Review

Molecular and Cellular Mechanisms of Static and Repetitive Magnetic Stimulation in Cancer Therapy: A Scoping Review

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Review

Molecular and Cellular Mechanisms of Static and Repetitive Magnetic Stimulation in Cancer Therapy: A Scoping Review

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Abstract

Background/Objectives: Repetitive magnetic stimulation (rMS) and static magnetic stimulation (sMS) are currently used as adjunctive therapies for certain neurological conditions. Despite substantial advances in cancer treatment, unfavorable prognoses and outcomes persist, especially for aggressive neoplasms, including glioblastoma and acute myeloid leukemia. In this context, the application of magnetic fields has demonstrated significant anti-tumoral benefits in both in vitro and animal studies, indicating its potential as an effective non-invasive therapeutic strategy; nevertheless, the precise mechanisms of action remain unclear. This scoping review was intended to identify published research investigating the effects of sMS and rMS in in vitro and in vivo models to evaluate their impacts on morphological and molecular parameters. **Methods**: Four databases (PubMed, Embase, Web of Science, and Scopus) were assessed; the search strategy was limited to the past twenty-five years of data publication. Studies employing rMS or sMS as a primary therapy for conditions apart from neoplasms, and those not addressing these interventions as an adjuvant therapy were excluded. **Results**: Nine articles using rMS were included: three in vitro, two employing animal models, and the remaining four including both cellular and animal-based analyses. Seventeen studies using sMS were identified: thirteen in vitro and four in vivo. **Conclusions**: This review indicates that sMS and rMS are employed as adjuvant therapies for increasing the efficacy of conventional drugs like chemotherapy. Their efficacy relies on specific factors: type of cancer, location, cell type, metabolism, and exposure parameters, including intensity, frequency, and duration.

Keywords: neuromodulation; cancer; repetitive magnetic stimulation; static magnetic stimulation; preclinical; in vitro; in vivo

1. Introduction

Non-invasive neuromodulatory approaches, including those employing magnetic and electric fields have markedly progressed the domain of nonpharmacological disease therapy [1]. In the last years, extensive preclinical and clinical research examined the application of neuromodulatory techniques for several conditions, which has helped clarify its use in neurological conditions like epilepsy [2], Parkinson's disease [3], major depression [4], anxiety [5,6], chronic pain [7], and cancer-related pain [8,9], among others [10,11]. These are interventions aimed at modulating brain activity

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by stimulating specific neural networks, especially promising for cases resistant to pharmacological agents [12].

Among several non-invasive brain stimulation (NIBS) methods, transcranial magnetic stimulation (TMS) is acknowledged for its usefulness, being widely used in primary clinical neuroscience [13]. The first documented application of TMS took place in 1993 for drug-resistant major depression [14]. Currently, TMS is being used for Alzheimer's disease, stroke, multiple sclerosis, pain, anxiety disorders, and substance abuse [11,15]. Furthermore, a pilot study has suggested that repetitive TMS (rTMS) is a safe and effective therapeutic approach for improving peripheral nerve damage and relieving the symptoms of chemotherapy-induced peripheral neuropathy in patients with multiple myeloma [16]. The method requires an apparatus equipped with a high-current pulse generator that produces discharge currents flowing through a stimulating coil to generate a brief magnetic pulse with field strengths reaching several Tesla, generating secondary electric fields [13,17]. Upon placing the coil on the subject's head, the magnetic field suffers minimal attenuation by extracerebral tissues, generating an electric field sufficiently strong to depolarize superficial axons and stimulate neuronal networks [18]. TMS can be used for diagnostic and therapeutic purposes for numerous neurological disorders, noninvasively examining cortical excitability and connectivity, and motor processes [13]. According to the purpose, it is performed in many protocol patterns, encompassed by a wide variety of intensities, frequencies, and durations. While single and paired pulses are used for diagnostic purposes, rTMS is mostly aimed at treating neurological diseases [13,19].

Studies demonstrate that rTMS at frequencies over 3 Hz enhances neuronal activity, whereas rTMS at lower frequencies (below 1 Hz) typically reduces synaptic efficacy [20]. Additionally, rTMS can be administered using a method referred to as theta burst stimulation (TBS), characterized by magnetic pulses in bursts of three, at high frequency (50 Hz), with an interburst interval of 200 ms (5 Hz, which is in the range of theta frequency). TBS can be configured for continuous (cTBS), which primarily causes inhibitory effects via long-term depression (LTD), or intermittent (iTBS), which applies bursts with pauses, leading to excitatory effects via long-term potentiation (LTP) [10]. In contrast, static magnetic stimulation (sMS), unlike other stimulation modalities, does not induce electric currents [21]. It employs neodymium magnets, which can be positioned on the subject's scalp, generating static magnetic fields that primarily affect the synapse, changing the properties of membrane ion channels, influencing neuronal excitability, and potentially resulting in enduring changes in neuronal plasticity [21,22]. In addition to recent research employing repetitive magnetic stimulation (rMS) [23], emerging studies using sMS, including 2 conducted in our research group, have demonstrated its capacity to inhibit the migration and telomerase function in vivo, diminish the survival and viability of neuroblastoma cells in vitro, and induce cisplatin resistance by enhancing apoptosis pathways and genotoxicity in cancer cell lines, exhibiting significant antineoplastic effects [24–28].

Cancer is one of the leading causes of mortality worldwide, accounting for nearly 10 million deaths in 2020 [29] and impacting countries across all income levels. According to the American Cancer Society [30], the existing cancer burden is expected to increase substantially as populations grow, age, and adopt habits that elevate their susceptibility to this disease [31]. Cancer arises from a genetic abnormality that causes the body's cells to proliferate uncontrollably and metastasize to body regions distinct from the original site [32]. Cancer therapies can incorporate multiple approaches, including surgical intervention, radiotherapy, chemotherapy, immunotherapy, targeted therapy, hormone therapy, and hematopoietic stem cell transplantation. Some treatments may be administered independently, while others are combined to target cancer cells effectively [33].

While significant progress in cancer treatment has been made in the past few decades, poor prognosis and outcomes persist, particularly for aggressive malignancies such as glioblastoma and acute myeloid leukemia. Despite the promise of novel therapies, factors such as tumor heterogeneity, treatment resistance, and patient-specific characteristics can still lead to unfavorable outcomes [34]. Moreover, cancer treatment can induce several side effects, including fatigue, nausea, alopecia,

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neuropathies, and chronic pain, as well as oral lesions, cognitive impairments, mental health, and appetite, gastrointestinal, dermatological, fertility, and sexual alterations [35].

