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Literature Review
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# Biological Effects of High Radiofrequency Radiation on Wistar Rats: A Literature Review

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Radiofrequency Radiation Effects on Wistar Rats

## Abstract

**Aim and Objective:** Despite the growing concerns about the relationship between exposure to radiofrequency radiation (RFR) and detrimental health effects due to the changes in biological processes of experimental animals, there is still ongoing debate on the significance of these findings in causing significant public health problems with the growing advancement in internet technology. The aim of this study is to review existing literature on the effects of high RFR on wistar rats.

**Method:** A search was conducted on Google scholar and PubMed to identify relevant peer-reviewed articles to be included into the review. Studies eligible for inclusion included free full text articles on wistar rats exposed to ≥ 2.45GHz RFR conducted in the past 5 years. Studies included in this review were written or transcribed in English language. From 286 titles, 36 eligible studies were included in the review and assessed for quality using the Strengthening the Report of Observational Studies in Epidemiology – Veterinary Extension (STROBE-Vet) quality assessment tool.

**Results:** Studies included in this review generally had good quality (>60%) based on the STROBE-Vet assessment. This review identified numerous biological changes in wistar rats exposed to high RFR including variations in biochemical, cholinergic, genetic, histopathologic, psychological, optical, and dermatological parameters. In this review, studies identified variations in protein and liver enzymes while high RFR was found to induce oxidative stress and cellular damage of exposed wistar rats compared

to the unexposed groups. This was seen in the changes in protein, lipids, enzymatic and non-enzymatic antioxidants. Studies also identified changes in expression of genes and neurotransmitters with imbalance in hormones. In addition, this review identified structural changes of cells, tissues and organs indicative of apoptosis, damage and death. Exposed rats were identified to have behavioral changes indicative of anxiety and memory decline while studies identified optical and dermatologic changes in exposed rats compared to the unexposed.

**Conclusion:** With numerous biological changes identified in wistar rats exposed to high RFR, there is an increasing risk of detrimental health events giving the advancement in internet technology and limited regulations to control exposures to RFR. Therefore, studies should be conducted to identify strategies to mitigate human exposure to RFR while policies are developed and enforced to protect human health.

## Introduction

Over the past two decades, the utilization and expansion of Wireless Fidelity (Wi-Fi) communication has rapidly grown, Worldwide there is an exponential growth of wireless communication. As a result, Wi-Fi communication devices and technology have been largely utilized to transmit or access information from the internets, cell phones, computers and other appliance, hence the emission of large degrees and magnitudes of radiofrequency radiation (RFR) [1].

With rapid expansion in this non-ionizing radiation considering its significance role in enhancing communication, there have been growing concerns about the potential public health impact [2-4]. This has led to the conduct of numerous studies in recent times to evaluate the potentially harmful impact of long-term exposure on human health and the environment. In addition, programs and policies have been developed and implemented to limit human exposure and its harmful impact [5,6].

Two major countries (France and Russia) have the world's longest research history on the harmful effects of microwaves and have come out with laws to minimize exposure to Wi-Fi among school children [7.8]. These policies have been proposed by the council of Europe, to restrict the use of cell phones and accessibility of Wi-Fi internet devices in schools in order to protect the young ones from the possible harmful effect of radiation [9].

The globe continues to advance in wireless technology with little or no actions to prevent and eliminate its harmful impact on human health and the environment. Although recent findings have linked RFR exposure to detrimental health effects in experimental animals, the globe continues to experience immense development and increase in wireless networks with high radiofrequencies and increased levels of exposure to RFR [10]. This study reviews the effect of RFR exposure on wistar rats.

## Method/ Design

*Study Design*

A literature review was conducted to review existing studies that assessed the effect of high RFR Electromagnetic field (EMF) on wistar rats using two databases.

*Literature Search and Search Term*

From 31st August - 14th September, 2021, a search was conducted using Google Scholar, PubMed and references from other articles to identify relevant articles for this systematic review. Key search term for the review include mobile phone radiation, Wi-Fi radiation, microwave radiation, high radiofrequency radiation, 4G radiation, 2.4GHz Radiofrequency radiation, non- ionizing radiation, EMF radiation.

*Inclusion and Exclusion Criteria*

Studies relevant to this review were screened for inclusion into the review. As indicated in Table 1, only peered reviewed, in-vivo studies conducted within the past 5 years, in English (or English translation) were included into the review. In addition, studies conducted on wistar rats with comparison groups, studies that utilized high RFR (≥2.4GHz) were included into the review. Other studies that failed to meet the inclusion criteria were excluded from the review.

Table 1. Inclusion and Exclusion Criteria for Selection of Literature

| **Inclusion Criteria** | **Exclusion Criteria** |
|---|---|
| In-vivo studies | In-vitro studies |
| Peered reviewed articles conducted in the past 5 years | Peered reviewed articles conducted in later than the last 5 years |
| Studies conducted on wistar rats | Studies conducted on other animal model |
| Full text articles in English or English transcription | |
| Studies utilizing RFR for exposure | Studies that did not utilized RFR for exposure |
| Studies that utilizes 2.4GHz+ radiofrequency | Studies that utilize lower radiofrequency |
| Study that had comparison groups (i.e. sham/control and exposure group) | Studies without comparison groups |

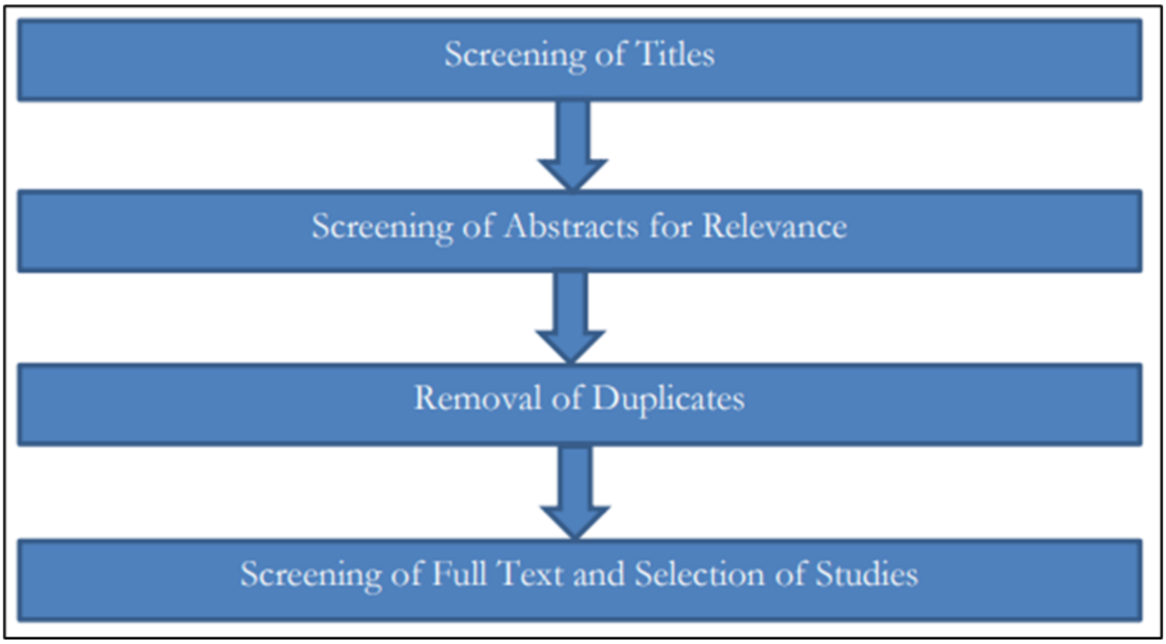


Figure 1. Search strategy for Literature Review

*Search Strategy*

Figure 1 summarizes the stages in which studies were screened for relevance and selected based on the inclusion criteria. In order to review the effect of high RFR on wistar rats, titles were screened for relevance and inclusion into the review after which abstract were screened and included based on relevance. After removal of duplicates, full text of abstract screened and included were then reviewed for relevance and final inclusion into the study. At all stages, studies that failed to meet the inclusion criteria were excluded out of the review.

*Quality Assessment and Data Extraction*

To assess the quality of studies selected for this review, strengthening the Report of Observational Studies in Epidemiology – Veterinary Extension (STROBE-Vet) was adopted. Quality studies refer to studies that are appropriately conducted to answer research questions. This process puts into consideration the assessment of the study objectives, appropriate selection of study sample and administration of exposure, while taking into consideration all ethical standards. A quality study must also be able to provide smart findings that are understandable to the proposed audience. Although STROBE was previously adopted in conducting observational studies related to human health, this guideline has been modified to assess the quality of studies conducted on animal subjects [11]. The scope of the STROBE-Vet guideline encompasses observational studies that utilize animal models and outcomes provided that are related to animal health, food safety and welfare and can be used to assess studies estimating the frequency and distribution of diseases and other health outcomes [11]. The STROBE-Vet guideline assesses issues around methodological quality, ethics and bias, precision and presentation of findings.

