Exposure to Low Levels of Radiofrequency Electromagnetic Fields Emitted from Cellphones as a Promising Treatment of Alzheimer's Disease: A Scoping Review Study

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ABSTRACT

Background: Alzheimer's disease (AD) is one of the most significant public health concerns and tremendous economic challenges. Studies conducted over the past decades show that exposure to radiofrequency electromagnetic fields (RF-EMFs) may relieve AD symptoms.

Objective: To determine if exposure to RF-EMFs emitted by cellphones affect the risk of AD.

Material and Methods: In this review, all relevant published articles reporting an association of cell phone use with AD were studied. We systematically searched international datasets to identify relevant studies. Finally, 33 studies were included in the review. Our review discusses the effects of RF-EMFs on the amyloid β (Aβ), oxidative stress, apoptosis, reactive oxygen species (ROS), neuronal death, and astrocyte responses. Moreover, the role of exposure parameters, including the type of exposure, its duration, and specific absorption rate (SAR), are discussed.

Results: Progressive factors of AD such as Aβ, myelin basic protein (MBP), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and neurofilament light polypeptide (NFL) were decreased. While tau protein showed no change, factors affecting brain activity such as glial fibrillary acidic protein (GFAP), mitogen-activated protein kinases (MAPKs), cerebral blood flow (CBF), brain temperature, and neuronal activity were increased.

Conclusion: Exposure to low levels of RF-EMFs can reduce the risk of AD by increasing MAPK and GFAP and decreasing MBP. Considering the role of apoptosis in AD and the effect of RF-EMF on the progression of the process, this review indicates the positive effect of these exposures.

Keywords

Neurodegenerative Diseases; Dementia; Alzheimer's Disease; Non-Ionizing Radiation; Cellphone

Introduction

Alzheimer's disease (AD) is one of the most significant public health and economic challenges in the present century [1]. It is an age-related and irreversible neurodegenerative disorder [2] characterized by progressive loss of memory and cognition [3]. Moreover, the formation of neurofibrillary tangles (NFTs) and accumulation

of amyloid-beta (Aβ) plaques are part of the process of the disease accompanying neuronal inflammation, increased oxidative stress, and reduced level of neurotransmitters like acetylcholine (ACh) and Butyrylcholinesterase (BChE), a nonspecific cholinesterase enzyme that hydrolyses many different choline-based esters [4].

Approximately 50 million people worldwide live with AD and a type of dementia. This number has been estimated to increase to 132 million by 2050 [5]. Furthermore, 10% of people over 65 suffer from AD, representing a worldwide epidemic [1].

Despite decades of substantial investment and intense research, no approved disease-modifying therapies have been found for AD [6]. None of the pharmacologic treatments available today for AD slow or lessen the damage and destruction of neurons that cause AD symptoms and make the disease fatal [7]. In addition, acetylcholinesterase inhibitors and other drugs like N-methyl D-aspartate (NMDA) antagonists, which are currently in use, can only treat or diagnose AD symptoms for about one year. Due to the inability of drug therapies to effectively treat AD, it is imperative that we explore and develop novel treatments, especially non-pharmaceutical procedures that are safe and disease-modifying. Such interventions can be expeditiously and efficiently tested in the treatment of AD [8].

Radiofrequency radiation (RFR) (3 MHz to 300 GHz) is generated by radio and television broadcasting antennas, Wi-Fi hotspots, routers, mobile phone stations, and handheld devices such as smartphones, tablets, and cordless phones [9]. This paper addresses the effects of low-level electromagnetic fields on AD. A second paper will address the impact of low-level ionizing radiation exposures.

Cell phones are a known source of electromagnetic fields (EMFs). Considering the exponential growth of the use of cell phones, it would be of crucial importance to study the effects of EMFs on the human brain [10]. Studies on the health effects of exposure to EMF and the issue of individual sensitivities, and the potential interactions between EMF and other environmental factors are receiving global attention. Recent studies have shown that very heavy cell phone use may be linked to neurobehavioral dysfunction, cancer promotion, and an increase in the risk of neurodegenerative disorders [11, 12]. Moreover, substantial evidence shows that long-term exposure to EMFs can increase the risk of certain cancers, AD, and male infertility [13].