In light of the lack of effectiveness and adverse effects of the current anti-tumoral therapies, researchers must explore novel approaches, especially as a complement for cancer management [for review, see 36]. While the use of magnetic fields has exhibited remarkable anti-tumoral effects in both in vitro and in vivo experimental models, suggesting it as an effective non-invasive therapeutic approach [37–39], the exact underlying mechanisms of action remain unclear. Therefore, this scoping review intended to identify research investigating the effects of sMS and rMS in both in vitro and in vivo trials to evaluate protocols and their impacts on morphological and molecular parameters.

2. Materials and Methods

To identify literature concerning rMS and sMS for possible adjunct treatment for cancer, four databases (PubMed, Embase, Web of Science, and Scopus) were electronically searched. We designed and implemented a search strategy within the designated databases, which included terms related to “cancer”, “repetitive magnetic stimulation” OR “static magnetic stimulation”, “in vitro”, and “rodents” OR “animal model”. Boolean operators (AND/OR) have been used to combine terms appropriately for each database.

In the assessed databases, the keyword “pulsed magnetic field” was used to denote rMS, whereas the term “magnetic field” refers to both rMS and sMS. Furthermore, the search strategy was limited to the last twenty-five years of data publication (from 2000 to June 2025) to include all studies in this field that use newer techniques and parameters for MS (Magnetic Stimulation) applications.

The selection of articles encompassed studies conducted in vitro using human or animal cell lines, as well as animal studies that evaluated the effects of MS on rodent species. Eligible studies must have reported on outcomes such as cell viability, gene expression, or histopathology responses in animals. Studies using other treatment methods, like chemotherapy, were also included, assuming that MS was also employed.

The exclusion criteria have been established on the following basis: full text in languages other than English, studies devoid of definitive outcomes or relevant interventions, studies that focused on human subjects or in silico methods, studies that did not regard rMS/sMS as an adjunctive therapy, studies with rMS or sMS as a form of treatment for conditions apart from neoplasms, studies that used rMS/sMS to address symptoms of diseases in oncology patients, and studies that employed rMS as a surgical aid or diagnostic tool for benign and malignant tumors.

Titles and abstracts were independently screened by two reviewers. Disagreements have been resolved by consensus, and a third reviewer was consulted if needed. Full-text screening was performed for eligible studies. In the process, the software Rayyan was used to organize and delete duplicated articles. The data extraction was performed using a qualitative descriptive approach to categorize the included studies based on the name of the authors, year of publication, type of study, stimulation protocol, outcome assessment, and conclusion of the intervention (Tables 1 and 2).

Table 1. Studies employing repetitive magnetic stimulation (rMS) as a potential anti-tumoral therapy in in vitro models.

First author (year)	Cell line	Stimulation protocol Magnetic Field	Outcome	Main results
Jo et al. (2025) [23]	• U-87 MG (U87MG) likely glioblastoma human cell line • TS15-88 glioblastoma cell line • TS21-117 glioblastoma cell line	• Customized rMS (Bicon-1000Pro, McubeTechnology, Seoul, Korea) • Frequency 0.5 Hz on-off interval of 3 s • Intensity 18 mT • Stimulation delivered a monophasic pulse with a rise time of 370 μs • 3 d for 10 min/day	• CCK-8 assay CFAn • RNA-seq transcriptome analysis • RT-qPCR • Western blot • TUNEL assay • Sphere formation assay	• Suppression cell proliferation by downregulating the expression of FLNA and FLNC • Suppression and sphere formation • Induction of apoptosis by downregulating ERK/JNK/p38 and PI3K/AKT/mTOR pathways • Prevented invasion of glioblastoma by downregulating the expression of MMP2 and MMP9
Ashdown et al. (2020) [41]	• A549 human lung cancer cells • Lung lymphatic endothelial cells (control)	• Solenoid magnet (#R-2016-12; Magnatech) interrupted by a circuit and connected to a standard power supply (BioRad Power Pack, 10 V DC current; Bio-Rad, Hercules, CA) • Intensity: 20 mT • Rate of rise (dB/dt) in the msec range • Sequential 50- and 385-Hz oscillating • 10-min exposure	• Cell membrane integrity assay • AAf-glo cytotoxicity • Heparin Lyase III • Cell viability - Cell Titer • Cell proliferation • Scanning electron microscopy	• Intracellular protease release • Alterations to membrane integrity and subsequent viability • No changes in control cells
Heng et al. (2022) [42]	• HuH7 human hepatocellular carcinoma cells • HCT116 human colorectal carcinoma cell	• Magstim Rapid2 Plus" instrument (Magstim1 Ltd., U.K.) equipped with the D70 air film coil (AFC) • **iRMS:** Frequency 1 - 40 Hz; Intensity 0.8 T • **bRMS**: Frequency 40 Hz; intensity 0.4-0.8 T	• MTT	• Opposite trends in CRC and HCC cells respond to the frequency, temporal patterns, and magnetic field flux density considered as the parameters of the experimental RMS • High frequency of pulses, burst patterns, and shorter cycles were able to suppress the viability of the cells
Jo et al. (2022) [43]	• N2a - mice neuroblasts with neuronal cells	• Customized rMS (Bicon-1000Pro, McubeTechnology, Seoul,Korea)	• CCK-8 assay CFAn	• Suppression on cell proliferation and progression of neuroblastoma

		• Frequency 0.5 Hz on-off interval of 3 s • Intensity 18 mT • Stimulation delivered a monophasic pulse with a rise time of 370 μs • 3 d for 10 min/day	• RNA-seq transcriptome analysis • RT-qPCR • Western blot • TUNEL assay • IHC	• Downregulating the Wnt/β-catenin signaling pathway • Induction apoptosis
Lee et al. (2015) [44]	N2a - mice neuroblasts with neuronal cells	Frequency 0.5 Hz on-off interval of 3 s 100% machine output stimulation intensity 20 min / day	• Expression of BDNF, GDNF, NT-3, and PDGF • Expression of ERK and Akt • Cell proliferation: microscopy	• High frequency significantly increased proliferation in neuroblastoma cells • Low-frequency stimulation decreased cell proliferation
Yamaguchi et al. (2004) [45]	• B16-BL6 murine melanoma cell line	• Magnetic stimulator (Nihon Kohden Co., Tokyo, Japan) which delivered biphasic cosine current pulses with a period of 238 ms. • Frequency: 25 pulses/second • Four patterns of stimulation: 1) 40-s duration (1000 pulses); 2) 80 s (2000 pulses); 3) 120 s (3000 pulses); 4) 1000 pulses/day • Intensity: peak at 0.75 T • Duration: 3 days	• MTT assay	• No significant differences were observed in cell viability between the control and stimulated cellular groups
Yamaguchi et al. (2006) [46]	• B16-BL6 murine melanoma cell line	• Magnetic stimulator (Nihon Kohden Co., Tokyo, Japan) which delivered biphasic cosine current pulses with a period of 238 ms • Intensity: 0.25 T • Frequency: 25 pulses/s, and 1000 pulses/sample/day, 80 s for 17 days • Evaluations at 3 and 7 days	• MTT • TNF-α • IL-2	• No effect of rMS