Relevant data from all peered review articles that met the inclusion criteria was extracted and summarized for the purpose of the review. For every selected study, relevant data such as objective of study, date of study, study sample, sample size, sample weight, radiofrequency, duration of exposure, specific absorption rate, power density and study outcome were extracted and organized in a tabular format for the purpose of the review.

## Results

Out of 1870 outputs from Google Scholar and PubMed, a total of 268 titles were selected for screening of abstract. After removal of duplicates, 256 titles were retrieved for the screening of abstracts of which 178 were excluded and 78 were retrieved from screening of full text. After screening of full-text, 38 articles eligible for selection into the review of which 2 were excluded and 36 were finally included in the review figure 2.

Table 2 summarizes the assessment of the quality of studies included in this review. Majority of the studies had a mean quality score of 50% or higher compared to only one study that had a mean quality assessment score of 43.81% respectively [12]. However, only one reviewer assessed the quality of one of the study that performed poorly [12]. Table 3

*Biochemical Effects of High Radiofrequency Radiation*

Biochemical changes were observed; exposure significantly decreased testosterone levels in exposed groups compared to the unexposed [13]. Also, electromagnetic radiation (EMR (2.450 GHz) exposure significantly increased the level of basal plasma corticosterone compared to unexposed groups in a study conducted to determine the effects of long-term exposure of 2.45GHz EMF on stress induced anxiety in experimental animals [14].

Studies in this review have found alteration in protein activities of exposed rats. In addition, testicular protein levels in week 6 and 8 exposed groups were significantly higher compared the control with this effect being affected by the duration of exposure [15]. In line other findings, EMF-exposed groups had significantly elevated hepatic total protein compared to the control [15]. Additionally, testicular protein levels were significantly higher than the control, while the heart total protein was significantly lower in the EMR-exposed groups [15]. Another study revealed that exposure to high RFR resulted in variations in protein activities inside and/

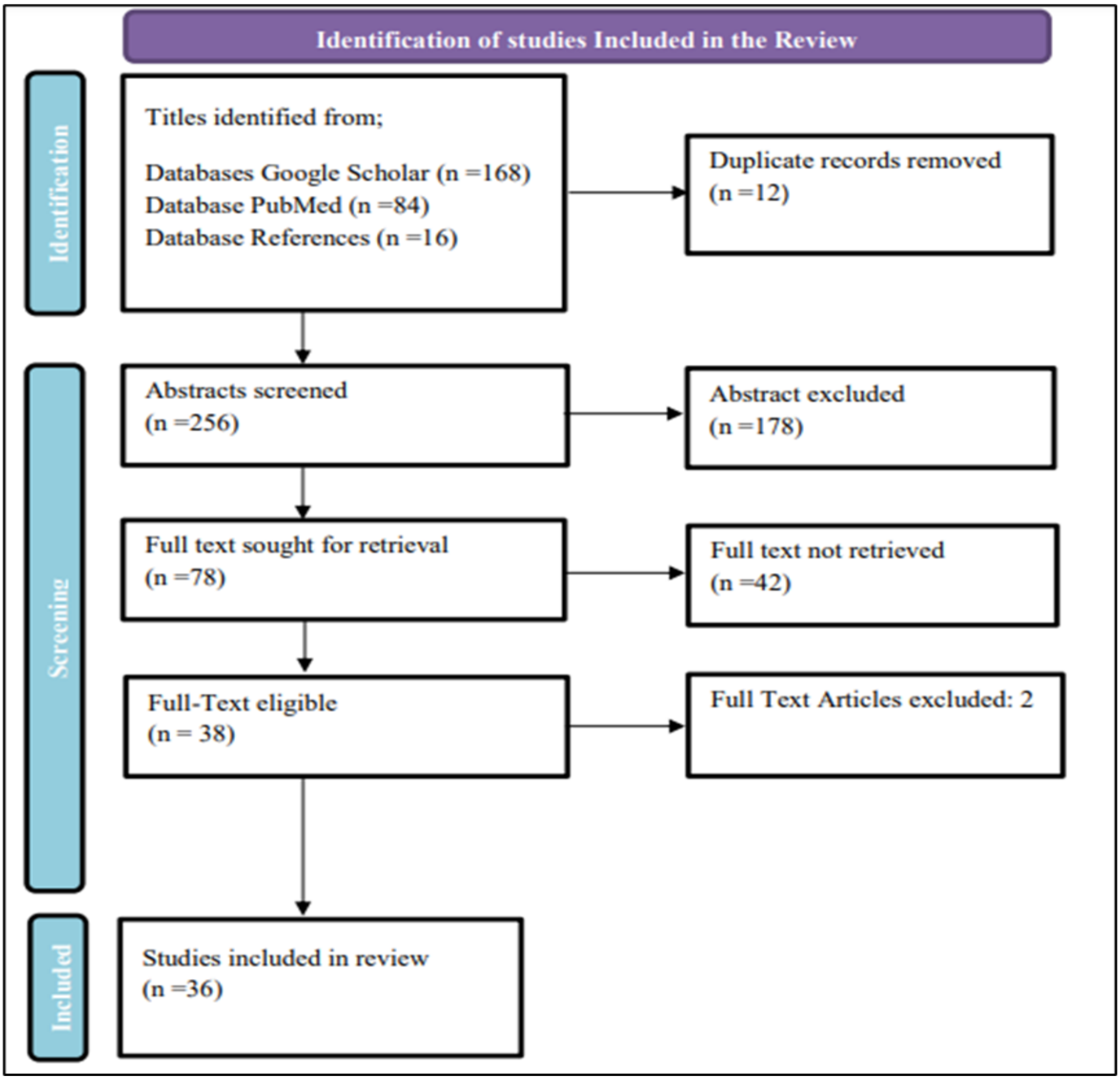


Figure 2. PRISMA Flowchart of Selection of Articles

Table 2. Quality Assessment Outcome of Studies included in the Review

| S/No | Author, Year | Reviewer P | Reviewer S | Reviewer I | Reviewer C | Total | Mean |
|---|---|---|---|---|---|---|---|
| 1 | Polyakova et al. 2016 | 61.43 | 41.67 | 64.52 | 92.86 | 260.48 | 65.12 |
| 2 | Bas et al. 2018 | 71.43 | 77.62 | 80 | 94.29 | 323.34 | 80.835 |
| 3 | Ali et al. 2017 | 62.38 | 59.05 | 59.52 | 95.23 | 276.18 | 69.045 |
| 4 | Iheme et al. 2018 | 68.57 | 61.42 | 45.24 | 77.62 | 252.85 | 63.2125 |
| 5 | Yu¨ksel, et al. 2015 | 79.05 | 76.19 | 68.1 | 100 | 323.34 | 80.835 |
| 6 | Afolabi et al. 2019 | 50.95 | 59.52 | 50 | 95.24 | 255.71 | 63.9275 |
| 7 | Rui et al. 2021 | 88.57 | 61.9 | 55.24 | 94.29 | 300 | 75 |
| 8 | Gupta et al. 2019 | 61.9 | 70.48 | 64.76 | 98.57 | 295.71 | 73.9275 |
| 9 | Varghese et al. 2018 | 95.24 | 74.29 | 76.67 | 97.62 | 343.82 | 85.955 |
| 10 | Kamali et al. 2018 | 84.76 | 51.9 | 92.86 | 89.52 | 319.04 | 79.76 |
| 11 | Özdemir et al. 2021 | 91.9 | 42.38 | 40.47 | 80.95 | 255.7 | 63.925 |
| 12 | Zhu et al. 2021 | 84.62 | 44.76 | 45.24 | 94.29 | 268.91 | 67.2275 |
| 13 | Owolabi et al. 2021 | 50.95 | 37.62 | 54.76 | 60.48 | 203.81 | 50.9525 |
| 14 | Hassanshahi et al. 2017 | 91.43 | 58.1 | 61.9 | 97.62 | 309.05 | 77.2625 |
| 15 | Fahmy & Mohammed 2020 | 78.09 | 54.29 | 68.57 | 87.62 | 288.57 | 72.1425 |
| 16 | Almášiová et al. 2017 | 78.1 | 46.67 | 65.71 | 80.48 | 270.96 | 67.74 |
| 17 | Ibitayo et al. 2017 | 79.52 | 39.52 | 50 | 64.29 | 233.33 | 58.3325 |
| 18 | Kumar et al. 2021 | 91.9 | 61.9 | 45.33 | 85.71 | 284.84 | 71.21 |
| 19 | Chauhan et al. 2016 | 88.57 | 53.81 | 43.33 | 90.48 | 276.19 | 69.0475 |
| 20 | Yorgancliar et al. 2017 | 92.38 | 52.38 | 54.29 | 60.95 | 260 | 65 |
| 21 | Sharaf et al. 2019 | 88.1 | 62.38 | 48.57 | 81.43 | 280.48 | 70.12 |
| 22 | Bayat et al. 2021 | 91.43 | 42.86 | 80 | 84.76 | 299.05 | 74.7625 |
| 23 | Akkaya et al. 2019 | 92.38 | 48.1 | 92.38 | 90.48 | 323.34 | 80.835 |
| 24 | Haifa et al. 2021 | 89.05 | 46.67 | 78.1 | 89.52 | 303.34 | 75.835 |
| 25 | Bilgici et al. 2018 | 94.29 | 46.67 | 86.67 | 76.19 | 303.82 | 75.955 |
| 26 | Haifa et al. 2021 | 92.38 | 58.1 | 79.05 | 70.95 | 300.48 | 75.12 |
| 27 | Oyewopo et al. 2017 | 96.19 | 71.43 | 73.33 | 74.29 | 315.24 | 78.81 |
| 28 | Saygin et al. 2016 | 92.38 | 58.57 | 65.24 | 95.24 | 311.43 | 77.8575 |
| 29 | Kuybulu et al. 2016 | 49.05 | 53.33 | 43.81 | 95.24 | 241.43 | 60.3575 |
| 30 | Kesari et al. 2017 | 80.48 | 45.24 | 67.62 | 90.48 | 283.82 | 70.955 |
| 31 | Obajuluwa et al. 2017 | 86.67 | | 71.9 | | 158.57 | 79.285 |
| 32 | Aderemi et al. 2019 | 85.24 | | 73.33 | | 158.57 | 79.285 |
| 33 | Vamsy et al. 2021 | 86.67 | | 73.81 | 100 | 260.48 | 86.82667 |
| 34 | Tan et al. 2017 | | 43.81 | | | 43.81 | 43.81 |
| 35 | Delen et al. 2021 | 88.1 | 46.67 | 72.85 | 95.24 | 302.86 | 75.715 |
| 36 | Akdag et al. 2016 | 74.76 | 53.33 | 59.52 | 77.14 | 264.75 | 66.1875 |

