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Review

Effects of electromagnetic fields exposure on the antioxidant defense system

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ABSTRACT

Technological devices have become essential components of daily life. However, their deleterious effects on the body, particularly on the nervous system, are well known. Electromagnetic fields (EMF) have various chemical effects, including causing deterioration in large molecules in cells and imbalance in ionic equilibrium. Despite being essential for life, oxygen molecules can lead to the generation of hazardous by-products, known as reactive oxygen species (ROS), during biological reactions. These reactive oxygen species can damage cellular components such as proteins, lipids and DNA. Antioxidant defense systems exist in order to keep free radical formation under control and to prevent their harmful effects on the biological system. Free radical formation can take place in various ways, including ultraviolet light, drugs, lipid oxidation, immunological reactions, radiation, stress, smoking, alcohol and biochemical redox reactions. Oxidative stress occurs if the antioxidant defense system is unable to prevent the harmful effects of free radicals. Several studies have reported that exposure to EMF results in oxidative stress in many tissues of the body. Exposure to EMF is known to increase free radical concentrations and traceability and can affect the radical couple recombination. The purpose of this review was to highlight the impact of oxidative stress on antioxidant systems.

1. Introduction

Electromagnetic fields (EMF) are emitted by many natural and man-made sources that play important roles in daily life. More than 3 billion people across the world are exposed to EMF every day [1]. Lifetime exposure to EMF is becoming the subject of significant scientific investigation since it has the potential to cause crucial changes and deleterious effects in biological systems. The biological impacts of EMF can be classified as thermal and non-thermal. Thermal effects are associated with the heat created by EMFs in a certain area. This mechanism occurs via an alteration in temperature deriving from radiofrequency (RF) fields. It is possible that every interaction between RF fields and living tissues causes an energy transfer resulting in a rise in temperature. The skin and other superficial tissues usually absorb the non-thermal radiations emitted by mobile phones; this causes the insignificant increase of temperature of the brain or other organs in the body [2]. Nonthermal mechanisms are those that are not directly associated with this temperature change but rather to some other changes in the tissues in association with the amount of energy absorbed [3,4]. Studies on the health effects of RF energy from communication systems have revealed that non-thermal effects should also be discussed. The fact that the possible biophysical mechanisms of RF-EMF interaction with living cells have not yet been fully elucidated is one of the reasons for these discussions [4]. A significant part of many studies concerning EMF have investigated the "non-thermal" effects of RF on biological tissues [5,6]. It has been observed that this effect is mediated by generation of reactive oxygen species (ROS) [7]. ROS are involved in various cellular functions. They can be essential or extremely toxic to cellular homeostasis [8]. Their cytotoxic effects derive from peroxidation of membrane phospholipids. This creates a change in the conductivity of the membrane and loss of membrane integrity [9]. Exposure to EMF has been observed to cause increased free radical production in the cellular environment. Living organisms have anti-oxidative mechanisms, such as glutathione (GSH), glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD), in order to alleviate the damage caused by ROS and their products [10]. This defense mechanism acts by sup-

Abbreviations: EMF, electromagnetic fields; RF, radiofrequency; ROS, reactive oxygen species; GSH, glutathione; GPx, glutathione peroxidase; GR, glutathione reductase; GST, glutathione S-transferase; CAT, catalase; SOD, superoxide dismutase; HSP, heat shock protein; EMF/RFR, electromagnetic frequency and radiofrequency exposures; ELF-EMFs, exposure to extremely low frequency; MEL, melatonin; FA, folic acid; MDA, malondialdehyde.

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pressing or impairing the chain reaction triggered by ROS. In this case, antioxidant defense mechanisms are impaired by being subjected to an agent that causes overproduction of ROS, including EMF, thus resulting in oxidative stress [11,12]. Studies in recent years have reported that free radicals play a major role in the mechanism behind many diseases, such as diabetes and cancer [13–15]. However, there is still much uncertainty on the subject, and several questions remain to be answered.

This review evaluated the effect of exposure to EMF on biological tissues by concentrating on alterations in several antioxidant enzyme activities and different parameters of oxidation.

