004) Low power microwave radiation inhibits the proliferation of rabbit lens epithelial cells by upregulating P27Kip1 expression. *Mol Vis*, **10(25):** *138-143*.
46. Wang LF, Wei L, Qiao SM, Gao XN, Gao YB, Wang SM, Zhao L, Dong J, Xu XP, Zhou HM (2015) Microwave-induced structural and functional injury of hippocampal and PC12 cells is accompanied by abnormal changes in the NMDAR-PSD95-CaMKII pathway. *Pathobiology Journal of Immunopathology Molecular & Cellular Biology*, **82(5):** 181.
47. Qiao S, Peng R, Yan H, Gao Y, Wang C, Wang S, Zou Y, Xu X, Zhao L, Dong J (2014) Reduction of phosphorylated synapsin I (Ser-553) leads to spatial memory impairment by attenuating GABA release after microwave exposure in Wistar rats. *Plos One*, **9(4):** *e95503*.
48. Wang L F, Tian D W, Li H J, Gao Y B, Wang C Z, Zhao L, Zuo H Y, Dong J, Qiao S M, Zou Y (2016) Identification of a novel Rat NR2B subunit gene promoter region variant and its

[DOI: 10.52547/ijrr.19.3.483]

association with microwave-induced neuron impairment. *Molecular Neurobiology*, ***53(4):*** *2100-2111*.
49. Wang L, Peng R, Hu X, Gao Y, Wang S, Zhao L, Dong J, Su Z, Xu X, Gao R (2010) Abnormality of synaptic vesicular associated proteins in cerebral cortex and hippocampus after microwave exposure. *Synapse*, ***63(11):*** *1010-1016*.
50. Zhu W, Shen N, Zhong X, Hou J, Lü S, Cai J (2015) [The cardiac injury effect of microwave radiation on rabbit and its mechanism]. *Wei sheng yan jiu = Journal of Hygiene Research*, ***44(5):*** *818*.
51. Cao Y, Xu Q, Jin ZD, Zhang J, Lu MX, Nie JH, Tong J (2010) Effects of 900-MHz microwave radiation on γ-Ray-induced damage to mouse hematopoietic system. *Journal of Toxicology & Environmental Health Part A*, ***73(7):*** *507-513*.
52. Wang LF, Hu XJ, Peng RY, Wang SM, Gao YB, Dong J, Zhao L, Li X, Zuo HY, Wang CZ (2012) Application of 1H-NMR-based metabolomics for detecting injury induced by long-term microwave exposure in Wistar rats' urine. *Analytical & Bioanalytical Chemistry*, ***404(1):*** *69-78*.
53. Zhang Y, Li Z, Gao Y, Zhang C (2015) Effects of fetal microwave radiation exposure on offspring behavior in mice. *Journal of Radiation Research*, ***56(2):*** *261-268*.
54. [54]. Guo S, Wang X, Xu J, Lei J, Sun K, Jiang X, Xu H, Lü S (2011) [Effect of microwave radiation on the rat hematopoietic system]. *Wei sheng yan jiu= Journal of Hygiene Research*, ***40(2):*** *223-226*.
55. Nawrot P, McRee D, Galvin M (1985) Teratogenic, biochemical, and histological studies with mice prenatally exposed to 2.45-GHz microwave radiation. *Radiation Research*, ***102(1):*** *35-45*.
56. Kesari KK, Behari J (2010) Microwave exposure affecting reproductive system in male rats. *Applied Biochemistry and Biotechnology*, ***162(2):*** *416-428*.
57. Shahin S, Mishra V, Singh SP, Chaturvedi CM (2014) 2.45-GHz microwave irradiation adversely affects reproductive function in male mouse, Mus musculus by inducing oxidative and nitrosative stress. *Free Radical Research*, ***48(5):*** *511-525*.
58. Wu H, Wang D, Meng Y, Ning H, Liu X, Xie Y, Cui L, Wang S, Xu X, Peng R (2018) Activation of TLR signalling regulates microwave radiation-mediated impairment of spermatogenesis in rat testis. *Andrologia*, ***50(Suppl. 1):*** *e12828*.
59. Zaeemzadeh N, Hemmati A, Arzi A, Jalali M, Rashidi I (2011) Protective Effect of Caffeic Acid Phenethyl Ester (CAPE) on Amiodarone-Induced Pulmonary Fibrosisin Rat. *Iran J Pharm Res*, ***10(2):*** *321-328*.
60. Mortazavi SMJ, Foadi M, Mozdarani H, Haghani M, Mosleh -Shirazi MA, Abolghasemi P, Nematollahi S, Sharifzadeh S (2015) Future role of vitamin C in radiation mitigation and its possible applications in manned deep space missions: Survival study and the measurement of cell viability. *Int J Radiat Res*, ***13(1):*** *55-60*.
61. Zhang X, Gao Y, Dong J, Wang S, Yao B, Zhang J, Hu S, Xu X, Zuo H, Wang L (2014) The compound Chinese medicine "Kang Fu Ling" protects against high power microwave-induced myocardial injury. *Plos One*, ***9(7):*** *e101532*.
62. Swerdlow AJ, Maria F, Green AC, Leeka Kheifets LK, Savitz DA (2011) Mobile phones, brain tumors, and the interphone study: Where are we now? *Environmental Health Perspectives*, ***119(4):*** *232–233*.
63. Bolouri B and Fathollahi Y (2007) Low-power density of 950 MHz radiation does not affect long-term potentiation in rat dentate gyrus. *Int J Radiat Res*, ***5(3):*** *119-124*.
64. Jadidi M, Firoozabadi SM, Rashidy A (2009) Does whole body exposure to GSM-950 MHz electromagnetic fields affect acquisition and consolidation of spatial information in rats? *Int J Radiat Res*, ***7(1):*** *57-62*.
65. Haghani M, Mortazavi S M J, Sardari D, Mosleh-Shirazi M A, Mansouri A (2013) Assessment of the role of specific absorption rate of mobile phones on the induction of microwave-induced survival adaptive responses after exposure to lethal doses of gamma radiation. *Int J Radiat Res*, ***11(3):*** *167-173*.
66. Balci M, Devrim E, Durak I (2007) Effects of mobile phones on oxidant/antioxidant balance in cornea and lens of rats. *Current Eye Research*, ***32(1):*** *21*.
67. Levis AG, Minicuci N, Ricci P, Gennaro V, Garbisa S (2011) Mobile phones and head tumours. The discrepancies in cause-effect relationships in the epidemiological studies - how do they arise? *Environmental Health*, ***10(1):*** *1-15*.
68. Jensh RP (1997) Behavioral teratologic studies using microwave radiation: is there an increased risk from exposure to cellular phones and microwave ovens? *Reproductive Toxicology*, **11*(4):*** *601-611*.
69. Inaloz S S, Aksunger A, Sari I, Dasdag S, Deveci E (1997) Do microwave ovens affect eyes? *Japanese Journal of Ophthalmology*, ***41(4):*** *240-243(244)*.
70. Mcgill JJ and Agarwal A (2014) The impact of cell phone, laptop computer, and microwave oven usage on male fertility. *Male Infertility,* ***7:*** *161-177.*

[DOI: 10.52547/ijrr.19.3.483]