Table 3. Articles Selected to Review the Effects of Radiofrequency Radiation on Wistar Rats

| S/No | Ref, Country of study | Study sample &Sample Size, sample weight Radiofrequency and Duration of Exposure | Objective of Study | Study Outcome |
|---|---|---|---|---|
| 1 | (Polyakova et al. 2016) Moscow | Study Sample: 15 Male Wistar rats; control (n=5), intact (5) and exposure group (n=5)<br>Weight: 250– 300 g<br>Radiofrequency: 53.57–78.33 GHz<br>Duration of Exposure: daily for 7 days<br>Distance:<br>SAR:<br>Power Density: | Determine the effect of millimeter wavelengths on the intensity of free radical-mediated oxidation and antioxidant properties in Wistar rats | Significant changes total antioxidant reserves, catalase (CAT) activity of blood blood, lipid peroxidation (LPO), free radical mediated oxidation, superoxide dismutase (SOD) activity and malondialdehyde (MDA) concentration. |
| 2 | (Baş et al. 2018) Turkey | Study Sample: 18 Female Sprague-Dawley rats control group (n=6), the EMR group (n=6) and the EMR + vitamin C group (n=6)<br>Weight: 250-300g Radiofrequency: 2.45GHz<br>Duration of Exposure: 1 h / day 9:00 a.m.-12:00<br>p.m. for 30 days Distance of Exposure:<br>SAR: 2.63 mW/kg<br>Power Density: >80db 0.1-4.45V/m | To assess the effect of 2.45 GHz radiofrequency (RF) emissions on renal damage | Significant pathological changes upon exposure to 2.45Ghz RFR with higher tubular and glomerular damage in EMR group. |
| 3 | (Ali et al. 2017) Pakistan | Study Sample: 40 Sprague dawley rats, Control (n=10), Experimental 2G (n=10), Experimental C 3G (n=10), Experimental D 4G (n=10).<br>Age: 3-4 months Weight:250-350g Radiofrequency: 2.1- 2.6GHz<br>Duration of Exposure: 60 mins daily for 2 months<br>SAR:<br>Power Density: | To determine the histomorphological changes induced by mobile phones electromagnetic fields on Purkinje cell layer of cerebellum | Significant alteration in the organization of Purkinje cell layer of cerebellum. |

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| 4 | (Iheme et al. 2018) Nigeria | Study Sample: 60 Male Wistar Albino Rats<br>Age: 32 days<br>Weight: 42.6-78.8g Radiofrequency: 2.4GHz Duration of Exposure: 24 hrs/ day exposure for 90 and 180 days<br>Distance of Exposure:<br>5m<br>SAR: ?<br>Power Density: ? | Effects of Mobile Phone Frequencies and Exposure Durations on Selected Oxidative Stress Biomarkers | Significant duration mediated changes in enzyme activities (CAT,<br>SOD, MDA concentration and LPO) |
| 5 | (Yu¨ksel, et al. 2015) | Study Sample: 32 Female Wistar Albino Rats and 40 newborns Age: 12 weeks old Weight: 180 ± 21 g<br>Radiofrequency: 2.45 GHz<br>Duration of Exposure: 60 mins/day from four generations (5 days/week)<br>Distance of Exposure: SAR: 0.1 W/kg<br>Power Density: 20 dB and 11 V/m | Determine the effects of mobile phone (900 and<br>1800 MHz) and<br>Wi-Fi (2450 MHz)-induced electromagnetic radiation (EMR) exposure on uterine oxidative stress and plasma hormone levels in pregnant<br>rats and their offspring. | Time dependent significant changes in LPO, glutathione peroxidase (GSH-Px) and variation in dorsal temperature compared to controls |
| 6 | (Afolabi et al. 2019) | Study Sample: 16 Male Wistar Albino Rats<br>Age: 12-week old<br>Weight: ? Radiofrequency: 2.5GHz Duration of Exposure: 4,6 & 8 weeks<br>Distance of Exposure:<br>10 cm<br>SAR: ?<br>Power Density: ? | Evaluate effects of EMF radiation from WiFi on biochemical and hematological parameters | Significant difference in hematology [mean corpuscular volume (MCV), major histocompatibility complex (MHC), packed cell volume (PCV) and hemoglobin], protein concentration and liver enzymes [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], MDA concentration in the liver, testes and heart |

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| 7 | (Rui et al. 2021) | Study Sample: 75 Male Sprague-Dawley Rats Age: days<br>Weight: 258±5g Radiofrequency: 5.8 GHz<br>Duration of Exposure: 2h and 4hrs daily for 15 days<br>Distance of Exposure: SAR: 2.33 W/kg<br>Power Density:<br>74.25 W/m2 | Determine the effects of exposure to 5.8 GHz microwave on learning and memory ability of rats | No significant difference in the spatial learning, memory ability, scene memory ability, % rigidity time (emotional memory ability), Neuron specific enolase (NSE) and S100 calcium-binding protein B (S110B), content of mitochondrial JC-1 monomer in hippocampal neurons, density of apical and basal dendritic spines in CA1 region of hippocampus, synaptic ultrastructure in hippocampus and hippocampal synaptic plasticity |
| 8 | (Gupta et al. 2019) | Study Sample: 24 Inbred Charles-foster albino male rats<br>Age: ?<br>Weight: 180 ± 20 g Radiofrequency: 2.45GHz<br>Duration of Exposure: 1hr/day for 28 days Distance of Exposure: SAR: 0.042 W/kg<br>Power Density: s 0.1227 W/ m | Determine the effects of long- term exposure of 2.45GHz EMF on stress induced anxiety in experimental animals | Significant inducement of anxiety-like behaviors with variation in stress markers [plasma corticosterone levels, corticotrophin releasing hormone-2 (CRH-2) and Glucocorticoid receptor (GR) expression] in amygdala.<br>Significant impairment in mitochondria function and integrity (changes in the expression of Bcl2 and Bax and Bcl2) in mitochondria and cytoplasm and expression of cytochrome-c, caspase-9 and neuronal cells in amygdala. Necrotic and apoptotic amygdalar cell death |

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| 9 | (Varghese et al. 2018) | Study Sample: 12 Female Sprague Dawley rats<br>Age: ?<br>Weight: 180–220 g Radiofrequency: 2.45GHz<br>Duration of Exposure: 4 hrs/day for 45 days Distance of Exposure: SAR: 0.04728 W<br>Power Density: 7.88 W/m2 | Investigate and explore the effects of NI-EMR<br>especially the radiation frequency used in Wi-Fi devices, on the brain of rats focusing on some of the parameters of oxidative stress and apoptosis | Memory decline and anxiety behavior in exposed rats.<br>Significant variation in SOD, O2 anions, CAT and MDA, with variation in apoptotic marker capase 3, number of dendritic branching and intersections indicative of alteration in dendritic structure of neurons and affected neuronal signaling |
| 10 | (Kamali et al. 2018) | Study Sample: 20 male rats<br>Age: 3 months<br>Weight: 160 ± 10 g Radiofrequency: 2.45GHz<br>Duration of Exposure: 24 hrs/day for 10 weeks Distance of Exposure: 30cm<br>SAR: ?<br>Power Density: ? | Determine the effect of exposure of WiFi signal on oxidative stress | Significant variation in Ferric reducing ability of plasma (FRAP) assay (FRAP) value, total antioxidant capacity, plasma and RBC CAT, SOD, Glutathione- Px (GSH-Px) and glutathione S -transferase (GST) |
| 11 | (Ozdemir et al. 2021) | Study Sample: 32 Male Wistar Albino Rats<br>Age: days Weight: 200-250 g Radiofrequency: ?<br>Duration of Exposure: 2hrs/day for 6 weeks Distance of Exposure: 23 cm and 37 cm<br>SAR: 0.01 W / kg<br>Power Density:? | investigate the effect of mobile phone working with LTE- Advanced Pro (4.5 G) mobile network on the optic nerve | Significant morphometric variation in axonal diameter and myelin sheath thickness and G-ratio. Variations in visual evoked potential (VEP) recordings and mean VEP amplitude and relationship with oxidative stress markers. Significant variation in MDA, SOD and CAT activities |