2. Electromagnetic field effects

A wide spectrum of electromagnetic waves are today emitted by radar, communication equipment, mobile phone base stations, high voltage lines, radio and television transmitters, substations, and electrical equipment at home and work, in addition to many electrical systems in the environment [16]. The Global System for Mobile Communications (GSM, 850–900 MHz and 1850–1990 MHz) is currently the most extensive system for mobile telecommunications worldwide [17,18]. The mobile phone models (1800 MHz −2200 MHz), laptops (1000 MHz–3600 MHz) and wireless networks in use today function with high frequency (2.45 GHz) microwave radiation [19]. In parallel to technological developments in this century, technological devices are becoming ever more important in daily life. However, despite making life easier, they may also cause a number of health problems. In particular, the average age of beginning mobile phone use has decreased rapidly to elementary school age, and durations of exposure to EMF are also increasing. One study reported that extremely low exposure to EMF from mobile phones may cause health problems [20]. Several studies have reported findings such as stress, headache, tiredness, anxiety, decreased learning potential, impairment in cognitive functions and poor concentration in case of exposure to microwave radiation emitted from mobile phones [2,21,22]. EMFs influence metabolic processes in the human body and exert various biological effects on cells through a range of mechanisms. EMF disrupts the chemical structures of tissue since a high degree electromagnetic energy absorption can change the electric current in the body [23]. As a result of this exposure, the functions of organs are affected. Electric fields exert an oscillatory force on every free ion on the both sides of the plasma membrane and cause them to cross it. This movement of ions causes deterioration in the ion channels on the membrane, biochemical changes in the membrane and consequently impairment of all cellular functions [24].

Exposure to EMFs can damage biological tissues by inducing changes, which can be explained in terms of thermal or non-thermal mechanisms [25]. Thermal effects can occur with the conversion and absorption of heat by the body's electromagnetic energy. Increased body temperature is stabilized and alleviated by blood circulation. Although non-thermal effects do not raise the body temperature sufficiently to impair the structure of tissues, their effects can still be seen as an increase in free radical production in tissues [3]. EMFs, no matter where they occur in the frequency spectrum, are reported to causes a rise in levels of oxygen free radicals in an experimental environment in plants and humans [26].

3. EMF-related oxidative stress and effects on tissue

Free radicals are reactive molecules produced during the conversion of foods into energy through oxygen. The formation of free radicals is an oxidation reaction that occurs on an oxygen basis. [27]. Since oxygen is essential for survival, the formation of free radicals cannot be avoided. However, factors including ionizing and non-ionizing radiation alter the transcription and translation of genes such as JUN, HSP 70 and MYC, via the epidermal growth factor receptor EGFR-ras, leading to the generation of ROS [28,29] and resulting in the overproduction of ROS in tissues [30].

The Fenton reaction is a catalytic process that converts hydrogen peroxide, a product of mitochondrial oxidative respiration, into a highly toxic hydroxyl free radical. Some studies have suggested that EMF is another mechanism through the Fenton reaction, suggesting that it promotes free radical activity in cells [31,32]. Although some researchers have reported that ROS perform beneficial function, a high degree of ROS production may cause cellular damage, resulting in a range of diseases. These radicals react with various biomolecules, including DNA (Fig. 1). Namely, the energy of free radicals is not enough, and for this reason they behave like robbers who seize energy from other cells and rob a person to satisfy themselves [33]. Many studies have suggested that EMF may trigger the formation of reactive oxygen species in exposed cells in vitro [34–37] and in vivo [7,31,38]. The initial stage of the ROS production in the presence of RF is controlled by the NADPH oxidase enzyme located in the plasma membrane. Consequently, ROS activate matrix metalloproteases, thereby initiating intracellular signaling cascades to warn the nucleus of the presence of external stimulation. These changes in transcription and protein expression are observed after RF exposure [39]. Kazemi et al. investigated the effect of exposure to 900-MHz on the induction of oxidative stress and the level of intracellular ROS in human mononuclear cells. Excessive elevation in ROS levels is an important cause of oxidative damage in lipids and proteins and nucleic acids. It therefore causes changes in enzyme activity and gene expression, eventually leading to various diseases, including sleep disorder, arthrosclerosis, loss of appetite, diabetes, dizziness, rheumatoid arthritis, cardiovascular disease, nausea and stroke [40–42]. In addition, degradation of the pro-oxidant-antioxidant balance due to an uncontrolled increase in ROS may also result in lipid peroxidation. Lipid peroxidation is the process in which cell membranes are rapidly destroyed due to the oxidation of components of phospholipids containing unsaturated fatty acids. By continuing this reaction, lipid peroxides (-C0, H) accumulate in the membrane, and transform polyunsaturated fatty acids into biologically active substances [43]. Consequently, lipid peroxidation leads to significant damage in the cells, such as disturbances in membrane transport, structural changes, cell membrane fluidity, damage to protein receptors in membrane structures, and changes in the activity of cell membrane enzymes [44]. Hoyto et al. demonstrated significant induction of lipid peroxidation after exposure to EMF in the mouse SH-SY5Y cell and L929 fibroblast cells [45]. Epidemiological studies have also suggested that oxidative damage to lipids in blood vessel walls may be a significant contributor to the development of atherosclerosis [46–48].