BDNF: Brain-Derived Neurotrophic Factor; CFA: Colony formation assay; CRC: colorectal cancer; CT: cycle time for bRMS; dB/dt: the rate of change of b with respect to time; DT: duration of time of a single train for iRMS; F: frequency; GDNF: Glial cell line-derived neurotrophic factor; HCC: hepatocellular carcinoma; I: intensity; ICT: intercycle of cycles of bRMS;

IHC: Immunohistochemistry assay; IL-2: Interleukin-2; iRMS: intermittent Repetitive Magnetic Stimulation; ITI: intertrain interval for iRMS; mT: milliTesla; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; NPB: number of pulses per burst for bRMS; NPT: number of pulses per train for iRMS; NSS: Neurological Severity Score; NT-3: Neurotrophin-3; NT/NC: number of trains for iRMS or number of cycles for bRMS; PDGF: platelet-derived growth factors; rMT: resting motor threshold; RT-qPCR: reverse-transcriptase polymerase chain reaction; s: seconds; T: Tesla; TNF-α: Tumor Necrosis Factor alpha; TUNEL assay: Terminal dUTP Nick End-Labeling.

Table 2. Studies employing repetitive magnetic stimulation (rMS) as a potential anti-tumoral therapy in in vivo models.

First author (year)	Animal model	Stimulation protocol Magnetic Field	Outcome	Main results
Jo et al. (2025) [23]	• Mice: male athymic nude mouse orthotopic xenograft model: U87MG TS cells implanted into the right frontal lobe by stereotaxic injection	• Customized rMS (Bicon-1000Pro, McubeTechnology, Seoul, Korea) • Frequency 0.5 Hz on-off interval of 3 s • Intensity: 18 mT • Stimulation delivered a monophasic pulse with a rise time of 370 μs • 3 days - 10 min/day	• RT-qPCR • Western blot • TUNEL assay • ATP assay • IHC • Bioluminescence imaging for tumor progression	• Suppression of tumor progression by downregulating the expression of FLNA and FLNC
Tatarov et al. (2011) [38]	• Swiss outbred female nude mice (Cr:NIH(S)-nu/nu injected with metastatic mouse breast tumor cell line EpH4-MEK-Bcl213	• Helmholtz coil driven by a controllable high-power alternating-current supply (SDR TH 40–250, Sodilec, Bordeaux, France) • Intensity: 100 mT • Frequency: 1 Hz • Duration: daily for 60, 180, or 360 min for 4 weeks	• TUNEL assay for fragmented nuclei • Tumor growth progression • Histopathology	**rMS 360 min daily/4 wk:** • Suppressed tumor growth • Induced extensive areas of necrosis and apoptosis
Jo et al. (2022) [43]	• Mice: BALB/c nude xenograft model: suspended N2a cells inoculated subcutaneously into the right hind limb anterior root ganglion	• Customized rMS (Bicon-1000Pro, McubeTechnology, Seoul, Korea) • Frequency: 0.5 Hz on-off interval of 3 s • Intensity: 18 mT • Monophasic pulse with a rise time of 370 μs • 3 days - 10 min/day	• RT-qPCR • Western blot • TUNEL assay • IHC • Tumor progression	• Suppression of cell proliferation and progression of neuroblastoma • Downregulation of the Wnt/β-catenin signaling pathway • Induction of apoptosis
Perrino et al. (2024) [47]	• Male Sprague–Dawley rats injected with C6 glioma cells	• The coil was connected to a Rapid2 stimulator (Magstim Ltd., Oxford, UK) • Repetitive stimulation, modified butterfly TMS coil with a customizable tilt angle between wings	• Tumor Size • NSS	• rTMS increased the anti-tumor effect of IGF-Trap during the early phases of tumor growth

	• Male NSG mice injected with the murine glioma GL261 cells	• rTMS administered at 130% of the resting motor threshold (rMT) • Repetitive stimulation consisting of 50 s train duration, 60 s inter-train interval, 5 trains, and 250 pulses in total		
Yamaguchi et al. (2004) [45]	• C57BL/6J mice inoculated with B16-BL6 murine melanoma cell line	• Magnetic stimulator (Nihon Kohden Co., Tokyo, Japan), which delivered biphasic cosine current pulses with a period of 238 ms • Frequency: 25 pulses/s, 1000 pulses/day. • Intensity: 0.75 T at the center of the coil • Duration: 16 days	• Tumor weight	• No significant differences in the tumor weight between the stimulated group and the sham group
Yamaguchi et al. (2006) [46]	• Female C57BL/6J mice inoculated with B16-BL6 murine melanoma cell line	• Magnetic stimulator (Nihon Kohden Co., Tokyo, Japan), which delivered biphasic cosine current pulses with a period of 238 ms • Intensity: 0.25 T • Frequency: 25 pulses/s, and 1000 pulses/sample/day, 80 s for 17 days • Evaluations at 3 and 7 days	• Tumor weight • TNF-α • IL-2 • Histopathology	**rMS induced:** • Suppression of tumor growth • Extensive areas of necrosis • Increase of TNF-α levels after 3 and 7 days of stimulation

CRC: colorectal cancer; F: frequency; GDNF: Glial cell line-derived neurotrophic factor; HCC: hepatocellular carcinoma; I: intensity; IGF-Trap: IGF signaling inhibitor; IHC: Immunohistochemistry assay; IL-2: Interleukin-2; NSS: Neurological Severity Score;; rMT: resting motor threshold; RT-qPCR: reverse-transcriptase polymerase chain reaction; s: seconds; T: Tesla; TNF-α: Tumor Necrosis Factor alpha; TUNEL assay: Terminal dUTP Nick End-Labeling.

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3. Results

3.1. Repetitive Magnetic Stimulation (rMS)

As per the search strategy shown in Figure 1, nine articles were identified involving the application of rMS (standard rMS = 8, patterned rMS = 1) as a therapeutic intervention for cancer, either independently or in combination with other treatments.