On the other hand, a cumulative body of evidence shows that living organisms exposed to different carcinogens at a specific window of doses may demonstrate hormetically or J-shaped dose-response relationships [14-16]. According to J-shaped models, the biological effects of low doses of a stressor may show beneficial or stimulatory effects. In contrast, high doses of the same stress may cause detrimental effects [17]. In light of this phenomenon, it is not surprising that low levels of RF-EMF may induce neurohormetic effects [18, 19]. It is worth noting that similar neurohormetic effects might be observed after exposure to low doses of ionizing radiation.

Based on different studies that have elucidated the relationship between EMFs and neurodegenerative diseases, especially AD, we designed a pattern of examination that combined various human and animal studies concerning EMFs radiation. Our research aimed to evaluate the effects of cell-phone radiation (between 450 and 1800 (MHz) on the incidence of AD or the cells involved in the progression of this disease and to show its harmful or beneficial effects on the different stages of the disease and to determine the severity of these effects based on the duration of exposure.

Material and Methods

This study was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist and ex-

planation [20]. On 29 March 2021, the final protocol was prospectively registered by the Open Science Platform (OSP) (https://osf.io/hg8qn/).

A. Inclusion and Exclusion criteria

Inclusion criteria: All published original and review articles reporting on the association of cell phones (450 to 3800 (MHz)).

Exclusion criteria: Case reports, case series, letters to the editor without data, commentaries, and editorials.

Participants

No limit to the study population was defined for this scoping review, and all human (female, male) and animal samples were analyzed.

Outcome measures

Finally, the effects of radiations on Aβ, oxidative stress, apoptosis, reactive oxygen species (ROS), neuronal death, responses of astrocytes, exposure type, duration of exposure, and specific absorption rate (SAR) were discussed.

Search strategy

We systematically searched through international databases to identify relevant studies, including ISI Web of Science, Medline, Scopus, inception, PROSPERO, ALZFORUM, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Science Direct, and EMBASE, using medical subject headings (MeSH) terms such as "cell phone", "mobile phone", "Global System for Mobile (GSM)", "radiofrequency", "smartphone", "microwave" and were combined with key terms like "dementia", "Alzheimer's", "Alzheimer's disease", "astrocytes", and "β-amyloid". Additionally, data published between the years 1980-2020 was reviewed, and we also went through the reference lists manually to find relevant publications.

B. The data extraction method and quality assessment

Two reviewers independently did the initial screening, considering the selection criteria; then, the data was extracted and cross-checked. Following this, the inconsistencies were resolved by consultation with other reviewers. The author's name, target group, publication year, location, exposure, exposure time (h), and extracted outcomes were all included in the data. In addition, quality assessment of the selected studies was individually performed by two researchers using the modified Jadad scale for randomized controlled trial [21], Methodological Index for Non-randomized Studies (MINORS) tool for nonrandomized interventional study [22], the Newcastle-Ottawa Scale (NOS) tool for observational research [23] and the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) tool for animal study [24].

Results

Finally, 472 studies were identified and reviewed, and after the title and abstract screening, 439 studies were excluded, and 33 studies were included for this review (Figure 1). Out of 33, 19 original research papers were in vivo [25-43], 14 studies were in vitro [44-57]. Also, 29 target groups were animals, two target groups were human, and two others were human and animal (Table 1).

Exposure equipment

The range of frequency used was 835 MHz-2.45 GHz with SAR 0.012-6 W/kg. The type of exposure equipment used included Radiofrequency (RF) radiation, Code-division multiple access (CDMA), GSM, continuous wave (CW) RF radiation, and EMF.

Animal Models (*in-vivo* studies)

Wistar rat as an animal model used in six studies [25, 32, 34, 36, 38, 43]. Some experimental studies suggested that no significant cell-phone radiation effects on increased cell proliferation, heat-shock protein 60 (HSP60), heat shock cognate 71 kDa protein (Hsc70)