Studies generally focus on the brain, since cell phones are held close to the head during use. There is considerable evidence that EMF can affect neural functions in the human brain [50]. The relation between EMF and neurological disorders can be explained in terms of the heat shock response [51]. The heat shock protein (HSP) response is generally concerned with heat shock, exposure to heavy metals and environmental insults such as EMF. Generally, HSP is a marker in cells under stress. Living organisms generate stress proteins in order to survive environmental stressors. The heat shock response is regarded as a general response to a wide variety of stresses, such as oxidative stress [52]. In humans and other mammals, many environmental stimuli causes ultraviolet radiation [53], ionizing radiation [54] and laser radiation [55] are caused by cellular stresses and alter Hsp90 and 70 levels. Non-ionizing radiation also causes HSP changes in various tissues, including the brain [56], myocardium [57], testis [5] and skin [58]. Studies have described these findings as an adaptation or readjustment of cellular stress

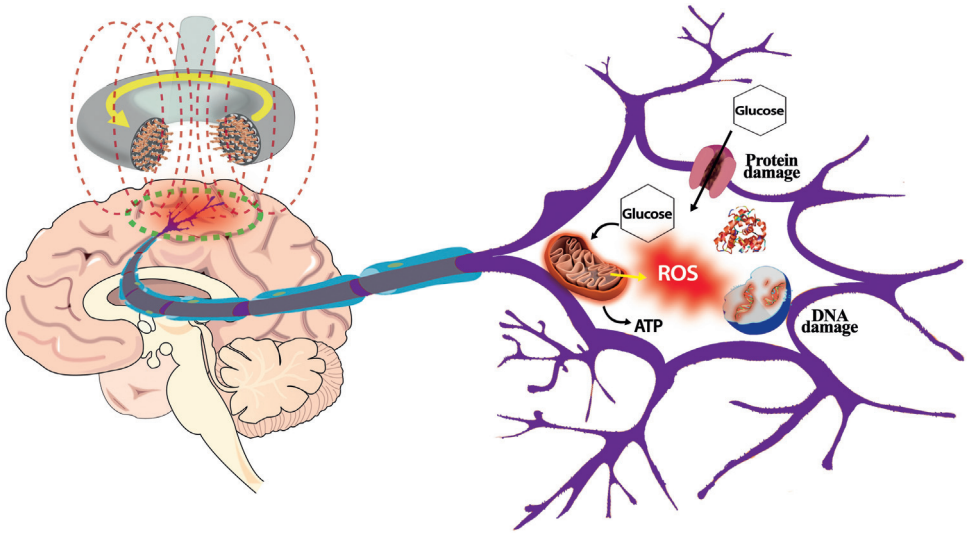

Fig 1. Reactive oxygen species generated by the effects of exposure to EMF can damage various cellular structures in neurons of the central nervous system [49].

proteins before preparing the cellular machinery for an adequate environmental change. Small, transitory readjustments of the circuits may thus decisively influence overall stress tolerance [59,60].

Low frequency (0–300 Hz) and RF (10 MHz–300 GHz) EMF has also been reported to alter the permeability of the blood–brain barrier [61–63]. At the same time, these changes in the blood-brain barrier may lead to excess accumulation of heavy metals and specifically of iron in the brain. This effect may trigger several neuronal disorders [64,65]. Some studies have reported that DNA damage and blood–brain barrier disruption is connected, and that autism spectrum conditions are associated with EMF exposure. The disruption of fertility and reproduction associated with EMF/RFR may also be related to the increasing incidence of autism spectrum conditions [66–68].

Oxidative stress plays an important role in DNA damage process, general and specific gene expression and cell apoptosis. The brain has a high metabolic rate, making it more prone to damage by ROS and oxidative damage compared to other organs [69]. Excessive amounts of ROS in tissues may lead to necrosis, the death of neurons and neuronal damage in brain tissue, as well as to neurological disorders such as Alzheimer's disease, spinal cord injury, multiple sclerosis, and epilepsy [70] (Fig. 2). Several studies have observed neuronal damage and cellular losses caused by exposure to EMF in many regions of the brain, including the cortex, basal ganglia, hippocampus and cerebellum [71–75]. One epidemiological study determined an association between amyotrophic lateral sclerosis and exposure to high intensity EMF, but no correlation was observed with other neurodegenerative diseases [76]. Rubin et al. noted that the pain level of headache may increase during exposure but decreased immediately when exposure ceased [77]. Haynal and Regli suggested that exposure to extremely low frequency (ELF)-EMF may be linked to amyotrophic lateral sclerosis, a fatal neurodegenerative disorder [78]. Maskey et al. investigated the effects on the brain of 835-MHz over different exposure times and observed a significant loss of pyramidal cells in the CA1 region of the hippocampus [79]. Another case control study by Villeneuve et al. reported a 5.3-fold increased risk of one brain cancer type, glioblastoma, in individuals exposed to EMF, but no increased risk for other brain cancers [80].