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| 12 | (Zhu, et al. 2021) | Study Sample: 140 Male Wistar Albino Rats<br>Age: 8-week-old Weight: 180–220 g<br>Radiofrequency:<br>4.3 GHz<br>Duration of Exposure: 6 mins and 12 mins/day daily for 28 days Distance of Exposure:<br>0.85 m<br>SAR: 0-10 mW/cm2<br>Power Density: 10 mW/cm2 | Evaluate the effects of 1.5 and 4.3 GHz microwave radiation (single-frequency effects and combined effects) on irradiated groups, Evaluate the frequency -specific effects of 1.5 and<br>4.3 GHz microwaves Evaluate possible combined effects of irradiation with<br>1.5 and 4.3 GHz microwaves. | Compromised learning, memory decline, hippocampal structural damage, prolonged average escape latency and cognition. Microstructural hippocampal, neuronal and synaptic damage. Vascular changes and variations in PSD thickness. |
| 13 | (Owolabi et al. 2021) | Study Sample: 42 pregnant Wistar Albino Rats<br>Age: ?<br>Weight: ? Radiofrequency: Duration of Exposure: 6, 12 and 24 hrs/day for 21 days of pregnancy and 35 post-natal days<br>Distance of Exposure: ? SAR: ?<br>Power Density: ? | Determine intrauterine and postnatal exposure to RFR on brain structures, functions and behaviors in Wistar rats. | Significant changes in neurotransmitters and enzyme neurochemistry (Cytochrome C oxidase enzyme dopamine, gamma -amino butyric acid, serotonin glutamate and serotonin) in tissue and brain |
| 14 | (Hassansha hi et al. 2017) | Study Sample: 80 Male Wistar Albino Rats<br>Age: ?<br>Weight: 200–250 g<br>Radiofrequency: 2.4 GHz<br>Duration of Exposure: 12 h/day for 30 days Distance of Exposure: 50 cm<br>SAR: ?<br>Power Density: ? | investigate the effect of 2.4 GHz Wi-Fi radiation on multisensory integration in rats | Insignificant Increased in expression of muscarinic receptor 1 (M1 mRNA). |
| 15 | (Fahmy & Mohamme d. 2020) | Study Sample: 24 Female Wistar Albino Rats<br>Age: 40 days Weight: 101 + 3.00g Radiofrequency: 2.45 GHz<br>Duration of Exposure: 24 h/day for 40 days Distance of Exposure: 25 cm<br>SAR: 0.01 W kg-1<br>Power Density: ? | Impact of standard 2.45 GHz radio frequency on the liver of Wistar female rat | Significant difference in SOD, glutamic pyruvic transaminase (GPT) levels, increase in MDA |

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| 16 | (Almášiová et al. 2017) | Study Sample: 20 male Wistar Albino Rats Age: ?<br>Weight: ? Radiofrequency: 2.45 GHz Duration of Exposure: 3h/day for 21 days Distance of Exposure: ? SAR: ? Power Density: f 28 W/m2 | Determine the potential thermal and/or non-thermal effects of immediate, whole body electromagnetic irradiation of rat testes | Significant difference in local temperature of testes Dilation of the testes, congestion of blood vessels within tunica albuginea and interstitium. Degeneration of seminiferous epithelium and ultrastructural changes in developing sex cells, sertoli cells and endotherlial cells, spermatozoa motility |
| 17 | (Ibitayo et al. 2017) | Study Sample: 20 male Wistar Albino Rats<br>Age: ?Weight: 80–120 g Radiofrequency: 2.5 GHz<br>Duration of Exposure: 30, 45, 60 days<br>Distance of Exposure: 10 cm<br>SAR: ?<br>Power Density: ? | Investigate the injurious effect of radiofrequency emissions from installed Wi-Fi devices in brains of young male rats | Progressive DNA fragmentation in the band pattern with larger band size in prolonged duration indicative of apoptosis. Alteration in harvested brain tissues and DNA damage in brain with prolonged RFR exposure. Histopathological alterations in harvested brain tissues, vascular congestion and perivascular congestion and tissue damage |
| 18 | (Kumar et al. 2021) | Study Sample: 96 male Wistar Albino Rats Age: ?<br>Weight: 100±10 g Radiofrequency: 0.9GHz, 1.8GHz, 2.45 GHz<br>Duration of Exposure: 2 h/day for 6 months Distance of Exposure: 1m<br>SAR: 6.4 × 10– 4 W/kg<br>Power Density: 1 mW | Determine the effect of mobile phone signal radiation on epigenetic modulation in the hippocampus of Wistar rat | Duration of exposure dependent variation in DNA methylation, histone methylation in the hippocampus, epigenetic modulations in the hippocampus and gene expression |

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| 19 | Chauhan et al. 2016 | Study Sample: 24 male Wistar Albino<br>Rats Age: 60 days<br>Weight: 180 ± 10 g<br>Radiofrequency: 2.45 GHz<br>Duration of Exposure: 2 hrs/day for 35 days Distance of Exposure: 10 cm<br>SAR: 0.14 W/kg<br>Power Density: 0.2 mW/cm2 | Explore the effect of 2.45 GHz microwave radiation on histology and the level of lipid peroxide (LPO) in Wistar rats | Significant LPO and histological changes in liver, brain, kidney and spleen. |
| 20 | (Yorgancli ar et al. 2017) | Study Sample: 16 male Wistar Albino<br>Rats Age: ?<br>Weight: 313 ± 25 g<br>Radiofrequency: 2.4 GHz<br>Duration of Exposure: 24 h/day for one year Distance of Exposure: 50 cm<br>SAR: ?<br>Power Density: 0.00036 mW/cm2 | long-term effects of radiofrequency radiation (RFR) emitted from Wi-Fi systems on hearing | Significant distortion product otoacoustic emissions (DPOAE) values and hearing frequency |
| 21 | (Sharaf et al. 2019) | Study Sample: female Wistar Albino<br>Rats Age: 3 months Weight: 120±5g<br>Radiofrequency: 2.4 GHz<br>Duration of Exposure:<br>24 h/day for 6 months<br>Distance of Exposure:<br>25 cm<br>SAR: 0.091 W/kg<br>Power Density: 0.00036 mW/cm2 | Determine impact of Wi-Fi signals exposure on cognitive function and its relevant brain biomarkers<br>The possible role of designed Bio-Geometrical forms in restoring the neurobehavioral alterations resulting from the exposure<br>to the emerging radiation | Elevated anxiety level and impaired spatial memory with variations in dopamine, serotonin, acetylcholine and melatonin levels in the brain, cortex, striatum and hippocampus.<br>Depleted heat shock protein in the cortex. |
| 22 | (Bayat et al. 2021) | Study Sample: 30 male Sprague-Dawley rats Age: 8-9 week<br>Weight: 200–250 g Radiofrequency: 2.45GHz<br>Duration of Exposure: 2 h/day for 45 days Distance of Exposure: 35 cm<br>SAR: 0.0346-0.0060 W/Kg<br>Power Density: 0.018-0.0032 mW/cm2 | Assess the effects of 2.45 GHz Wi-Fi signal on learning memory and synaptic plasticity in y vascular dementia ( VaD) rat model induced by permanent occlusion of bilateral common carotid artery (2- VO) | Impairment in spatial learning and memory associated with long-term potentials impairment, variation in basal synaptic transmission, neurotransmitter release-probability, hippocampal cell loss and GABA transmission. |