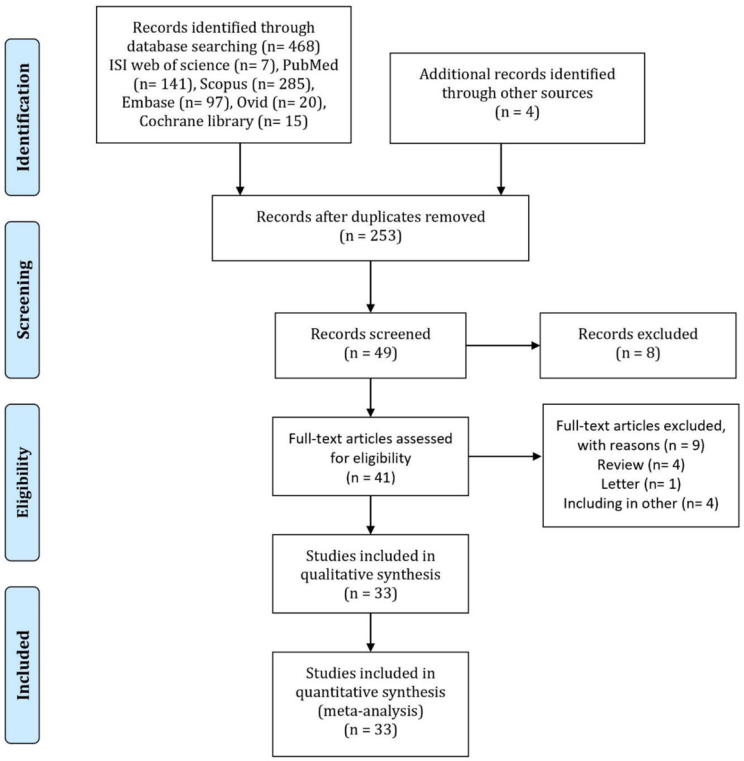

Figure 1: Prisma flowchart diagram.

or heat shock protein 90 (HSP90), glutamate transporter-1 (GLT-1), and glutamate aspartate transporter (GLAST), astroglial expression and microglial marker proteins or glial fibrillary acid protein (GFAP), and iron in the brain were observed [25, 32, 36]. However, two studies indicated that after exposure to 900 MHz RF radiation - Aβ, carbonyl proteins and malondialdehyde levels were found to be increased. Besides, a decrease in rno-miR107 was related to AD [34, 38]. Yet another study found that cell phone radiation increased GFAP immunoreactivity in the cortex and hippocampus [43].

Sprague–Dawley rat was used in five studies [26-28, 31, 39]. These studies have put forward that cell-phone radiation induces glial reactivity, hypertrophy of glial cells, persistent astroglia activation-induced astrogliosis at a SAR 6 W/kg, increase in GFAP levels in the striatum and hippocampus and neuronal activation, induced astrogliosis, but no myelin essential protein (MBP) or Aβ1–40 expression in the brain [39]. Also, SAR 1.5 W/kg failed to increase GFAP expression in the brain [27].

Mice as animal models were used in five studies [29, 30, 33, 35, 37]. Further, long-term EMF effects may increase neuronal activity, cerebral blood flow (CBF), brain temperature, and reduced brain Aβ deposition [29]. But another study has established that 918 MHz radiation could reduce CBF and cerebrovascular constriction induced by freeing Aβ [33]. On the other hand, two studies suggested that RF exposure increased GFAP [30, 35]. However, another study showed no change in astrocytic GFAP and produced no astrocytic reaction [37].

Two studies used pregnant female rats [40, 42]. *Nicolas Petitdant et al*. in 2016 showed that RF-EMF radiation in the intervention group compared with sham-exposed and controls did not show any neurobiological impairment [40]. However, *Mei-Li Yang et al., 2020*

Table 1: General characteristics of the included studies.