Some studies have shown that microwave exposure failed to induce a detectable genotoxic effect by itself, and have reported interference with DNA-repair mechanisms [82–85]. Oxidative damage in DNA occurs as a result of interaction between free radicals and DNA, with the addition of bases or abstractions of hydrogen atoms from sugar moiety. Modified nucleotides emerge as products of damage (8-OH-dG) when DNA is modified by the oxidative damage caused by reactive oxygen molecules [86]. These products are markers of oxidative stress measured using analytical methods [87,88]. Agarwal and Saleh and Aitken et al. have reported that ROS may have harmful effects on sperm DNA and other biomolecules, proteins and lipids, consequently leading to male infertility [89,90].

At the same time, men carrying phones in their pocket or on their belt and therefore, most of adverse effects of the EMF are seen in reproductive organs. Sepehrimanesh et al. showed that exposure to RF-EMF produces increases in testicular proteins in adults that are related to carcinogenic risk and reproductive damage [6]. Neuroendocrine changes caused by EMFs are a key factor in changing hormone functions [91]. Eroğlu et al. stated that exposure to cell phone radiation reduces the motility and changes the morphology of isolated sperm cells. They also discussed the effects of EMFs on female infertility [92]. Goldhaber et al. reported a significant increase in fetal abnormalities and spontaneous abortions in pregnant women exposed to EMF [93]. Many of these effects may occur due to hormonal changes [94,95].

Studies on the effects of EMF on tissues discussed here are set out in Tables 1 and 2.

4. The antioxidant defense system and EMF

Antioxidant defense systems have developed in organisms to control the formation of free radicals and to prevent the harmful effects of these molecules [122]. These antioxidants reduce or impair the damage mechanism of ROS via their free radical scavenging activities [123]. Two major mechanisms have been identified for antioxidants [124]. The first is a mechanism of chain disruption in which the primary antioxidant releases an electron to the free radical found in the systems. The second mechanism includes elimination of the initiators of species of ROS/reactive nitrogen (secondary antioxidants) by suppressing chain-initiating catalysts. Antioxidants may also impact on biological systems by various mechanisms involving electron releasing, metal ion chelation, co-antioxidants, or by maintaining the expression of genes [125]. If these antioxidant defense mechanisms are impaired through exposure to an agent that causes the overproduction of ROS, including EMF, antioxidants may not be sufficient or free radical formation may increase to such an extent that it overpowers the defense

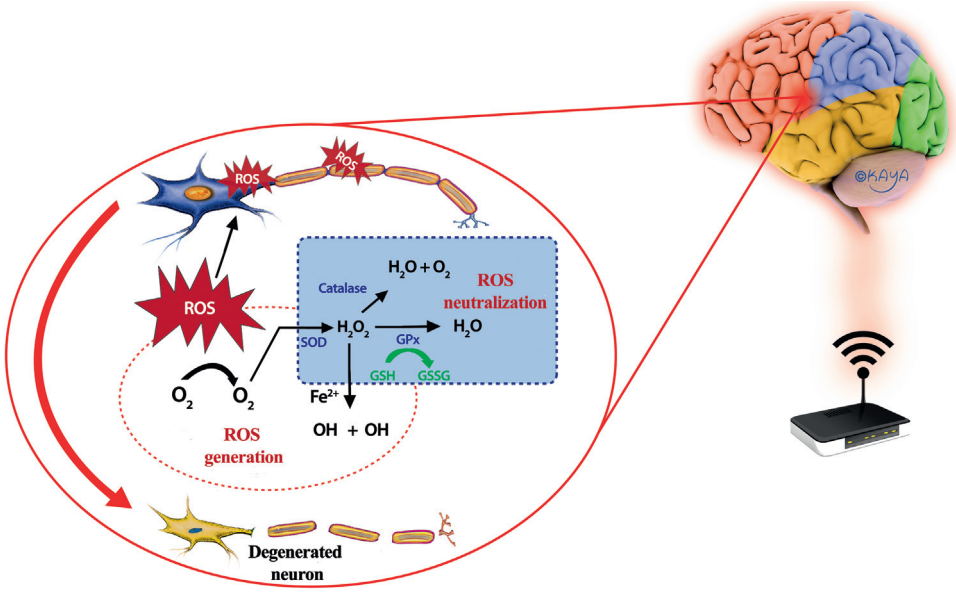

Fig. 2. The role of EMF emitted from several devices, depicting an increase in the generation of ROS and consequent oxidative stress in the central nervous system resulting from the inability of the antioxidant defense system to cope with this increase in ROS [81].

capabilities of antioxidants [10]. This is known as oxidative stress. EMFs can initiate various biochemical and physiological changes, including oxidative stress, in the systems of various species. Several studies in the literature show that plasma membrane receptors are possible targets for field interactions [126,127].