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| 23 | (Akkaya et al. 2019) | Study Sample: 30 male Wistar Albino rats<br>Age:<br>Weight: 230–250 g Radiofrequency: 2.4GHz Duration of Exposure: 12hrs/day for 30 days Distance of Exposure: 60 cm<br>SAR: ?<br>Power Density: ? | Investigate the effect of Wi-Fi on melatonin anticonvulsive effect and oxidative damage in pentylene tetrazole induced epileptic seizures in rats | Significant difference in Total Oxidant Status (TOS) and Oxidative Stress Index (OSI). Behavioral changes associated with epilepsy and reduction in anticonvulsive and antioxidant effects of melatonin.<br>Significant variation in the percentage of dark neurons in CA1, CA3, and DG regions. |
| 24 | (Haifa et al. 2021) | Study Sample: 24 male Wistar Albino rats<br>Age: ? Weight: 120 g<br>Radiofrequency:<br>2.45GHz<br>Duration of Exposure: 2hrs/day for 14 days Distance of Exposure: 25 cm<br>SAR: ?<br>Power Density: ? | Evaluate the neurological effects of exposure to WiFi radiation on wistar rats | Significant difference in center entries and time indicative of anxiety, cerebral MDA, SOD levels, brain Iron , lead and cadmium |
| 25 | (Bilgici et al. 2018) | Study Sample: 22 male Wistar Albino rats<br>Age: ?<br>Weight: 250-300 g Radiofrequency: 2.45GHz<br>Duration of Exposure: 1 hour/day for 30 days Distance of Exposure: 15 cm<br>SAR: 0.0233W/kg<br>Power Density: ? | Determine the inflammatory effect and testicular damage on rats exposed to low level of electromagnetic fields (EMF) | Significant differnece in interleukin-6 and C-Reactive protein. Iindication of necrosis and changes in spermatogenesis with increase in necrosis score and slight damaged spermatogenesis |

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| 26 | (Othman et al. 2017) | Study Sample: 24 female Wistar Albino rats and their offsprings<br>Age: ?<br>Weight: 230- 250g Radiofrequency: 2.45GHz<br>Duration of Exposure: 2 h per day for gestation period<br>Distance of Exposure:<br>25 cm<br>SAR: ?<br>Power Density: ? | Evaluate the effects of maternal concurrent exposure to stress and WiFi signal on the postnatal development and behavior of rat offspring | Detrimental effect of gestational progress, outcomes and neuromotor maturation. Gender dependent defect in physical development of pups and Inducement of anxiety like behavior, motor deficit and exploratory behavior impairment in both male and female progeny. Significant variation in MDA, CAT, SH, SOD phosphorus, and magnesium levels in male, and MDA, SH, CAT, Lactate dehydrogenase (LDH), glucose, triglycerides and magnesium level in female progenies. |
| 27 | (Oyewopo et al.2017) Nigeria | Study Sample: 20 sexually matured male Wistar rats; group A (control; n = 5), group B (n = 5), group C (n = 5) and group D (n = 5) Weight: 180-200 g Radiofrequency: Duration of Exposure: group A (switched off mode exposure), group B (1-hr exposure), group C (2-hr exposure) and group D (3-hr exposure).<br>Exposure for 28days<br>Distance:<br>SAR:<br>Mean power Density: 28 W/m2 | Investigate the effects of the emitted radiation by cell phones on testicular histomorphometry and biochemical analyses | Significant alteration in lumen diameter, sera levels of MDA, SOD, follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone. Uneven distribution of germinal epithelial cells |

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| 28 | (Saygin et al. 2015) Turkey | Study Sample: 48 Six- week-old male Sprague Dawley rats divided into four groups: Sham (n = 12), EMR only (n = 12), EMR+ gallic acid (GA) (n = 12), Gallic Acid (n = 12)<br>Weight: 150–170 g<br>Radiofrequency: 2.45 GHz<br>Duration of Exposure: Sham, EMR only (EMR, 3 h day−1 for 30 days), EMR + GA (30 mg/kg/daily), and GA (30 mg/kg/daily) groups.<br>Distance: SAR:<br>Power Density: | Investigate electro-magnetic radiation (EMR) transmitted by wireless devices (2.45 GHz), which may cause physio pathological or ultrastructural changes, in the testes of rats. | Significant difference in MDA, TOS and TAS activities. Insignificant variations in testosterone and vascular endothelial growth factor (VEGF) levels.<br>Changes in prostaglandin E2 (PGE2) and calcitonin gene related peptide (CGRP) staining in tubules of the testes. Fewer spermatozoa in most of the tubules of the testes. |
| 29 | (kuybulu et al. 2016) Turkey | Study Sample: 12 3 months old female Wistar albino rats and 8 male offspring<br>Weight: ? Radiofrequency:2.45GH z<br>Duration of Exposure: Prenatal group: utero exposure for1hr/day during pregnancy and exposure of offspring at 16 days of life until the 12 week<br>Postnatal group:1hr/day from 18 days till the 12th week<br>Distance: ?<br>SAR: 0.1 W/kg<br>Power Density:? | Investigate oxidative stress and apoptosis in kidney tissues of male Wistar rats that pre- and postnatally exposed to wireless electromagnetic field (EMF) with an internet frequency of 2.45 GHz for a long time. | Significant difference in MDA, SOD levels in prenatal group,<br>significant variation in kidney TAS and TOS levels.<br>Significantly higher ratio of spot urine N-acetyl-β-D-glucosaminidase (NAG)/creatinine in prenatal group.<br>Significantly higher Bcl-2 immunohistochemically staining intensity in the cortical and medullary areas in prenatal group and postnatal. Bax immunohistochemical staining intensity in the cortical area in the prenatal and postnatal groups were significantly lower with significant increase in Bcl-2/Bax staining intensity ratio in medullar and cortical areas. |

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| 30 | Kesari et al. 2017 | Study Sample: 60 days old male wistar rats Weight: 180±10g Radiofrequency: 2.45GHz<br>Duration of Exposure: 2 h per day for 35 days Distance: ?<br>SAR: 0.14 W/kg<br>Power Density: 0.2 mW/cm2 | Explore the computational elucidation of melatonin in repair system induced by microwave radiation exposure | Statistically significant difference in lipid peroxidation, reactive oxygen species in brain tissues of exposed rats. |
| 31 | Tan et al. 2021 | Study Sample: 120 male wistar rats Weight: 200±20g Radiofrequency:2.856G Hz and 1.5GHz Duration of Exposure: 2.856 GHz microwave group: 6 mins/day for Distance:<br>SAR: 3.3 W/kg<br>Power Density: 10 mW/cm2 | Evaluate the acute effects of 2.856 and 1.5 GHz microwaves on spatial memory and cAMP response element binding related pathways | Significant changes in the Average Escape Latency. Significant difference in the frequency of electroencephalogram, power amplitude of α, β, θ, and δ waves.<br>Significant Injuries in the dentate gyrus areas of the hippocampus indicative of karyopyknosis and cell edema with significant increase in the mean optical density of the nuclei in the hippocampus.Apoptosis of the neuron and significant difference in the expression of p- CaMKII/CaMKII and p-CREB/CREB |
| 32 | Obajuluwa et al. 2017 | Study Sample: 24 male albino rats Weight:? Radiofrequency: 2.5GHz Duration of Exposure: 24 h/d for 4, 6 and 8 weeks respectively Distance: 50 cm<br>SAR:?<br>Power Density: ? | Investigate the effect of 2.5 GHz band radiofrequency electromagnetic waves exposure on cerebral cortex acetylcholinesteras e activity, their mRNA expression level and locomotor function and anxiety-linked behavior of male rats | Significant duration of exposure dependent variation in locomotive activity (line crossing frequency), acetylcholinesterase gene expression |

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| 33 | Vamsy et al. 2021 | Study Sample: 108 male Wistar rats of 30 days old Weight: Radiofrequency:2.4GHz Duration of Exposure: 96 min/day for 6 months Distance: ?<br>SAR: 1.6 W/kg<br>Power Density: ? | Examine the effects of mobile phone radiation on the histology of Wistar rats | Mild to moderate duration of exposure dependent inflammation and necrosis on the portal tract which worsens with duration of exposure. Observed congestion of the sinusoids and central vein, random clustering, congestion and inflammation of the Kupffer cell and formation of granuloma.<br>Gradual change in the shape of the nucleus from vesicular to pyknotic, increase in number of inflammatory cells in the liver parenchyma, portal and lobular areas. Significant difference in total bilirubin, SGOT and SGPT levels. |
| 34 | Tan et al. 2017 | Study Sample: 175 Male Wistar Rats<br>Weight: 200 ± 20 g Radiofrequency: 2.856 GHz<br>Duration of Exposure: 6 mins<br>Distance:<br>SAR: 1.7 W/Kg<br>Power Density: 5 and 10 mW/cm2 | the relationship between the effects and the power and frequency of microwave and analyzed the accumulative effects of two different frequency microwaves with the same average power density | Significant dose-dependent prolonged AELs, karyopyknosis, irregular arrangement, cell edema, and broadening pericellular space distributed in hippocampus region (DG, CA1 and CA3). Decline in spatial learning and memory and fluctuations of brain electric activities. Features of cognitive dysfunction, protein-based metabolic disorder in neurons in exposure groups. |