A total of 78 studies were identified for screening after excluding duplicates. After the abstract review, 18 full-text articles were assessed for inclusion and exclusion criteria. Following full-text review and resolution of conflicts, 9 articles met the inclusion criteria. The excluded studies presented rMS as a treatment for symptoms such as pain and major depression [11]. Some studies also highlighted how rMS can be used for imaging diagnosis and as an adjunct to surgery to remove tumor masses [40].

By assessing the 9 selected studies, we found 3 in vitro and 2 conducted in animal models, while the remaining 4 include both cellular and animal-based analyses (Table 1). Figure 1 shows the PRISMA flow diagram displaying the search results and process.

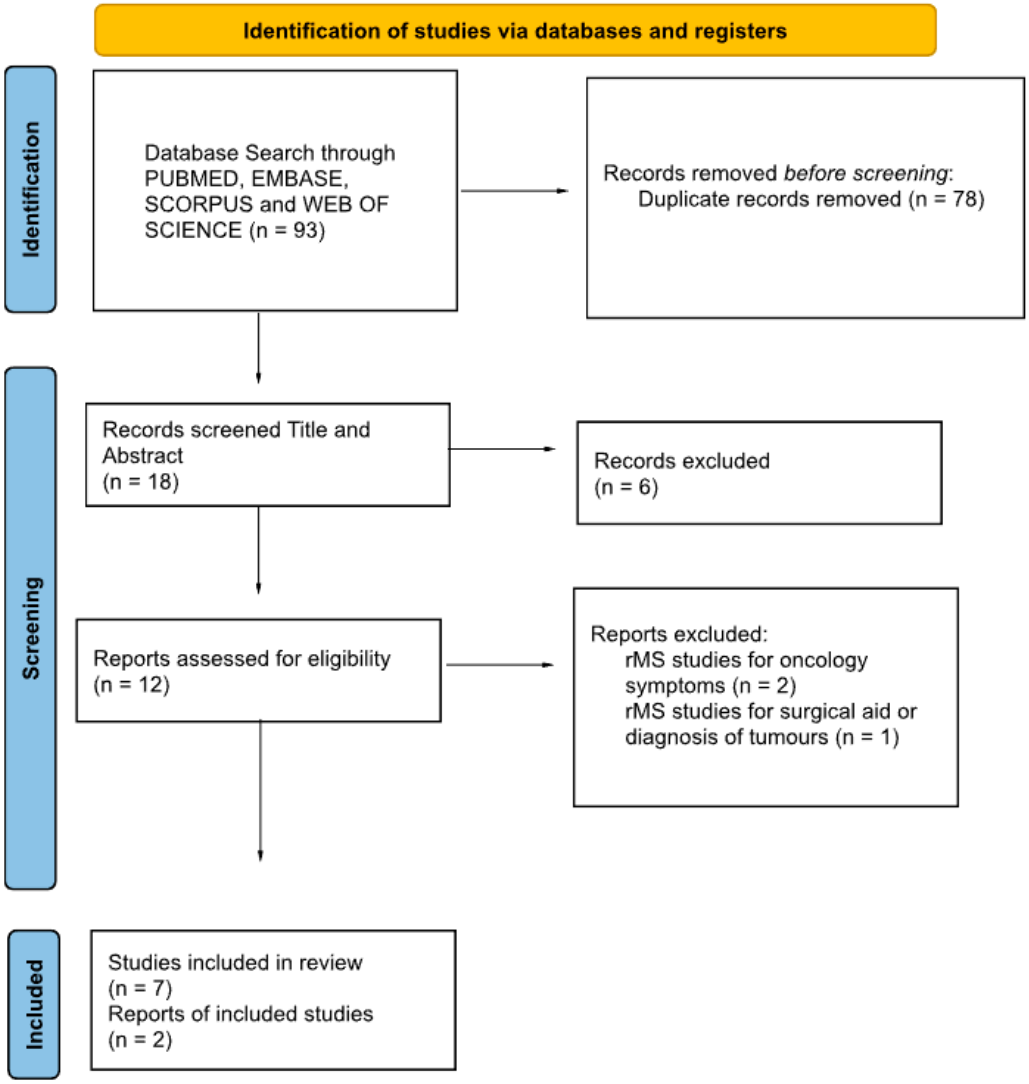

Figure 1. PRISMA flowchart depicting the search results for rMS.

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3.1.1. rMS Stimulation Devices and Protocols

Most of the studies used circular or elliptical coils (n=7), which are characteristic of clinical research, and none of the studies presented a specific device for use in cells or rodent models, only customized devices. Two of the studies used the same stimulation device, the Magstim Rapid2 Plus (Magstim Ltd., UK) [42,47]. In addition, the South Korean authors used the same rTMS device and stimulation equipment, the customized rMS (Bicon-1000Pro, Mcube Technology, Seoul, Korea) [43,44]. Yamaguchi and colleagues used the same equipment, the magnetic stimulator (Nihon Kohden Co., Tokyo, Japan) [45,46].

Ashdown et al. [41] employed two types of alternating frequencies to evaluate cell integrity. Furthermore, standard microscope slides were used to establish a platform for adjusting the elevation of the plated cells relative to the magnetic field.

The majority of the studies implemented a low-frequency protocol, revealing that the low frequency exerted an inhibitory effect. Lee et al. [44] substantiate this hypothesis, confirming the disparity between high and low frequency in a neuroblastoma cell line.

The duration of each stimulation session varied across the selected studies, with the shortest being 80 seconds [46] and the longest lasting 360 minutes [38]. Regarding the treatment period, Tatarov et al. [38] reported a 4-week stimulation period, with sessions occurring daily. Three trials employed a total treatment period of three days [43,44,46]. Only one study failed to disclose consecutive intervention days, although it performed stimulation for five days [47]. Yamaguchi et al. [45] also developed three distinct protocols concerning the duration of each stimulation session and the pulse pattern employed.

Heng et al. [42] was the only study among the eight selected publications that included five experimental protocols of intermittent rMS (iRMS) and two of burst rMS (bRMS) applied to cell monolayers in a single treatment session, distinguishing it from conventional rMS protocols.