Generally, antioxidants have been divided into exogenous groups (carotene, C, and vitamin E), and endogenous groups (melatonin (MEL)), SOD, GSH-Px, CAT, including; protein (MEL), vitamins (vitamin C), trace elements (Mg, Se), complexes of compound, hydrophilic (ascorbic acid, urate, flavonoids) and hydrophobic (β-carotene, α-tocopherol) substances, with direct impacts (SOD, CAT), and indirect effects (vitamin E). Substances with functions concerning the membrane (vitamin A and E, β- carotene), circulation (vitamin C, amino acids and polyphenols), cytosol (co-enzyme Q10) are classified as antioxidants [122,128].

4.1. Glutathione

Glutathione (GSH) is an endogenous antioxidant and an important cellular defense agent against oxidative damage. GSH reacts with the free radicals in the cell and reduces the entry of hydrogen peroxides [129]. GSH also prevents the oxidization of sulfhydryl groups in the protein structure. GSH levels in tissues are often used as a marker for measuring radical damage. It acts as a substrate for antioxidant enzymes that causes resistance to radical-induced damage, behaving like a radical scavenger. GSH is especially important for the activity of glutathione peroxidase (GSH-Px), glutathione reductase (GR) and glutathione-S-transferase (GST). In the oxidative stress process, levels of GSH decrease, while glutathione disulfide increases. In this case, accumulation of hydrogen peroxide (H_2O_2) is scavenged by the effects of reductase and glutathione peroxidase (GSH-Px). GSH-Px is also an important enzyme, which prevents damage to phagocytic cells caused by free radicals. A decrease in GSH-Px activity leads to the accumulation of hydrogen peroxide and to cell damage. GSH-Px also prevents the initiation of lipid peroxidation [65]. EMF emitted by cellular phones is known to be related to a decreased level of GSH in brain tissue and blood [97]. However, a decreased level of blood GSH may possibly be explained by an elevated oxidation rate and use of GSH during the elimination of lipid and other peroxides [130]. Awad and Hassan investigated the brains of rats exposed to 900-MHz EMF from mobile phones for 1 h/day for one week. They observed an increase in lipid peroxidation after exposure to mobile phones [131]. Aydın and Akar studied the effect of 900-MHz EMF for 2 h/day for 45 days on lymphoid organs in immature and mature rats. They reported that CAT and GPx activities decreased significantly compared to a control group. Similarly, an increase in lipid peroxidation and a concomitant demolition in GSH levels were seen in all lymphoid organs after EMF exposure, suggesting that increased levels of lipid peroxidation may have been a consequence of depleted GSH stores [32]. Luo et al. investigated that the whether the protective effects of LSPCs performed by oral gavage on oxidative stress injury induced by ELF-EMF exposure. According the results, GST activity was significantly decreased in the ELF-EMF group when compared with the control group. They found that LSPCs could effectively prohibit oxidative stress damage induced by ELF-EMF exposure, it may be related to the ability to remove free radicals and induce antioxidant enzyme activity [132]. Singh et al. investigated the biochemical mechanism of the interaction of 900-MHz mobile phone EMF with root formation in mung bean hypocotyls. The obtained results showed up regulation of the activities of antioxidant enzymes such as CAT and GR, which protect against oxidative damage induced by EMF [133]. Sepehrimanesh et al. studied that effect of 900-MHz electromagnetic field (EMF) exposure on rat serum and testes antioxidant enzyme levels. They observed that after 30 days exposure both SOD and GPx activities decreased in the long-time EMF exposure group [134]. In the other study RF-EMF exposure caused increase antioxidant stress response via increase of CAT and GR activity it lead to the generation of lipid and protein oxidative damage [135].

4.2. Catalase

CAT is a common enzyme present in organisms exposed to oxygen, such as vegetables, fruits and animals. It catalyzes the reaction that degrades hydrogen peroxide to water and oxygen. It is a crucial enzyme in the protection of the cell against oxidative damage caused by ROS. CAT exerts its peroxidase activity in vivo. It can also catalyze the reaction of oxidation, by hydrogen peroxide, of numerous metabolites and toxins, not excluding formaldehyde, formic acid, phenols, acetaldehyde and alcohols. Its basic function is to remove hydrogen peroxide and peroxide ROOH in molecular oxygen in order to prevent irreversible damage to the membranes

Table 1
Some experimental studies on the oxidative effects of EMF.