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| 35 | Akdag et al. 2015 | Study Sample: 16 Male Wistar rats Weight: 313 ± 25 g Radiofrequency: 2.4GHz Duration of Exposure: 24 h/d for 12 months Distance:<br>SAR: 1.41 W/kg and<br>71.27 W/kg<br>Power Density: | Effect of long term exposure of 2.4 GHz RF radiation on DNA damage of different tissues (brain, kidney, liver, and skin tissue and testicular tissues of rats). | Significant DNA damage in the testis of rats and insignificant for other tissues. |
| 36 | Delen et al. 2021 | Study Sample: 36 Male Wistar albino rats Weight: 250–300 g Radiofrequency: 2.6GHz Duration of Exposure: 30 min, 5 days/week for 30 days<br>Distance:<br>SAR: 0.616 W/kg<br>Power Density: | Investigate the effects of 2.6 GHz RFR and melatonin on brain tissue biochemistry and histology of male rats | Significant difference in GSH, GSH-Px, SOD, myeloperoxidase (MPO), MDA, and NOx levels.<br>Dilated blood vessels, pyramidal neurons with abnormal morphology. Edema and apoptotic neurons were observed in the cortex and around neuroglia cells in the CA1 region of the hippocampus.<br>Lose of normal course and random placement in neurons of the hippocampus CA3 region, number of neurons decreased semi quantitatively and the number of astrocytes increased<br>Strong immunoreactivity of Glial fibrillary acidic protein (GFAP) in in the cortical astrocytes compared with the hippocampal regions. Large number of TUNEL-positive neurons and neuroglia cells in both cortex<br>and hippocampus in RFR group. |

Note: Ref=Reference; S/No: Serial number; Stud. Samp.=Study Sample; Sam. Size=Sample size; Samp. Wght.=Sample Weight; RF=Radiofrequency; Dur. Exp.=Duration of Exposure or outside the cell of exposed rats compared to the unexposed [16]. Also the prolactin levels in the adult and 6-week-old rats were significantly lower in the exposure groups compared to in the control group in another study [17].

This review identified significant decrease in brain Iron, lead and cadmium of exposed wistar rats while there was significant increase in phosphorus levels while magnesium levels decreased in exposed male progenies [18,19]. In female progenies, there was significant decrease in phosphorus levels while glucose, triglycerides and magnesium level significantly increased [19]. Serum glutamic-oxaloacetic transaminase (SGOT) values significantly declined within the first 5 months and then elevated on the 6th month in the EMF exposed group compared to the control and the sham groups [21]. In line with one study, EMF exposure significantly reduced serum Aspartate Transaminase (AST) activities in 4 and 8 weeks of exposure to EMF, although there was a significant elevation in the SGOT levels at week 6 of EMF-exposure [15]. Although a significant increase was observed in the Week 6 of exposure, there was a significant decline in serum Alanine Transaminase (ALT) activities of the EMR exposed rats at week 4 and 8 [15]. On the other hand, Serum Glutamic Pyruvic Transaminase (SGPT) levels which was significantly increased in the first 2 months declined in the next 4 months while alkaline phosphatase (ALKP) significantly elevated upon 1-5 months exposure to 2.45GHz EMF [21].

*Lipid Damage*

Increased lipid peroxidation (LPO) in the blood and tissues (liver, brain and spleen) of exposed groups compared to unexposed was identified [22]. Also, exposure to 2.45 GHZ RFR was found to result in severe oxidative damage in wistar rats [23]. Findings from this review identified statistical increase in Malondialdehyde (MDA) concentration in exposed groups compared to the unexposed [19, 22-27]. However, there was no significant difference in thiobarbituric acid reactive substance (TBARS) and lipid peroxidation (LPO) in exposed compared to unexposed group in another study [17,23,26,28,29]. In contrast, there were no statistical differences in the mean plasma levels of lipid peroxidation of exposed rats in another study [17,30]. Also there was significant decline in LPO among low intensity Extremely High-Frequency-Electromagnetic Radiation (EMI EHF) exposed groups compared to controls with notable decrease in free radical-mediated oxidation [26]. MDA concentration in exposed group was significant lower compared to controls while there was significant increase in reactive oxygen species in brain tissues of rats exposed to microwave radiation compared to control and melatonin group [26,30].

*Enzymatic Antioxidant*

In this review, significantly lower levels of superoxide dismutase (SOD) and catalase (CAT) and glutamic pyruvic transaminase (GPT) levels in exposed rats was identified[14,19, 22,24,28,29,31]. On the contrary, there was significant increase in SOD and CAT concentration in rats exposed to high RFR [25,29,32]. Prenatal exposure to high RFR also resulted in a significant decrease in Lactate dehydrogenase (LDH) level [19]. Additionally, Glutathione peroxidase (GSH-Px) level was significantly decreased in while the Glutathione S-transferase (GST) levels in plasma was significantly increased in exposed wistar rats compared to the unexposed [28,29]. However, there were no significant differences in the mean uterine levels of reduced glutathione (GSH), glutathione peroxidase (GSH-Px), vitamin A, vitamin C, and vitamin E with short term exposure compared to week 4 and 6 where there was a significantly increased lipid peroxidation in exposed groups compared to the unexposed [17]. Microwave radiation had significant effect on oxidative damage to the tissue of exposed wistar rats compared to the unexposed [33].

*Total Oxidant and Antioxidant Status*

To assess the effects of RFR exposure on testes function, a study identified significant increase in the total oxidant status (TOS) and decrease in the total antioxidant status (TAS) upon exposure to high RFR [34,23]. Also, TOS was significantly higher while TAS in prenatally exposed group were significantly lower in the kidney, blood and tissue upon exposure of wistar rats to high RFR compared to controls [17, 23,24, 26]. However, there was no statistical difference in the mean plasma TAS upon exposure to high RFR [17]

*Genetic Effects of High Radiofrequency Radiation*

In one study, long term exposure of EMF (2.450 GHz) led to the increment of plasma corticosterone levels apart from decreased corticotrophin releasing hormone-2 (CRH-2) and glucocorticoid receptor (GR) expression in amygdala [14] . Although no significant difference was observed at 4 weeks after exposure to high RFR, there was a significant decrease in acetylcholinesterase (AChE) activity in exposed rats when compared with the control rats as indicated by [14]. In contrast, there was also a significant increase in AChE mRNA expression level in rats exposed to RFR when compared to the control rats as presented in another study [16]. There was an increase in the expression of muscarinic receptor 1 (M1 mRNA) suggesting that Wi-Fi exposure may abolish the encoding of a new object in different facets of the spontaneous object recognition task including the Cross-modal object recognition task [35]. However, this variation was not significant [35].

Neurotransmitters and enzyme neurochemistry were altered as a result of 4g RFR exposure of Wistar rats at pre-natal stage of life [36,37]. Also, during the post-natal period, the brain chemistry of exposed rats was significantly altered compared to controls as indicated in a study [36]. The activities of the cytochrome C oxidase enzyme and neurotransmitters, particularly dopamine, gamma-amino butyric acid, glutamine, and serotonin, was significantly increased with effects based on duration of exposure [36]. In contrast, there was a significant decrease in dopamine, serotonin and acetylcholine levels in the brain [38]. Also melatonin levels were significantly decreased in the cortex, striatum and hippocampus [38].

There was increased apoptotic marker caspase 3 in 2.45 GHz radiation exposed group compared to sham exposed group [29]. In agreement with Saygin and co, reduced leydig cells and spermatogenesis increased caspase 3, caspase 8 but not tumor necrosis factor-α (TNFα) and they suggested that increased extrinsic apoptosis in the testis of exposed rats [23].

More so, basal synaptic transmission, neurotransmitter release-probability and hippocampal cell loss were significantly lower while there was an increase in GABA transmission in exposed rats compared to controls [39]. There was also significant decrease in the expression of B-Cell lymphoma 2 (Bcl2) while Bcl2-associated X protein (Bax) and Bax:Bcl2 ration increased in the mitochondria and vice versa in cytoplasm indicating altered regulation of apoptosis [14]. EMR exposure also resulted in the release of cytochrome-c and expression of caspase-9 ensuing activation of apoptotic cell death [14,29]. Furthermore, this study revealed necrotic and apoptotic amygdalar cell death after EMR exposure of wistar rats [14].

*Behavioral Effects of High Radiofrequency Radiation*

This review identified changes in behavioral pattern of wistar rats exposed to high EMF. Although insignificant, a study identified delayed eye opening upon utero exposed 2.45GHz pups [32]. Also, there was significant falling at 10 days postnatal among prenatally exposed male offspring while there was a significant decreased suspension time at postnatal day 13 among 2.45 GHz Wi-Fi exposed offspring [32].

Varghese and co identified increased time in the closed arm of plus maze with increase in number of rearing among 2.45GHz exposed groups compared to control [29]. Similarly, the rats exposed to 2.45 GHz had increased number of rearing in the light box which is consistent with the anxiety behavior in rats [29]. Anxiety-like behaviors was observed in both male and female progenies compared to controls with decrease in the number and time of center entries, locomotive time, peripheral crossing, mobility and exploratory behaviors using open field test [32]. Additionally, 2.45 GHz EMR exposure resulted in increased time in reaching the target platform in training and testing phase indicative of impairment in spatial memory [29]. 2.45GHz EMR also significantly attenuated the percentage arm entries and total time spent in arms after 21 days of exposure [14]. Also, exposure to EMF induced anxiety like behavior by deregulating the hypothalamic pituitary adrenal (HPA) axis in rats [14]. In one study, there was elevated anxiety level and impaired spatial memory due to exposure to high RFR EMF in wistar rats [38]. Also, there was significant decrease in dopamine, serotonin and acetylcholine levels in the brain of exposed rats including a significant decrease in melatonin in the cortex, striatum and hippocampus [38].