Study ID	Study design	Target group	Exposure	Exposure duration	Outcomes	Country
K Fritze et al., 1997 [25]	Experimental (in vivo)	Animal Male Wistar rats	890-915Hz, SAR 0.31.57.5 W/kg	4 h	The proliferation of cells increased. The expression of astrocyte and microglial marker proteins was altered.	Germany
A Schirmacher et al., 2000 [49]	Experimental (in vitro)	Animal Astrocytes of Male Wistar rats	1.8 GHz, SAR 0.3 w/kg	4 d	GFAP mRNA levels did not rise.	Germany
Anne-Laure Mausset-Bonnefont et al., 2004 [43]	Experimental (in vivo)	Animal Adult male rats Wistar	900 MHz, SAR 6 w/kg	15 min	Immunoreactivity to GFAP has increased (in cortex, hippocampus, and striatum)	France
Jae-Seon Lee et al., 2006 [53]	Experimental (in vitro)	Animal Rat Primary Astrocytes	1763 MHz RF radiation CMDA, SAR 2 W/kg	--	There was no stress response elicited by RF exposure. TPA-induced phosphorylation of MAPK	South Korea
Thorleif Thorlin et al., 2007 [47]	Experimental (in vitro)	Animal Rat Primary Astrocytes	900 MHz GSM, SAR of 3 W/kg	4 or 24 h	Microwave radiation has no influence on glial cells, astroglial morphology, or microglia cell morphology.	Sweden
Tian-Yong Zhao et al., 2007[44]	Experimental (in vitro)	Animal Pregnant female ICR mice, Primary astrocytes	1900 MHz	2h	Short-term cell phone exposure in astrocytes, RF radiation can upregulate components of apoptotic pathways.	USA
A Höytö et al., 2007 [54]	Experimental (in vitro)	Human and Animal Secondary astrocytes (Murine L929 fibroblasts, rat C6 glioblastoma cells, human SH-SY5Y neuroblastoma cells), and rat primary astrocytes	872 MHz CW RF radiation, GSM	2, 8, or 24 hours	ODC activity in primary astrocytes was statistically considerably reduced.	Finland
Elsa Brillaud et al., 2007 [26]	Experimental (in vivo)	Animal 48 male Sprague–Dawley rats	SAR=6W/kg, 900MHz signal	2, 3, 6, and 10 days	GSM induces glial reactivity. Hypertrophy of glial cells,	France
Mohamed Ammari et al., 2008 [27]	Experimental (in vivo)	Animal Twenty-four male Sprague Dawley rats	900 MHz, 1.5, and 6 w/kg	5 days a week for 24 weeks for 45 min/day at 1.5 w/kg and 15 min/day at 6 w/kg	Short time GSM exposure induced persistent astroglia activation.	France
Giovanna Del Vecchio et al., 2009 [56]	Experimental (in vitro)	Animal SN56 septal neurons	900 MHz GSM, SAR 0.5 w/kg	--	RF did not affect the vitality of cortical neurons. RF had no cooperative effects with glutamate or 25-35AA beta-amyloid.	Italy
Xuesen Yang et al., 2010 [45]	Experimental (in vitro)	Animal Mouse microglial cell line N9	2.45 GHz, SAR 6 W/kg	20 min	EMF was shown to increase JAK2 and STAT3 phosphorylation significantly.	China
Mohamed Ammari et al., 2010 [28]	Experimental (in vivo)	Animal Forty-eight male Sprague-Dawley rats	900 MHz EMF, SAR 1.5 W/kg	45, 15 min	A rise in GFAP expression in several brain regions.	France

Study ID	Study design	Target group	Exposure	Exposure duration	Outcomes	Country
Gary W Arendash et al., 2010 [29]	Experimental (in vivo)	Animal 96 mice carrying the mutant AβPPK670N, M671L gene (AβPPsw)	918 MHz, SAR 0.25 w/kg	Long term EMF	Increased neuronal activity, CBF, and decreased amyloid- (A) in the brain.	USA
Dhiraj Maskey et al., 2010 [30]	Experimental (in vivo)	Animal Male ICR mice (6 weeks old), 20–30 g (Orientbio Inc.) (n=20)	835 MHz with low energy (SAR=1.6 W/kg)	8 h/d for 3 months	Increase of GFAP and abnormal astrocytes.	South Korea
Tomonori Sakurai et al., 2011 [50]	Experimental (in vitro)	Human fetus-derived astroglia cell SVGp12	2.45 GHz, continuous wave	1, 4, 24 h	RF Exposure did not affect gene expression in SVGp12 cells.	Japan
M Carballo-Quintás et al., 2011 [31]	Experimental (in vivo)	Animal Seventy-two adult male Sprague-Dawley rats	900 MHz EMF, SAR = 0.05 W/kg minimum and 0.18 W/kg maximum	2 h	Elevated neuronal activation, glial reactivity, and GFAP expression. Reduced activity in the piriform and entorhinal cortices.	Spain
Aurélie Watilliaux et al., 2011 [32]	Experimental (in vivo)	Animal Female Wistar rats	1800 MHz EMF, SAR 1.7 to 2.5 W/kg	--	No influence on the abundance of HSP60, HSC70, or HSP90, as well as serine racemase, glutamate transporters, or GFAP.	France
Gary W Arendash et al., 2012 [33]	Experimental (in vivo)	Animal 41 aged mice	918 MHz, SAR 0.25-1.05 W/kg	--	Lower regional CBF in the cerebral cortex. Freed/disaggregated Aβ was induced.	USA
Adamantia F Fragopoulou et al., 2012 [35]	Experimental (in vivo)	Animal 18 healthy adult male mice	GSM 900 MHz, SAR 0.17-0.37w/kg, 1880–1900 MHz SAR 0.012-0.028 W/kg	3 h daily for 8 months	EMF had a substantial impact on GFAP, Alpha-synuclein, GMF, and apoE.	Greece
Yu-xiao Liu et al., 2012 [52]	Experimental (in vitro)	Animal Rat astrocytes and C6 glioma cells	1950 MHz	12, 24, 48 h	After 48 hours of exposure, an increase in Caspase-3 was seen in Astrocytes.	China
Suleyman Dasdag et al., 2013 [34]	Experimental (in vivo)	Animal 17 Wistar Albino adult male rats	900 MHz	2 h / day Every week for 10 months	A protein, protein carbonyl, and malondialdehyde were more significant.	Turkey
Karima Maaroufi et al., 2014 [36]	Experimental (in vivo)	Animal Subjects Twenty-four one-month-old male Wistar rats	900 MHz EMF, SAR = 0.05 W/kg minimum and 0.18 W/kg maximum	21	There are no synergistic effects between EMF and a high iron concentration.	Tunisia
Chunhai Chen et al., 2014 [57]	Experimental (in vitro)	Animal Embryonic neural stem cells (eNSCs) (pregnant Balb/c mice)	1800 MHz, SAR 4 W/kg	1 and 3 days	Exposure to 1800 MHz RF-EMF affects eNSC neurite development but does not affect the ratio of eNSC differentiated neurons to astrocytes.	China