Reference	Biological endpoint	Results
Ghodbane et al. [96]	Kidney	In the study investigated that whether Static magnetic fields induces oxidative stress and apoptosis in rat tissues and to evaluate the possible protector effect of selenium (Se) and vitamin E (vit E) supplementation. In the results have been shown exposure to SMF induced oxidative stress in kidney that will be able prevented by treatment with Se or vit E.
Meral et al. [97]	Brain	890-915-MHz EMF emitted by cellular phones may generate oxidative stress. MDA levels increased and GSH level and CAT enzyme activity decreased, while vitamin A, E and D3 levels remained unchanged in the brain tissue of guinea pigs
Misa-Agustiño et al. [98]	Thymus	The thymus tissue exhibited several morphological changes, including increased distribution of blood vessels along with the appearance of red blood cells and hemorrhagic reticuloepithelial cells
Balcı et al. [99]	Cornea and lens	To investigate the adverse effects of mobile-phone on the antioxidant balance in corneal and lens tissues and to observe any protective effects of vitamin C in this setting. The results of this study suggest that mobile telephone radiation leads to oxidative stress in corneal and lens tissues and that antioxidants such as vitamin C can help to prevent these effects.
Bodera et al. [100]	Antioxidant capacity of blood	EMF exposure at 1800 MHz significantly reduced antioxidant capacity in both healthy animals and those with paw inflammation
Ozorak et al. [101]	Kidney and testis	In the present study was investigated that the effects of both Wi-Fi and 900 and 1800 MHz EMF on oxidative stress and trace element levels in the kidney and testis of growing rats from pregnancy to 6 weeks of age. It has been observed Wi-Fi and mobile phone-induced EMR may cause precocious puberty and oxidative kidney and testis injury in growing rats.
Ozgur et al. [102]	Liver and kidney	RF exposure is reported to induce lipid peroxidation, accompanied by decreased activity of superoxide dismutase (SOD), myeloperoxidase (MPO) and glutathione peroxidase (GSH-Px), in various organs, such as guinea pig liver and rat kidney
İkinci et al. [103]	Spinal cord	The aim of this study was therefore to investigate changes in the spinal cords of male rat pups exposed to the effect of 900 MHz EMF. The study results showed that MDA and GSH levels in EMFG increased significantly while CAT and SOD levels decreased following application of 900-MHz EMF pathological changes may occur in the spinal cords of male rats following exposure to 900 MHz.
Gurler et al. [104]	Brain	In the study has been investigated that the oxidative damage and protective effect of garlic on rats exposed to low level of EMF at 2.45 GHz MWR. It may be concluded that EMF increases the DNA damage in both brain tissues and plasma of the rats whereas it increases protein oxidation only in plasma. It may also be argued that the use of garlic decreases these effects.
Türedi et al. [105]	Bladder	In the study investigated the effect on male rat bladder tissues of exposure to 900 MHz EMF applied on postnatal days 22-59, inclusive. In bladder tissue, degeneration in the transitional epithelium and stromal irregularity and an increase in cells tending to apoptosis were observed in EMFG.
Yan et al. [106]	Sperm	Rats exposed to 6 hours of daily cellular phone emissions for 18 weeks exhibited a significantly higher incidence of sperm cell death than control group rats.
Rajkovic et al. [107]	Thyroid gland	After significant morphophysiological changes caused by ELF-EMF exposure, the thyroid gland recovered morphologically, but not physiologically, during the investigated repair period.
Deniz et al. [108]	Kidney	In the results was observed the 900-MHz EMR cause to kidney damage and FA may exhibit a protective effect against the adverse effects of EMR exposure in terms of the total number of glomeruli.
Wang et al. [109]	Blood-testicle Barrier	In the study investigated the effect of electromagnetic pulse (EMP) exposure on cerebral micro vascular permeability in rats. It has been shown that exposure to 200 and 400 pulses (1 Hz) of EMP at 200 kV/m can increase the permeability of the blood-testicle barrier in mice
Avendaño et al. [110]	Sperm	Four-hour EMF exposure ex vivo to a wireless internet-connected laptop caused a significant decrease in progressive sperm motility and an increase in sperm DNA fragmentation
Narayanan et al. [111]	Human semen	RF exposure for one month induced oxidative stress in the rat brain, but the magnitude differed in the various regions studied, and RF-induced oxidative stress may be one underlying causes of the behavioral deficits seen in rats after RF exposure
Hancı [112]	Spleen and thymus	900 MHz EMF applied to spleen and thymus tissue caused significant histopathological changes at the TEM and LM levels

[136]. EMF is known to impact on biological systems by increasing ROS, which causes oxidative stress by altering the CAT levels of tissues [137–139]. Odaci et al. observed a decrease in CAT levels in an EMF-exposed group. Exposure to EMF during the prenatal period also caused oxidative stress in developing rat embryos. This oxidative stress persisted through postnatal day 21 [140]. Vuokko et al. reported that EMF exposure led to depression of antioxidant systems because of raised lipid peroxidation and generation of free radicals [141]. Mobile phones triggered oxidative damage in the living cell by increasing the levels of xanthine oxidase and carbonyl group activity and reducing CAT activity. Treatment with MEL significantly prevents oxidative damage in the brain [142]. Özgüner et al. reported that EMF exposure leads to renal tissue damage by raising nitric oxide and malondialdehyde (MDA) levels [143].

Table 2
Some clinical studies of the oxidative effects of EMF.