3.1.2. In Vitro rMS Studies [Table 1]

Of the nine selected studies, seven applied cellular analysis, indicating that a diverse array of tumor cell lines were employed [23,41–46]. The N2a and Me-115 murine neuroblastoma cell lines [43,44], along with the C6 glioma cell line [47] were used for inoculation in rats and mice. Jo et al. [23] analyzed the effects of rMS using three glioblastoma cell lines (U87MG, TS15-88, TS21-117). Heng et al. [42] research included two cell lines: hepatocellular carcinoma (HuH7) and colorectal cancer (HCT116). The research conducted by Yamaguchi et al. [45,46] used the B16-BL6 murine melanoma cell line, examined both in vitro and in vivo for inoculation in mice. For analysis in mice, Tatarov [38] used the EpH4-MEKBcl2 metastatic mouse breast tumor cell line. In Ashdown's [41] study, several cell lines were used in different experiments, including A549 (human lung cancer cells), LLC (Lewis lung carcinoma), and human lung microenvironment cells, with human lung lymphatic microvascular endothelial cells being the only non-immortalized culture used.

3.1.3. In Vivo rMS Studies [Table 2]

All studies used animals inoculated with tumoral cells. Five of these studies employed only mice [23,38,43,45,46], whilst only Perrino et al. [47] included both mice and rats as the species under investigation.

3.1.4. Outcome Assessments in rMS Studies

For cell viability analysis, the colorimetric 3(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) viability assay was used in three studies [42,45,46], and Jo et al. used the Cell Counting Kit 8 (CCK-8) test [23,43]. Ashdown et al. evaluated cell viability with a luminescence-based ATP production assay, which was assessed 4 hours post-exposure. In this same investigation, cell proliferation was assessed by the number of cells determined by an automated hemocytometer and counted for 4 days [41].

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Jo et al. [43] and Lee et al. [44] examined cell proliferation in different ways, the former using a colony formation assay, which is more specific for cell survival assays based on the ability of a single cell to grow into a colony, and the latter using microscopy of the different experimental groups. Molecular analyses were performed in the same studies. Lee et al. [44] presented the expression levels of brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3), platelet-derived growth factor (PDGF), and Akt and Erk expression by Western blotting.

Besides demonstrating protein expression by Western blotting both in vitro and in vivo, focusing on the AKT, ERK, and Wnt/β-catenin signaling pathways, Jo et al. investigated the biological processes downregulated by low-frequency rMS in neuroblastoma using Gene Ontology (GO) analysis [43].

In addition, Yamaguchi et al. measured specific cytokines, IL-2 (interleukin 2) and TNF-α (tumor necrosis factor), to analyze the immunomodulatory effect caused by rTMS using the Biosource Immunoassay Kit (Biosource Co., Camarillo, CA) [46].

Five in vivo studies present tumor size as an outcome assessment for tumor progression. Jo et al. [43] and Yamaguchi et al. [46] investigated the tumor mass by assessing tumor weight after euthanasia. Three of these studies present an in vivo imaging system to evaluate the tumor mass. Yamaguchi et al. [45] used a computational model constructed from a set of magnetic resonance images. Tatarov et al. [38] implement whole-body bioluminescence imaging to monitor the tumor growth. Perrino et al. [47] used a volumetric tool (Carestream Vue 12.1 Carestream Health, Rochester, NY, USA), measured by an experienced radiologist.

To detect signs of apoptosis, the TUNEL assay (Terminal dUTP Nick End-Labeling) was performed in two studies [38,43]. Jo et al. [43] conducted the assay on N2a cells as well as in vivo, using the DeadEnd™ Fluorometric TUNEL System (Promega, Madison, WI, USA). TUNEL-positive cells were increased in the low-frequency group compared to that in the sham group [43]. Tatarov et al. performed it exclusively in an in vivo model [38], showing by TUNEL assay that the stimulated animals presented fragmented cell nuclei, indicating apoptosis.

Ashdown et al. [41] analyzed the cell surface using a Zeiss scanning electron microscope, intending to complete the data assays of Dead Cell Protease Activity to analyze the cell membrane integrity. Additionally, the authors evaluated glycan enzymatic digestion. The experiment aims to investigate how manipulation of specific molecules on the surface of cells, such as heparan sulfate (HS) and sialic acid, affects their interactions with proteins and overall cellular behavior. Heparin Lyase III (H'ase III) was used to digest HS on the cell surface, and fibroblast growth factor 2 (FGF-2) binding was measured to assess how HS removal affects protein binding. In addition, sialidase is applied to remove sialic acid to further modify the cell surface. By examining these management methods, the experiment explores how changes in cell surface molecules affect cellular responses such as growth, adhesion, and interaction with external signals.

To analyze the morphology of the tumor mass, histopathology was performed in two studies [38,46] using the bioluminescent assay. However, with the same objective, Jo et al. [43] presented the results by immunohistochemistry, with staining using an antibody against Ki-67.

Perrino et al. [47] was the only study that employed animal behavioral analysis, specifically the Neurological Severity Score (NSS).

3.2. Static Magnetic Stimulation (sMS)

The search strategy used included fifteen papers examining the application of sMS as a therapeutic intervention for cancer, either independently or in conjunction with other treatments (Figure 2). Following the exclusion of 81 papers, 69 papers were analyzed based on their titles and abstracts. Three independent reviewers conducted screening, and in cases where there were disagreements over classification, the relevant 53 studies from the study were reviewed. Studies were excluded mostly due to inappropriate interventions or incorrect populations, specifically when the studies were clinical reports. Studies employing sMS alongside Extreme Low Frequency Stimulation

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as an intervention were not included in the review, as they involve two concurrent treatments, making it impossible to isolate the effects of a single stimulation. A total of fifteen studies were legible and extracted for this scoping review. Figure 2 shows the PRISMA flow diagram displaying the search results and process.