Study ID	Study design	Target group	Exposure	Exposure duration	Outcomes	Country
Yonghui Lu et al., 2014 [51]	Experimental (in vitro)	Animal Mouse microglial cells (N9) and astroglial C8-D1A	1800 MHz RF, SAR of 2.0 W/kg	1, 3, 6, 12 and 24	RF irradiation elicited distinct pro-inflammatory responses in astrocytes and microglia, activating STAT3 in microglia but not astrocytes.	China
Suleyman Dasdag et al., 2015 [38]	Experimental (in vivo)	Animal 14 Wistar Albino adult male rats	900 MHz RF, SAR 0.0369 W/kg	3 h per day (7 days a week) for 12 months	Reduced rno-miR107 and linked to AD.	Turkey
Stefan Court-Kowalski et al., 2015 [37]	Experimental (in vivo)	Animal Three groups of mice, comprised of 10 animals per group	900 MHz, SAR 4 W/kg	5 days/week	Astrogliosis hadn't been produced.	Australia
Nicolas Petitdant et al., 2016 [40]	Experimental (in vivo)	Animal Seventeen pregnant female rats	RF EMF 900 MHz, SAR 0, 1.5, or 6W/kg	45 min	Neurobiological impairment hadn't been shown.	France
Amélie Barthélémy et al., 2016 [39]	Experimental (in vivo)	6-week-old Sprague Dawley male rats (n = 68)	900 MHz RF-EMF 0, 1.5, 6 W/kg	15, 45 min	Total GFAP levels were higher in the striatum, hippocampus, and olfactory bulb. RF exposure induced astrogliosis.	France
Mikko Herrala et al., 2018 [55]	Experimental (in vitro)	Animal Rat primary astrocytes	Continuous-wave (CW) or GSM-type 872 MHz GSM, SAR 6.0 W/kg	24	GSM exposure hadn't induced genomic instability in primary astrocytes.	Finland
Aikaterina L Stefi et al., 2019 [48]	Experimental (in vitro)	Human SH-SY5Y cells	1800 MHz GSM, SAR; 0.23 W/kg	3 times, for 10 min, for 2 days	Oxidative stress and cell death induction	Greece
Tsoy A et al., 2019 [46]	Experimental (in vitro)	Human and Animal Wistar rats' astrocytes/Primary human astrocytes	EMF of 918 MHz/10 W peak power pulsed/SAR 0.20 W/kg	60 min	Aß42-induced cellular and mitochondrial ROS in primary astrocytes are reduced by 918 MHz EMF.	Kazakhstan
Marc Bouji et al., 2020 [41]	Experimental (in vivo)	Animal Samaritan rat model of AD	900MHz RF	1 month (5 days/week)	Increased hippocampus heme oxygenase-1 (HO1) staining while decreasing corticosterone. Memory has been improved after RF-EMF exposure. Higher hippocampal oxidative stress.	France
Mei-Li Yang et al., 2020 [42]	Experimental (in vivo)	Animal Pregnant rats	850-1 900 MHz mobile phone	6 h/d and 24 h/d mobile phone radiation for 1-17 days	MBP and NF-L expression were down-regulated, whereas GFAP expression was up-regulated.	China