Reference	Biological endpoint	Results
Lantow et al. [113]	Monocytes and lymphocytes	No significant ROS generation was measured in human cell lines exposed to 1800 MHz.
Baohong et al. [114]	Human blood lymphocytes	RF exposure for 1.5 and 4 h did not significantly exacerbate human lymphocyte DNA damage, but may reduce and increase DNA damage in human lymphocytes induced by ultraviolet C at 1.5 and 4 h incubation.
Ansarihadipour et al. [115]	Human blood proteins	EMF exacerbated oxidative damage to plasma proteins as well as conformational changes in Hb.
Wu et al. [35]	Human epithelial lens cells	RF at 4W/kg for 24 h significantly increased intracellular ROS and DNA damage.
Belyaev et al. [116]	Human blood lymphocytes	Decreased background levels of p53 binding protein 1 foci and may indicate a reduced accessibility of 53BP1 to antibodies because of stress-induced chromatin condensation.
Agarwal et al. [117]	Human ejaculated semen	900 MHz EMF emitted by mobile phones may cause oxidative stress in human semen.
Lewicka et al. [118]	Human blood platelets (in vivo)	The largest increase in ROS concentration vs. a control sample was observed after exposure to EMF of 220 V/m intensity for 60 min. The enzymatic activity of SOD-1 also decreased.
Lu et al. [119]	Human peripheral blood mononuclear cells	Cell apoptosis can be induced in human peripheral blood mononuclear cells by 900-MHz GSM radiofrequency electromagnetic field at a specific absorption rate of 0.4W/kg when exposure exceed 2 h.
De Iuliis et al. [120]	Human spermatozoa (in vitro)	Highly significant relationships were observed between SAR, the oxidative DNA damage bio-marker, 8-OH-dG, and DNA fragmentation after RF exposure.
Yao et al. [37]	Human lens epithelial cells	DNA damage was significantly increased by comet assay at 3 and 4 W/kg, whereas double strand breaks by histone variant foci were significantly increased only at 4 W/kg, while increased ROS levels were detected in the 3 and 4 W/kg groups.
Sefidbakht et al. [121]	Human embryonic kidney cells	Results showed that an increase in the activity of luciferase after 60 min of continuous exposure may be associated with a decrease in ROS levels caused by activation of the oxidative response.

4.3. Superoxide dismutase

SOD is an enzyme that catalyzes the reaction in which the toxic superoxide (O_2-) radical is partitioned into molecular oxygen (O_2) or hydrogen peroxide (H_2O_2). Superoxide is generated as a by-product as a result of the oxygen metabolism, leading to several types of damage to cells. Three forms of SOD can be encountered in humans; SOD_1 is present in the cytoplasm, SOD_2 in the mitochondria, and SOD_3 in the extracellular compartment. SOD is present in the cytosol and mitochondria and inactivates the existing superoxide radicals, as well as protecting cells from the harmful effects of the superoxide radicals [144]. Research has shown that the rat brain is susceptible to the effects of exposure to ELF-EMF. Decreased CAT and SOD activity results in after exposure suggested that EMF might change the antioxidant levels of the brain [145]. Gambari et al. reported that 50-day exposure to EMF causes oxidative stress by increasing MDA levels and reducing SOD activity, and observed that treatment with vitamin E prevented oxidative stress and lipid peroxidation in the substantia nigra [146]. Another study reported decreased antioxidant enzyme levels and increased levels of ROS in the kidneys of rats exposed to 900-MHz EMF for 30 min/day for 1 month [143].

5. Antioxidants alleviate the potential risks of EMF exposure

When applied antioxidant supplemented with EMF exposure, improved the hydrophilic, lipophilic and enzymatic antioxidant blood capacity and partially compensated for these changes [147,148]. Vitamin E (tocopherol) is one of the most important such antioxidants. Compounds of vitamin E, including alpha, beta, gamma and delta tocopherols, are soluble in lipid. Vitamin E is stored in the liver and has many functions. Its main antioxidant function is to prevent lipid peroxidation [149]. Several studies have shown the beneficial effects of vitamin E observed by reducing alteration in antioxidant capacity against the harmful effects of EMF [150,151]. Ghambari et al. observed that exposure to 3-MT EMF led to oxidative stress by reducing SOD activity and reported that treatment with vitamin E prevents the lipid peroxidation in the substantia nigra [146]. Mohammadnejad et al. studied ultrastructural changes in the thymus after exposure to EMF and investigated the protective effects of vitamin E in preventing these change. Their results demonstrated that exposure to EMF caused damage to the immune system and that vitamin E consumption can prevent ultrastructural alteration in tissue [152].