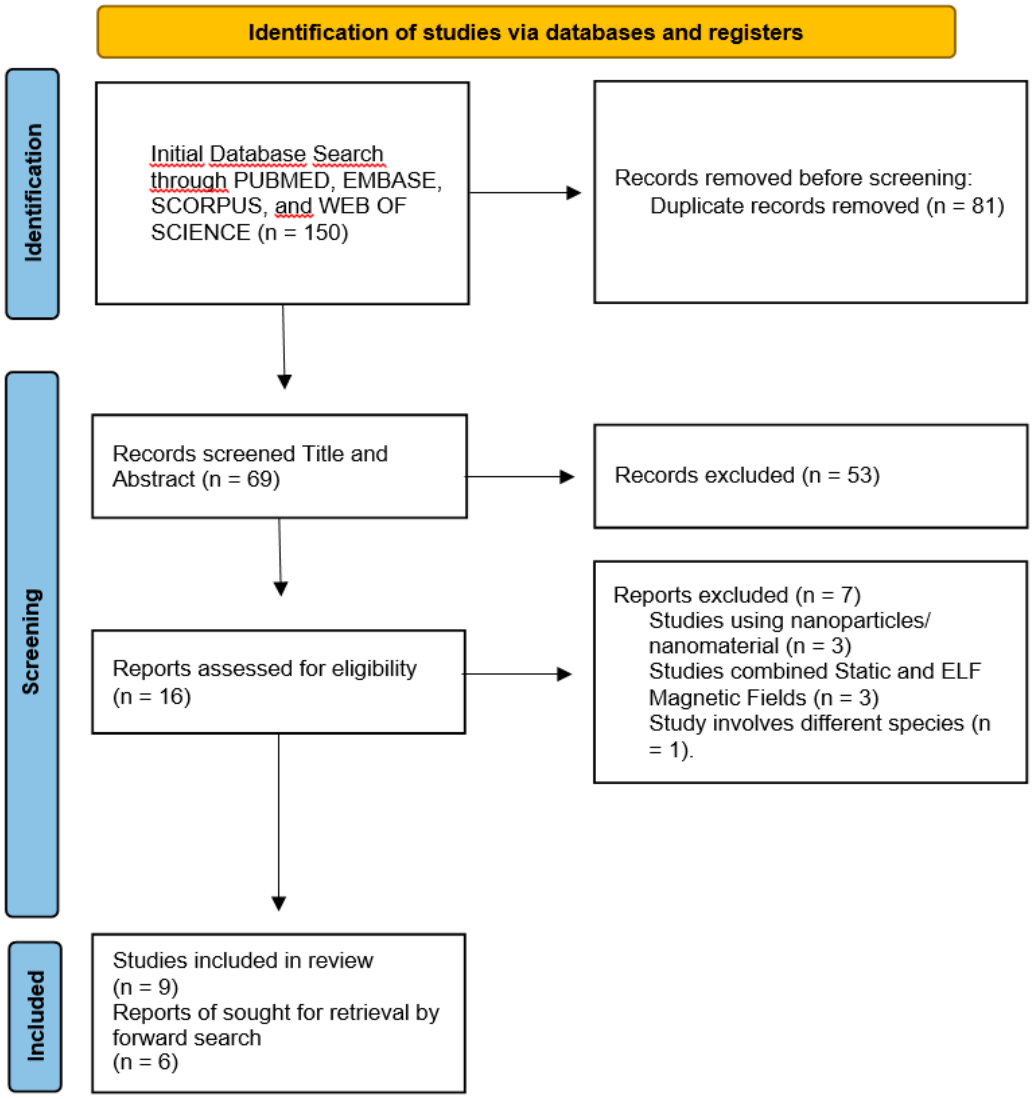

Figure 2. PRISMA flowchart depicting the sMS search results.

3.2.1. sMS Stimulation Devices and Protocols

Neodymium magnets have been employed in seven studies [25,26,48,50,54–56], establishing them as the most widely used tool. Zhang et al. [58] and Chen et al. [49] performed his studies with a solenoid made of copper wire wound around a ring with a radius. Jalali et al. [52] employed iron blades as the field conductor, while Zhao et al. [59] employed 16 T superconducting magnets for an identical purpose. In Kamalipooya et al. the exposure to sMS was performed using a locally designed SMF generator, consisting of two coils and a switching power supply [51]. Yang et al. selected two exposure systems to experiment with different intensities; the 150 mT was composed of 10 small magnetic plates, each containing eight north polar magnets, whose strength was 500 mT, and formed the upward 150 mT magnetic plate to the surface of mice. The 22 T sMS was generated by a water-cooled magnet (WM2) in the Chinese High Magnetic Field Laboratory [57]. Sun et al. does not specify the static magnetic stimulation equipment [37].

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The majority of studies employed an average magnetic field intensity of 0.2 T, which is considered moderate. Furthermore, Gray et al. [48] conducted his study at a moderate level of 0.11 T, which was lower than the intensity employed by the majority of other investigations included. On the other hand, Jalali et al. [52] employed much reduced intensities of 0.01 T, 0.015 T, and 0.025 T in his in vitro experimental methodology. Only Yang et al. used a high magnetic field intensity of 22 T [57].

The research applying sMS as the primary intervention exhibited variability in session duration, similarly to rMS studies. Medeiros et al. [25] reported a minimum session time of 60 minutes, while Zhao et al. [59] recorded a maximum session duration of 7 days. The remaining studies usually scheduled their sessions with an average interval of 48 hours.

Most research employed a Gaussmeter or Teslameter to quantify the intensity of the magnetic field, except for Gray et al. [48], Chen et al. [49] and Teodori et al. [56].

3.2.2. In Vitro sMS Studies [Table 3]

The inclusion of studies indicated that 13 out of the selected ones utilized cell culture as their methodology. Medeiros et al. [25,26] employed the human neuroblastoma cell line SH-SY5Y as the principal model in both studies, with the initial paper using SH-SY5Y cells differentiated in dopaminergic neurons with retinoic acid [25]. Furthermore, this study also made use of a non-neuronal tumor line, the human vaginal malignant melanoma HMVII, and adipose-derived mesenchymal stem cells for evaluation of the sMS effect. Kim et al. [53] and Sun et al. [37] also used neural tumor cells, specifically the glioblastoma U87MG and U251MG lines. Teodori et al. [55] used glioblastoma primary cell culture from four patients. Chen et al. [49] and Zang et al. [58] used the K562 cell line to analyze the sMS effects in myeloid leukemia. Tenuzzo et al. [55] analyzed the sMS effects in different cell lines, as isolated human lymphocytes, thymocytes from mice, FTRL-5 (cloned line of thyroid differentiated cells), U937 (monoblastic cells), G23DO cells (T hybridoma), HeLa (human cervical cancer), and HepG2 (human hepatocellular carcinoma). Chen et al. [50] also selected HepG2 to analyze the effects. Kamalipooya et al. [51] utilized the HeLa cell line and the Hu02 cell line to compare the sMS effects. Zhao et al. (2021) employed two tumor cell lines from distinct animal species: K7M2 from murine osteosarcoma and MG63 from human osteosarcoma. Jalali et al. [52] and Zafari et al. [27] investigated the sMS effects in cells with pharmacological resistance, using the A2780-CP human ovarian cancer cell line, which is resistant to cisplatin, in comparison to the non-resistant A2780 cell line.