MAPKs: Mitogen-activated protein kinases, ODC: Ornithine decarboxylase, CW: Continuous wave, Aβ 1–40: Beta-amyloid 1–40, MBP: Myelin basic protein, NF-L: Neurofilament-L, GFAP: Glial fibrillary acidic protein, EMF: Electromagnetic field, Aβ: Amyloid beta peptide, AD: Alzheimer's disease, RF-EMF: Radiofrequency electromagnetic fields, ROS: Reactive oxygen species, RF: Radiofrequency, CM-H2DCFDA: Chloromethyl derivative of 2',7'-dichlorodihydrofluorescein diacetate, NOX: NADPH oxidase, ERK 1/2: Extracellular signal-regulated kinases 1 and 2, HFIP: 1,1,1,3,3,3 hexafluoro-2-propanol, SAR: Specific absorption rate, GFAP: Glial fibrillary acidic protein, NADPH: Nicotinamide adenine dinucleotide phosphate, STAT3: Signal transducer and activator of transcription 3, eNSCs: Embryonic neural stem cells, GSM: Global System for Mobile, p38MAPK: p38 mitogen-activated protein kinases, GLAST: Glutamate aspartate transporter, GLT-1: Glutamate transporter-1, Hsp90: Heat shock protein 90, Hsc70: Heat shock cognate 71 kDa protein

conducted a study on long term cell-phone radiation group, MBP. It revealed that neurofilament light polypeptide (NFL) expressions were decreased, and GFAP expression was increased. Also, in male rat offspring, myelin and axon damage with the activity of astrocytes in the cerebellum was observed [42].

Marc Bouji et al., 2020 exposed 900 MHz RF to a Samaritan rat model with AD. After the exposure, results revealed that its memory was modified, oxidative stress in the hippocampus, hippocampal heme oxygenase-1 (HO1) was increased, and corticosterone reduction was reduced [41].

In-vitro Studies

Six studies used cell-cultured astrocytes [44, 46, 47, 49, 52-55]. Cell-phone radiation did not increase GFAP messenger RNAs, stress response, 12-O-tetradecanoylphorbol 13-acetate (TPA)-induced mitogen-activated protein kinases (MAPKs) phosphorylation, damage-related factors in glial cells, morphology, on microglia, and genomic instability [47, 49, 53-55]. However, other studies have demonstrated that RF radiation can increase caspase-3 that is detected dependently with bax and bcl-2, up-regulates apoptotic pathways, induces differential pro-inflammatory responses, and increases mitochondrial membrane potential astrocytes [44, 46, 51, 52]. Also, RF radiation can suppress H_2O_2 induced phosphorylation of p38 mitogen-activated protein kinases (p38MAPK), Aß42 activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and extracellular signal-regulated kinases (ERKs) ½ [46]

In microglia, RF radiation generated multiple pro-inflammatory cytokines and activated the signal transducer and activator of transcription 3 (STAT3) [45, 51]. Also, it increased the expression of CD11b, tumor necrosis factor-a (TNF-a), and inducible nitric oxide synthase (iNOS), the production of NO, and Janus family of tyrosine kinases (JAK) 2 [45].

Furthermore, cell phone radiation inhibits neurite development of embryonic neural stem cells (eNSCs) but does not affect the ratio of eNSC developed neurons [57]. Also, the 900 MHz GSM signal did not change the viability of cortical neurons and Aβ fragment 25-35 (Aβ25-35) in Dulbecco's modified Eagle's medium [56].

We found no evidence that exposure to RF fields affected humans. Also, gene expression in a normal human glial cell line, SVGp12 cells [50], but a study by *Aikaterina L Stefi et al*. suggested that RF radiation alters amyloid precursor proteins, introduces changes in monomeric alpha-synuclein (α-syn) accumulation, and induces oxidative stress in human SH-SY5Y cells [48].

Discussion

Some studies have shown that cell phone radiation can help improve memory in patients with AD [58-60]. Also, there has been research regarding the correlation between Aβ and AD [61]. Misfolded peptides appear to play an important role in several degenerative diseases, and may play a key part in the aggregation of Aβ in the brain during the pathogenesis of AD [62]. Exposure to EMFs enhances the Blood-Brain Flow (BBF) and neuronal cells activities such that Aβ clearance increases, and the chance of AB aggregation decreases [33]. In 2019, *Andrey Tsoy et al*. exposed that ordinary radiation of a cell phone (918 MHz) enhances the BBF and reduces oxidative stress and Aβ accumulation. Following this, Aβ by activating NADPH causes mitochondrial dysfunction, resulting in the formation of super oxidative astrocytes [46]. More so over, some studies have reported no changes [39], while other studies have elicited an increase of Aβ accumulation in EMFs [38].