Findings from this review identified EMF (2.450 GHz) exposure to be significant in decreasing the head dip, sniffing, head dip/sniffing and number of squares crossed in hole board test (HBT) on day 21 and 28 of exposure compared with control [14]. There was also decreased percentage in arm entries, and total time spent in arms upon, EMR-2450MHz exposure and no change in total number of arm entries in elevated plus mazes (EPM) among the groups [14]. Additionally, EMR (2.45 GHz) significantly decreased ambulation, rearing, grooming and number of central squares crossed in open field testing (OFT) in exposed group compared with the unexposed [14]. Certain study revealed that spatial learning and memory ability of wistar rats declined after prolonged exposure to 2.856GHz and 1.5GHz RFR microwaves [37]. Also, microwave EMF exposure led to prolonged the average escape latency (AELs) of rats, which suggested the spatial learning and memory ability was disrupted by microwave exposure [37,40].

However, there was no significant effect of high RFR on in the escape latency, frequency of plateau crossing and the percentage of time spent in target quadrant of three groups in the training trial [40,41]. Also, latency of the first arrival to the plateau of three groups after exposure for 15 days indicated no obvious effect on the spatial learning and memory ability of rats [40,41]. Similarly, the exploration time of novel and familiar objects, the percentage of exploring time of novel object, the discrimination index and the rigidity time after exposure to microwave EMF was insignificant [41]. Although 2.45 GHz microwave radiation resulted in detrimental changes in brain leading to lowering of learning and memory and expression of anxiety behavior in rats along with fall in brain antioxidant enzyme systems, there was no significant difference in the Morris water maze (MWM), novel object recognition (NOR), fear conditioning test (FCT) of exposed group compared to controls [41,42].

*Histopathologic Effects of High Radiofrequency Radiation*

To assess the histomorphological changes of exposure to mobile phones EMF on Purkinje cell layer of cerebellum, the Purkinje cells in 2.45GHz exposed groups had Purkinje cells significantly arranged in multiple layers compared to unexposed groups and groups exposed to lower RFR [42]. RFR exposure caused structural changes including increased apoptosis with severity of damage increasing with increased duration of exposure [34].

According to Tan and co, 2.856GHz microwave resulted in significant generalized injuries in nervous system [43]. Similarly, a study identified adverse effect of 2.5GHz RFR on histopathological assay of the brain tissues in exposed groups indicative of vascular congestion and deoxyribonucleic acid (DNA) damage in the brain [27]. Also, RFR exposure resulted in DNA damage in brain tissue of wistar rats [34]. Although DNA damage was significant in the testes of exposed rats, the percentage tail DNA values of the brain, kidney, liver, and skin tissues of the rats in the 2.4GHz experimental group was insignificantly increased compared to the control group after a year [44]. Also, the serum level of brain injury factors, hippocampal morphology, content of mitochondrial JC-1 monomer and hippocampal synaptic plasticity upon 2 and 4 hours microwave exposure did not change when compared with Sham group in another study [41].

Analysis of dendritic arborization of neurons showcased reduction in number of dendritic branching and intersections which corresponds to alteration in dendritic structure of neurons, affecting neuronal signaling [29]. Also, microwave had damaging effects on the neuron structure, which indicated that microwave could have destructive tendencies on the nervous system [43]. However, the serum level of brain injury factors, hippocampal morphology and the content of mitochondrial JC-1 monomer in Microwave 4 h group or microwave 2 h group did not change when compared with Sham group [29]. In contrast, one study identified insignificance in the changes in the density of dendritic spines, the ultra-structure of synapse and the level of postsynaptic density protein 95 (PSD95), Synaptophysin, phosphorylated adenosine 3'5' cyclic monophosphate response element binding (p-CREB) protein and CREB in hippocampus at 2 and 4 hours exposure compared with the Sham group [40,41]. Also, exposure to 5.8 GHz microwave did not affect the hippocampal synaptic plasticity of exposed rats [41].

To determine the effects of long-term exposure of 2.45GHz EMF on stress induced anxiety, there was a significant decrease in neuronal cells in amygdala of exposed rats compared to the unexposed [14]. Histopathological assay also revealed vascular and perivascular congestion with tissue damage upon exposure to RFR [27]. In contrast, no significant changes were observed in histopathological examinations and brain levels of tumor necrosis factor- α (TNF-α) [29]. EMR 2.450 GHz resulted in significant decrease in the mitochondria membrane potential and amygdalar mitochondrial complex activities of exposed rats compared to the unexposed [14]. Also, there was a decrease in number of neuronal cells and structural changes in amygdalar tissue indicative of neurodegeneration [14]. The percentage of necrosis and apoptosis in amygdala due to exposure with 2.45GHz EMR was significantly higher [14]. Additionally, vascular endothelial growth factor levels were significantly decreased with exposure to RFR. Mild histopathological lesion was also observed in form of vascular congestion, interstitial edema, tubular degeneration and necrosis of sperm cells [23].

Bcl2 immunohistochemical staining intensity was found to be significantly higher in the cortical and medullary areas in the prenatal exposed group and cortical area Bcl2 immunohistochemical staining intensity significantly higher in postnatally exposed groups [24]. Also, Bax immunohistochemical staining was lower in both pre and postnatal exposure while BCL2/Bax staning intensity ratio in prenatal group was significantly higher in the medullar and cortical area [24].

To determine the thermal and non-thermal effect of RFR on rat testes, there was a significant increase in the local temperature of the testes of exposed rats [33]. In addition, abnormalities were observed in the hispathological and immunohistochemical analysis of the testes [33]. This revealed congested and dilated blood vessels in tunica albuginea and intersitium, empty spaces between the spermatogenic cells of the seminiferous epithelium with germ cells found to be immature and congregated within the lumen of the tubules [33]. Similarly, deleterious effects were observed on the cytoarchitecture of the seminiferous tubule, lumen, interstitium, basement membrane and germinal epithelium upon exposure to RFR with longer duration of exposure resulting in degeneration of connective tissue, luminal vacuolation, distorted interstitium, basement membrane and germinal epithelium [13]. In addition, there was a significant decrease in the sperm count in EMF exposed rats with progressive decline in sperm count in relationship to the duration of exposure while sperm motility and viability remained unchanged in all exposure groups RFR [13].

The sex cells were also found to have damaged organelles with small round electron lucent vacuoles [33]. Testes of exposed rats revealed broken intercellular connections between the adjacent endothelial cells and basement membrane with uneven thickness in the blood capillaries of exposed rats [33]. Furthermore, degenerative alterations in the developing spermatogenic and somatic sertoli cells were observed with the sertoli cells reduced, swollen mitochondria, indicative of cell necrotization [33]. In line with the above, 3 hours exposure to high RFR EMF resulted in cellular necrosis, luminal vacuolation and distorted basement membraned, interstitium and germinal epithelium [13]. Similarly, there was significant decline in leydig cells and spermatogenesis in exposed rats compared to the unexposed groups [23].

As indicated in a study in this review, Wi-Fi exposure had a negative impact on liver function and altered its molecular structure [22]. Severe histological and ultrastructural changes in hepatic tissues, pointing to hepatotoxic consequences generated by Wi-Fi exposure was also observed [22]. In addition, Perivascular congestion and tissue degeneration were seen in histomorphometry examinations of brain tissues of exposed wistar rats in another study [27].

Exposure to high RFR resulted in gradual changes (from month 1-6) in the shape of the nucleus (vesicular to pyknotic), increase in number of inflammatory cells in the liver parenchyma (in the portal and lobular areas), and increase in the congestion of central vein and the sinusoids [45]. Also, there was more number of lymphoid cells in the sinusoids along with Kupffer cell granulomas with these changes observed in about 60-90% (i.e. 3-5 animals per month) in the exposed group [44].

The potential of exposure to RFR resulting in acute or chronic renal failure due to atrophic glomeruli and renal tubules with cytoplasmic vacuolation and pyknotic nuclei was observed [21]. Histopathological changes were observed that were significantly different among groups in the course of this study [21]. In the EMR group, renal slides revealed significant pathological changes, including tubular damage, glomerular damage, interstitial damage, and vascular damage. However, vitamin C administered before EMR decreased the tubular and glomerular damages [21]. Compared to the control group, tubular and glomerular damage was significantly higher in the EMR group [21].

*Other Effects of High Radiofrequency Radiation*

According to Gupta and co, the mean visual evoked potential (VEP) amplitudes of experimental group were significantly lower than the control group [14]. Also, the axonal diameter and myelin thickness were lower and the G-ratio higher in exposed groups compared to the sham group [14]. There was a correlation between VEP wave amplitudes and oxidative stress markers with exposure to high RFR EMF [14]. Skin ischemia, which developed to necrosis, was observed clinically in the distal parts of the flaps in all of the animals in the postoperative period on the 7th day of exposure to EMF [26].