3.2.3. In Vivo sMS Studies [Table 4]

Four sMS studies used rodents. Grey et al. [48] used female B6C3F1 mice, approximately 5 weeks old, inoculated with uniform fragments of murine mammary cancer. In the same study, static electric stimulation was employed; however, only the group that received sMS as an intervention was evaluated. Additionally, Zhao et al. [59] used four-week-old male Balb/c mice inoculated with osteosarcoma stem cells (OSCs). Yang et al. [57] used a total of 24 25-day-old (~16 g) male SPF BALB/c (Nu/Nu) mice with the A549 cell line inoculated. Only one used Syrian Golden Hamsters bearing syngeneic A-Mel-3 melanomas to perform the experiment [54].

Table 3. Studies employing static magnetic stimulation (sMS) as a potential anti-tumoral therapy in in vitro models.

First author (year)	Cell line	Stimulation protocol	Outcome	Main results
Chen et al. (2010) [49]	• K562 human erythroleukemia cell line • Cell groups were: **(1)** exposure to SMF for 12 hours; **(2)** incubated with 5, 10, and 20 mg/mL of cisplatin for 12 hours; and **(3)** exposure to SMFs + cisplatin	• SMF: solenoid made of copper wire wound around a ring • Intensity: 8.8 mT • Duration: 12 hours	• Cell Viability - MTT assay • Cell Cycle - PI by flow cytometry • Comet assay • FCM analysis • Atomic force microscopic observation	**SMF alone** • Increased cell death induced by cisplatin, reducing the effective concentration from 20 mg/mL to 10 mg/mL **SMF + cisplatin** • Inhibited cell proliferation. • Caused severe damage to cellular DNA (thinning, increased breaks and cross-links)
Chen et al. (2018) [50]	• HepG2 (human hepatocellular carcinoma cell line) • Cells treated with or without capsaicin and SMFs for 72h.	• The SMF groups were placed on cylindrical permanent magnets derived from the rare earth material neodymium iron boron • Intensity: ~ 0.5 T • Duration: 72 hours	• Cell Viability - MTT assay • Cell apoptosis - Anexin/PI by flow cytometry • Western Blot - Bax and Bcl-2 analysis • Immunofluorescence microscopy • Intracellular calcium assay	**SMF alone** • Did not cause anticancer effect **SMF + capsaicin** • Increased the anticancer effect • Increased the binding efficiency of capsaicin for the TRPV1 channel. • Intensified capsaicin induced apoptosis; • Increased the concentration of intracellular calcium
Kamalipooya et al. (2017) [51]	• Human cervical cancer • (HeLa) cell line and normal skin fibroblast cells (Hu02) • Both cell types were divided into **(1)** without treatment; **(2)** cisplatin; **(3)** SMF; **(4)** cisplatin + SMF	• Locally designed SMF generator, consisted of two coils and a DC switching power supply • Intensity: 7, 10, and 15 mT • Duration: 24 and 48 hours	• Cell Viability - MTT assay • Determination of intracellular ROS - DCF-DA Cellular ROS • Estimation of lipid peroxidation- by measuring malonyldialdehyde (MDA)	• SMF in 10mT had more effects on the HeLa cell line and lower effects on fibroblast cells • SMF sensitizes human cervical cancer cells to cisplatin through ROS accumulation • Membrane lipid peroxidation was higher in cancer cells (HeLa) than in normal cells (Hu02) 8191 **SMF + cisplatin** • Significantly increased ROS formation in HeLa cells
Jalali et al. (2019) [52]	• A2780 and A2780-CP human ovarian cancer cells	• SMF with a locally designed generator • Intensity: 10, 15, or 25 mT	• Cell viability (MTT assay); • IC50 (cisplatin sensitivity); • Cisplatin uptake (ICP-OES)	**SMF** • Did not affect cell viability

	• Both cell types divided into: **(1)** without treatment; **(2)** SMF alone; **(3)**. 1, 10, 50, 100 and 500 μM concentration of cisplatin; **(4)** SMF + cisplatin	• Duration: 24, 48, or 96 hours		• No significant increased cisplatin sensitivity in both cell lines • A2780 cells were more cisplatin-sensitive
Kim et al. (2016) [53]	• Human glioblastoma U87MG and U251MG cells	• SMF, Hirst Magnetic Instruments Ltda, Falmouth, England. • Intensity: 1.4 to 2.6 T • Duration: 48 hours	• WST-1 cell viability assay; • Apoptotic signal assessment of viability. Annexin V test • Immunocytochemistry • Protein expression related to the cell cycle (cyclin B1 and Cdk1)	**SMF** • Decreased cell viability • Reduced Cdk1 protein expression, affecting cell cycle regulation • No effects on apoptosis
Medeiros et al. (2020) [25]	• SH SY5Y (neuroblastoma cell) • SH SY5Y differentiated cells • HMV (human vaginal malignant melanoma cells) • Mesenchymal cells	• A custom-made stand for attaching 24-well standard plates used for sMS stimulation • NdFeB magnets • Intensity: 0.1, 0.2, and 0.3 T • Duration: 60 min, and 24 hours	• Cell viability (MTT assay); • Cell death (PI/Hoechst; • Annexin-V/PI staining); • Cell cycle analysis (PI staining) • BDNF gene expression	**sMS** • Reduced viability in SH-SY5Y cells; • Increase in necrotic cells • No effects on the cell cycle • No variation in BDNF expression in SH-SY5Y cells subjected to SMS, except for the analyses conducted between 24 and 48 hours
Medeiros et al. (2023) [26]	• SH SY5Y neuroblastoma cell • HMV (human vaginal malignant melanoma cell); • Mesenchymal cells	• A custom-made stand for attaching 24-well standard plates was used for sMS stimulation • NdFeB magnets • sMS at 0.3T, applied to SH-SY5Y neuroblastoma cells for 6, 12, 24, 36, 72 hours, and 6 days	• Cell viability (MTT assay) • Cell death (Annexin-V/PI staining) • Cell cycle (DNA content) • Proliferation (CFSE assay) • Autophagy (acridine orange staining) • Mitochondrial mass (MitoTracker Red)	**sMS** • Reduced cell viability at 24h and 6 days • Decreased autophagy and cell proliferation after 6 days • Reduced mitochondrial mass after 6 days • No effect on cell cycle arrest or cell death
Sun et al. (2025) [37]	• U251 and U87 glioblastoma cell line • U87 and U251 cells were treated with 10 ng/ml of TGF-β1	• Exposed to sMS • Intensity: 0.1 T • Duration: 72 hours	• Cell cloning and colony formation assay • EdU proliferation assay • Apoptosis assay • Migration and invasion assays • Western blot-N-cadherin, β-catenin, MMP-2	**TGF-β1** • Altered cell morphology • Increased proliferation • Promoted migration and invasion of glioblastoma cells • Reduced apoptosis **sMS alone** • Minimal impact on cell morphology