Vitamin B9 (folic acid and folate) is crucial for several functions in the human body, ranging from the production of nucleotides to homocysteine remethylation. In humans, folate is required for the body to make or repair DNA, and to methylate DNA, in addition to its function as a cofactor in various biological reactions. Moreover, this vitamin possesses antioxidant features [153]. It is especifically crucial during periods involving quick cell division and cellular growth. Folic acid (FA) is particularly required in pregnancy and for infant brain development. It is also necessary for the formation of new cells [154]. Our previous study revealed that FA prevented the adverse effect of exposure to EMF by preventing reductions in cell numbers in the cerebellum and brain. Kıvrak observed that EMF triggered oxidative damage by increasing the levels of CAT activity and reducing GPx activity. They also noticed that oxidative damage in the brain was significantly prevented by FA therapy [75] (Fig. 3).

MEL is a hormone secreted by the pineal gland and that is also known as N-acetyl-5-methoxy tryptamin. It functions as a first line of defense against oxidative stress [155]. This hormone acts together with other antioxidants such as CAT, SOD and GPx to increase the effectiveness of each antioxidant. As a free radical scavenger, it possesses amphiphilic properties and can easily cross cell membranes and the blood-brain barrier [156–158]. Previous studies have shown that MEL exhibits a protective effect against EMF-induced oxidative stress [159–161]. Koc et al. showed that MEL reduced neuronal damage in the hippocampus induced by 900-MHz EMF. Ozguner et al. showed that exposure to 900-MHz EMF led to mild skin alterations [162]. Ulubay et al. stated that exposure to 900-MHz EMF in the rat kidney during the prenatal period results not only in an increase in total kidney volume, but also in decreased numbers of glomeruli. The application of MEL was found to prevent the negative effects of EMF on the kidneys [148].

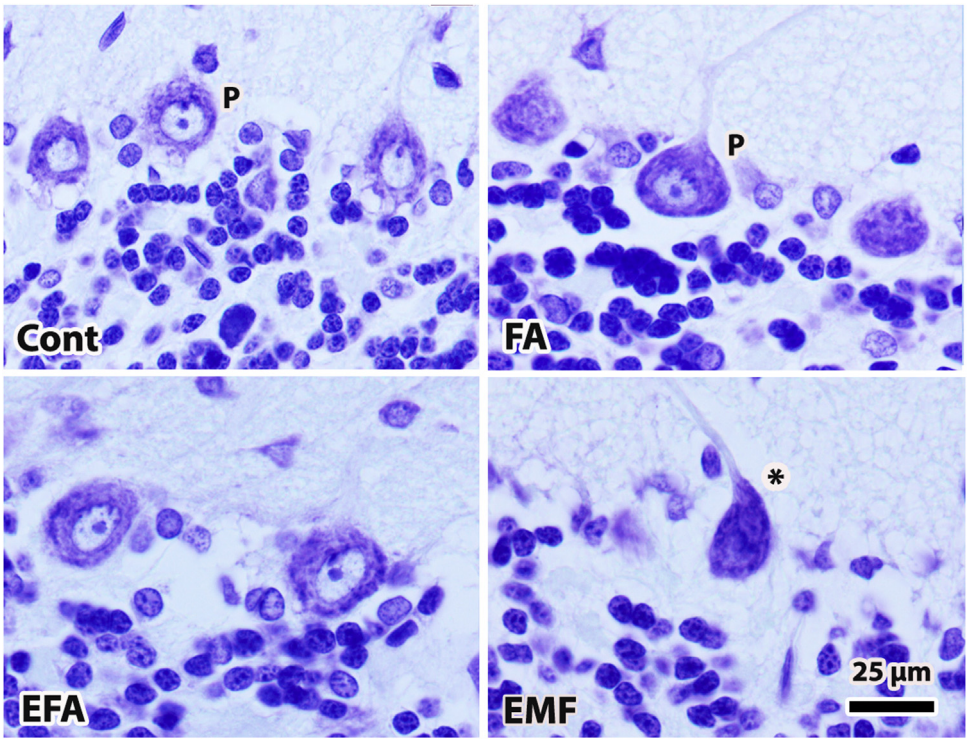

Fig. 3. Images of cerebellar tissues from the control (Cont), EMF exposure, FA and EMF + FA (EFA) groups. The letter P indicates healthy Purkinje cells in the Cont and FA groups. Necrosis of Purkinje cells is indicated with a star in the EMF group [72].

Lai and Singh demonstrated that MEL prevents EMF-induced DNA damage resulting from free radical generation in rat brain cells [31].

6. Conclusion

The biological effect of exposure to EMF is a subject of particular research interest. The results of the recent studies not only clearly demonstrate that EMF exposure triggers oxidative stress in various tissues, but also that it causes significant changes in levels of blood antioxidant markers. Fatigue, headache, decreased learning ability, and cognitive impairment are among the symptoms caused by EMF. The human body should therefore be protected against exposure to EMF because of the risks this can entail. As reported in many studies, people may use various antioxidants such as vitamin E, MEL and FA to prevent the potential adverse effects of exposure to EMF.

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