## Discussion

This review study was conducted to synthesize existing knowledge on the health effect of exposure to high RFR in studies conducted on wistar rats as experimental models. The studies included in this review identified numerous biochemical, genetic, behavioral, histological, optical and behavioral patterns that have been influenced by exposure to high RFR in wistar rats. Findings from this review are also consistent with recent reviews and studies conducted to identify RFR effects [46-49].

Numerous findings identified exposure to high RFR to be associated with oxidative stress and cellular damage [19,22-24,32,34]. As a result, there was increase in the release of cellular antioxidants among exposed animals compared to the unexposed [19,22-24,32,34]. In addition, there was increased level of basal plasma corticosterone which is indicative of oxidative stress in exposed animals [14]. The variation in the enzymatic antioxidants with exposure to high RFR EMF is as a result of the irradiation-influenced oxidative stress which stimulates cellular responses leading to the production of these protective enzymes (superoxide dismutase activity, catalase enzyme and other antioxidants) for different catalytic activities in supressing lipid peroxidation and production of free radicals capable of disrupting the cells.

Generally, when antioxidant defense is compromised, the expected outcome is reduced activities of enzymatic antioxidant and an increased level of lipid peroxidation (MDA levels). This review identified duration of exposure dependent reduction in enzymatic antioxidant activities among exposed group and thus may be as a result of a compromised cellular defence or oxidative damage from consistent response to oxidative stress as a result of exposure to high RFR.

There is evidence that oxidative stress could alter biological processes that can lead to apoptosis, necrosis and autophagy which could result to cancers and metabolic disorders [50]. The link between oxidative stress and cancer has been widely established with understanding of the mechanism of action and the epigenetic changes that occur as a result of instability of genes due to over production of cellular free radicals [51-55]. Studies in this review have identified variations in the expression of genes, receptors and hormones [14,16,23,29,35,38]. Furthermore, neurotransmitters were also found to be altered in studies included in this review [36,37]. Oxidative stress has been found to greatly alter biological processes that affect cellular integrity resulting in detrimental variation in cellular proteins, lipids amongst other macromolecules [56,57]. Due to these variations in the concentration of protein and lipids, oxidative stress may induce DNA damage that can lead to mutagenesis [58].

Exposure to high RFR in wistar rats have been found to be associated with cholinergic effects which is observed in the decrease in ACh levels [14,16]. Similarly, previous studies have identified variations in the cholinergic process with exposure to EMF of lower RFR [59-61]. This neurotransmitter plays an important role in the functioning of the brain and muscles and as a result, alteration in its activity could result in harmful defect associated with these organs. To corroborate this finding, studies in this review identified memory decline, anxiety like behaviors and increased stress markers in exposed groups which also had low cholinergic activities [14,16]. This is consistent with other findings that have linked cholinergic activities with learning disabilities as well as anxiety–like behaviors [62,63]. With RFR exposure resulting in the alteration of cholinergic activities, there is a higher possibility of neurological and memory defects.

It is important to note that there is evidence of the relationship between decreased cholinergic activities and the occurrence of chronic health conditions such as Alzheimer's disease [62,63]. Thus, exposure to high RFR EMF which is implicative in reducing the activity of neurotransmitters could result in increased risk of memory decline and other chronic health conditions.

Behavioral changes have also been found to be influenced by exposure to high RFR EMF [12,14,29,32,38,41]. This is in line with numerous studies that have identified the relationship between oxidative stress and behavioral impairments [63-65].These changes are due to the alteration of cognitive functioning of exposed animals. With these studies identifying behavioral changes and oxidative stress/damage, there could be a relationship between oxidative stress and variation in behavioral patterns due to exposure to high RFR EMF [14,19,22-24,28,29,32,34].

Organs, tissues and cells play very key roles in regulating the entire system. When they are altered, the normal functioning of the body is interfered resulting to effects that are detrimental to the entire body. Histopathological changes have been identified in this review. These changes are seen mostly in the liver, kidneys, testis, nervous system as well as the brain resulting in renal, metabolic, reproductive, neurologic and cognitive dysfunctions of exposed animals and based on exposure duration cell death [12-14,22,23,27,29,33,34,41,44]. As a result, high RFR EMF may increase the risk of cellular damage and deaths in highly exposed individuals.

This study synthesizes existing peer reviewed articles conducted in the past 5 years on the effects of high RFR on wistar rats. As a result, it provides a collection of more recent data on high RFR effects on health outcomes. While other reviews have been conducted for specific RFRs, this review is also the first to assess all RFR exposures and therefore provides more detailed information of the general effects of high RFR EMF on health outcomes. Also, this review only included studies conducted on wistar rats as the utilization of animal models can address certain variables that cannot be accounted for and may confound or modify the effects caused by exposure to high RFR. However, there are some limitations identified in this study. This review provided a summary of ≥ 2.45GHz RFR studies and did not consider comparing the radiation effects based on radiation type. This review identified a wide range of high RFR EMF effects and as a result, does not provide in-depth understanding of these effects and its public health significance. Rather, this review provides a summary of the effects of high RFR exposure on wistar rats. It is important to note that this study has the potential of promoting other systematic reviews and primary studies to assess RFR effects on specific study outcomes. This study also can potentially improve the awareness about the potential harmful effects of RFR on human health and can foster research and advocacy for public health actions to mitigate these effects on the population.

While there has been consistent advancement and expansion in technology and access to wireless technology globally, downlink, broadcast, uplink and Wi-Fi devices have contributed significantly to the general RFR exposures in humans [67-71]. With increase in exposure to RFR globally, there is a greater risk of harmful biochemical, genetic and behavioral changes that may result in poor health outcomes hence the increase in the burden of non-communicable diseases globally.

In this review, numerous effects of exposure to high RFR EMF on wistar rats were identified. With all studies being observational and conducted on this animal model which has similar genetic make-up with humans, the global population is at an increasing risk of poor health outcomes. It is recommended that while these effects have been identified, further experimental studies that measures periodic radiation exposure and its effects on human health should be conducted. Also, research should focus on adequately assessing the pathway between long-term high RFR EMF, occurrence of oxidative stress and the onset chronic health events such as organ damage, cognitive defects and cancers amongst others in exposed animals. Studies should explore plants that may be resistant to RFR as these plants could play a critical role in mitigating the level of exposure and the effects of exposure. Although advancement in wireless network technology is inevitable, it is important that studies are conducted to provide strategies and public health actions to mitigate or reverse these harmful effects. Also countries across the globe must take necessary actions to develop and enforce policies that set and monitor exposure limits to RFR EMF. This will help prevent the potential of poor health outcomes and promote a healthy population in a long run.

## Conclusion

This review study identifies numerous health defects as a result of exposure to high RFR. This includes significant alterations in the biochemistry, genetics, histopathology, behavior and other changes in wistar rats.


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## Conflict of Interest

The authors declare that there is no conflict of interest in the conduct of this review.

## Abbreviations

AChE: acetylcholinesterase

AELs: average escape latency

ALKP: alkaline phosphatase

ALT: Alanine Transaminase

AST: Aspartate Transaminase

Bcl2: B-Cell lymphoma 2

Bax : Bcl2-associated X protein

CAT: catalase

CRH-2: corticotrophin releasing hormone-2

DNA: deoxyribonucleic acid

EMF: Electromagnetic field

EMI EHF: Extremely High-Frequency-Electromagnetic Radiation

EMR: Electromagnetic radiation

EPM: elevated plus mazes

FCT: fear conditioning test

GHz: GigaHertz

GPT: glutamic pyruvic transaminase

GR: glucocorticoid receptor

GSH: reduced glutathione

GSH-Px: glutathione peroxidase

GST: Glutathione S-transferase

HBT: hole board test

HPA: hypothalamic pituitary adrenal

LDH: Lactate dehydrogenase

mRNA: Messenger-RNA

LPO: lipid peroxidation MDA: Malondialdehyde

M1 mRNA: muscarinic receptor 1RNA

MWM: Morris water maze

NOR: novel object recognition

OFT: open field testing

p-CREB : phosphorylated adenosine 3’5’ cyclic monophosphate response element binding

PSD95: postsynaptic density protein 95

RFR: Radiofrequency radiation

RNA: Ribonucleic acid

SAR: Specific Absorption Rate

SGOT: serum glutamic-oxaloacetic transaminase

SGPT: Serum Glutamic Pyruvic Transaminase SOD: superoxide dismutase

STROBE-Vet: Strengthening the Report of Observational Studies in Epidemiology – Veterinary Extension

TAS: total antioxidant status

TBARS: thiobarbituric acid reactive substance

TNF-α: Tumor necrosis factor alpha

TOS: total oxidant status

VEP: visual evoked potential

Wi-Fi: Wireless Fidelity

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