Additionally, misfolded Aβ and tau protein aggregation due to amyloid plaques and neurofibrillary tangles (NFTs) are the leading cause of AD pathology [63]. Deposition of Aβ plaques and tau protein in the CNS increases AD chances [64]. The studies we analyzed

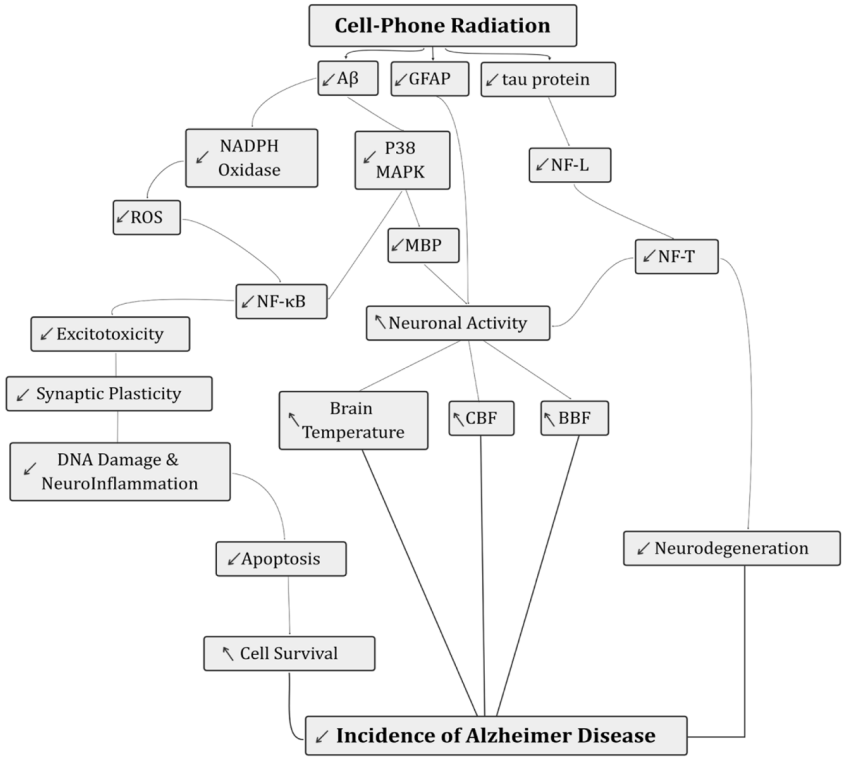

Figure 2: Mechanism pathways of cell-phone radiation on Alzheimer's Disease (AD).

Table 2: Factors change related to Alzheimer's Disease.

Factors	Human	Animal	Strength of Evidence	
			Human	Animal
Aβ	↓ [46, 29]	↓ [46]	Poor	Strong
tau protein	-	-	-	-
MAPKs	↑ [46, 53]	-	-	Fair
GFAP	↑ [28, 29, 43, 42]	↑ [35]	Poor	Hight
MBP	-	↓ [28]	-	Poor
NF-L	-	↓ [28]	-	Poor
NADPH oxidase	-	↓ [46]	-	Poor
Apoptotic	-	↑ [52, 44]	-	Poor
CBF	-	↑ [29]	-	Poor
Brain temperature	-	↑ [29]	-	Poor
Neuronal activity	-	↑ [29]	-	Poor
α-syn	↑ [48]	-	Poor	-
Oxidative stress	↑ [48]	-	Poor	Poor
BBF	↑ [46]	-	Poor	-

Aβ: Amyloid-beta peptide, MAPK: Mitogen-activated protein kinases, GFAP: Glial fibrillary acidic protein, CBF: Cerebral blood flow, NADPH: Nicotinamide adenine dinucleotide phosphate, MBP: Myelin basic protein, NF-L: Neurofilament-L, BBF: Blood-Brain Flow, up and down arrows show increase and decrease, respectively

have shown a decrease in Aβ, in most cases by exposure to EMF, so we have deduced that EMF generated by cell phones reduces the likelihood of AD (Table 2) (Figure 2).

The movement and transportation of biomolecules in eukaryotes occur with the help of protein kinases type 3 and 5, respectively. Also, motor KIF13B and Eg5, MAPKs (type 3&5) help myelination regulate p38 [65]. Recently, scientists have claimed to find a new way to treat AD by targeting p38 MAPK. Moreover, inhibition of p38 MAPK conduces to a new hope of AD treatment [66]. In 2019, *Tsoy et al.* claimed that EMF does not influence suppressing p38 MAPK and extracellular regulation kinase 1,2 (ERK1,2); it could be because of the second ROS-independent downstream pathway [46]. Exposure to EMF had no significant effect on MAPK phosphorylation in either human T-lymphocytes or rat astrocytes in *Lee et al.'s* study in 2006 [53]. Based on our review of the impact of EMF on MAPK, it appears that this exposure has no apparent effect on MAPK levels (Table 2) (Figure 2).

Glial fibrillary acidic protein (GFAP) is one of the human body's proteins and is a medium-length protein expressed in various body cells, including astrocytes. GFAP regulates cerebral blood flow (CBF) and suppresses neuronal cell proliferation [67].

In 2012, *Adamantia F Fragopoulou et al.* exposed adult male mice to radiation three hours a day for eight months. Data obtained at the end of the study showed an increase in GFAP [35]. In various studies performed by *Anne-Laure Mausset-Bonnefont et al., 2004*, *Mohamed Ammari et al., 2010*, *Mei-Li Yang et al., 2020* and *Amélie Barthélémy et al., 2016* have shown that GFAP levels would increase with exposed to EMFs [28, 29, 42, 43]. On the contrary, studies from *A Schirmacher et al., 2000*; *Aurélie Watilliaux et al., 2011*; *Stefan Court-Kowalski et al., 2015* concluded that there had been no apparent changes for GFAP in EMFs [32, 37, 49]. Human and animal-modeled studies based on the effect of EMFs on GFAP were reviewed (Table 2) (Figure 2).

Among the selected studies in our study, MBP changes have been considered in two studies. *Amélie Barthélémy et al., 2016* did not report apparent differences, but *Mei-Li Yang et al., 2020* showed a decrease in MBP and neurofilament-L (NF-L) expression along with the increase of GFAP expression in EMF [37, 42] (Table 2) (Figure 2).

Apoptosis is a natural phenomenon that occurs in the human body through molecular pathways in the mitochondria and endoplasmic reticulum. Various factors influence this phenomenon, for example, in neurodegenerative diseases such as AD, Aβ, tumor necrosis factor-α reactive oxygen species, etc. [68]. Two in vitro studies, *Tian-Yong Zhao et al., 2007* and *Yu-xiao Liu et al., 2012*, were designed to expose the animal model to 1900 and 1950 MHz, respectively. In the first study, after 12 hours, and in the second study, after 48 hours, there were significant changes in the enhancement of apoptosis [44, 52]. Pathways associated with necrosis and apoptosis followed by cell death are events in AD [69]. Therefore, following the review of animal studies on the effect of EMFs on apoptosis and increasing the rate of apoptosis as a mechanism of cell death in AD, it seems that EMFs contribute to the progression of AD by increasing apoptosis (Table 2) (Figure 2).

The lack of further studies on the effects of EMF on the human body was our most significant limitation. It is recommended that in the future and by designing other human studies and the relatively large number of animal studies in this field, making a significant contribution to EMF on the human body is positive or negative.

Conclusion

Studies included in this review show that exposure to RF-EMFs act as a double-edged sword. While the findings of some studies indicate a reduced incidence of AD, other stud-

ies show an acceleration of the course of the disease. We believe that parameters such as the level of exposure (e.g., specific absorption rate, exposure duration, cumulative exposure, etc.) can determine if the response to RF-EMFs will prove beneficial or detrimental. A future research effort should be conducted to determine if there is an optimum range of SAR values or radio frequency ranges that affect AD either positively or negatively. Moreover, it is crucial to determine how the animal data can be translated into human effects. Therefore, further studies in this field are clearly warranted.

Authors' Contribution

K. Shirbandi conceived the idea. The introduction of the paper was written by N. Sadeghian, S. Adiban and M. Khalafi gathers the images and the related literature and help with the writing of the related works. The method implementation was carried out by SAR. Mortazavi, F. Bahaeddini Zarandi and SH. Mortazavi. The whole project was supervised by SMJ. Mortazavi, JJ. Bevelacqua and JS. Welsh. SMJ. Mortazavi and JS. Welsh have equally contributed to this work. All the authors read, modified, and approved the final version of the manuscript.

Conflict of Interest

None

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