				• Increase apoptotic cells proportion in both U87 and U251 cell lines • Decreased protein levels of mesenchymal markers N-cadherin and β-catenin • Reduced expression of matrix metalloproteinase-2 (MMP-2) **sMS + TGF-β1** • Reduction in cell migration and invasion • Increase in apoptosis • Decreased protein expression of mesenchymal markers (N-cadherin and β-catenin) • Reduced levels of the MMP-2
Tenuzzo et al. (2006) [55]	• U937 • HeLa • HepG2 (human hepatocellular carcinoma cells • FRTL-5 cells • Apoptosis-inducing agents: cycloheximide (CHX), H_2O_2, puromycin (PMC), heat shock, and etoposide	• SMF: Neodymium magnetic disks (Calamit Ltd., Milano, Italy) • Intensity: 6 mT • Duration: 24 and 48 hours	• Cell viability - MTT assay • Cell growth rate • Apoptosis assay - Hoechst-33342/propidium iodide or hematoxylin/eosin-stained cells • Scanning Electron Microscopy • Measurements of Ca^{2+} levels	**SMF** • Promoted apoptosis and mitosis, but not necrosis or modifications of the cell shape • Recovered from apoptosis induced by pro-apoptotic drugs • Increased intracellular Ca^{2+} levels
Teodori et al. (2002) [56]	• Primary culture of human glioblastoma • Apoptosis induced by etoposide (VP16) or heat shock (HS)	• SMF of known intensities was produced by metal magnetic disks • Intensity: 6 mT	• Microfluorimetry: intracellular Ca2 concentration • Apoptosis assay: Hoechst 33342 and propidium iodide (PI) and Annexin V/fluorescein (FITC)	**SMF** • Increased [Ca2+] influx • Non-apoptogenic activity • Reduced the extent of stress-induced apoptosis • Increased cell survival • Reduced apoptosis cell-line dependent
Zafari et al. (2024) [27]	• Cisplatin-sensitive (A2780) and -resistant (A2780CP) ovarian carcinoma cells • Both cell types divided in: **(1)** without treatment; **(2)** SMF	• SMF via a local generator (two wire coils with 3.0 mm and inductance of 2 H, resistance of 3 Ω, and a heat resistance of up to 200 °C • Intensity: 15 T	• Comet assay • Cell cycle analysis • Apoptosis assay • Annexin V/PI	**SMF + cisplatin** • Increased DNA damage in both sensitive and resistant cell lines • A considerable increase in mortality of cells, via necrosis, and mostly apoptosis

	alone; **(3)** cisplatin; **(4)** SMF + cisplatin	• Duration: 24, 48, and 96 hours	• PCR: Gene expression of P53, P21, CTR1, and BCL2	• Increased expression levels of apoptotic genes (P53 and P21) • Minimal effect on the expression levels of BCL2 • Increased CTR1 gene expression
Zang et al. (2014) [58]	• K562 human erythroleukemia cell line	• SMF: solenoid made of copper wire wound around a ring • Intensity: 8.8 mT • Duration: 4, 8, or 12 hours	• Cell viability: MTT assay • HPLC Analysis • FAAS Analysis • Analysis of P-Glycoprotein Expression Using Flow Cytometry	**SMF + DDP** • Significantly inhibited the metabolic activity of K562 cells, while DDP or SMF alone did not
Zhao et al. (2021) [59]	• Murine osteosarcoma cell line K7M2 and human osteosarcoma cell line MG63	• SMF: 16-T superconducting magnet • Intensity: 0.2–0.4 T	• Light Microscopy • Crystal Violet Staining • Cell Counting Kit 8 CCK-8 assay • ROS detection • H&E staining • IHC • IF • Western blot • siRNA transfection • TEM • Fe^{2+} detection assay	**SMF** • Promoted the release of ferrous iron (Fe^{2+}); • Induced proliferation and tumor sphere • Provoked ROS in OSCs. • Stimulated the self-renewal ability of OSCs through autophagic degradation of ferritin

BDNF: Brain-Derived Neurotrophic Factor; CFA: Colony formation assay; DCFDA: 2′,7′-Dichlorofluorescin Diacetate; FAAS: Flame Atomic Absorption Spectrophotometer; Fe^{2+}: Ferrous Iron; GDNF: Glial cell line-derived neurotrophic factor; H&E: Hematoxylin–Eosin; HPLC: High-performance liquid chromatography; IF: Immunofluorescence; IHC: Immunohistochemistry / Immunohistochemistry assay; MMP-2: matrix metalloproteinase; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; NT-3: Neurotrophin-3; PDGF: platelet-derived growth factors; ROS: Reactive Oxygen Species; RT-qPCR: reverse-transcriptase polymerase chain reaction; siRNA: Small Interfering RNA Transfection; sMS: Static Magnetic Stimulation; SMF: Static Magnetic Fields; T: Tesla; TEM: Transmission Electron Microscope; TGF-β1: Transforming Growth Factor β1.

Table 4. Studies employing static magnetic stimulation (sMS) as a potential anti-tumoral therapy in in vivo models.

First author (year)	Animal model	Stimulation protocol	Outcome	Main results
Gray et al. (2000) [48]	• Female B6C3F1 mice transplanted 16/C mammary adenocarcinoma	• Static neodymium magnet field (SMF) • Intensity: 110 mT • Duration: 4-hour session	• Tumor regression (weight)	**SMF** • Enhanced tumor regression induced by adriamycin

	• Mice were treated: **(1)** control. **(2)** adriamycin (10 mg/kg). **(3)** SMF alone. **(4)** SMF + adriamycin			
Strelczyk et al. (2009) [54]	• Syrian Golden Hamsters bearing syngeneic A-Mel-3 melanomas	• SMF was generated by a cylindrical permanent magnet derived from the rare earth material neodymium iron boron (NdFeB, 250/175 h • Magnetfabrik Schramberg, Schramberg, Germany) • Intensity: 586 mT • Duration: 3, 24, 48, and 72 hours after tumor inoculation	• Tumor angiogenesis (in vivo fluorescence microscopy for functional vascular density, red blood cell velocity, vessel diameters) • Tumor growth • Histology (H&E staining); • Animal behavior and body weight	• Prolonged exposure to sMS retarded the growth of solid tumors • SMF impaired tumor angiogenesis • Reduced intratumoral functional vascular density and red blood cell velocity • Increased edema and impaired intercellular adhesion • No effects on the behavior or body weight
Yang et al. (2023) [57]	• Mice with A549 cell line inoculated • SMF associated with platycodin D (PD)	• SMF was generated by a water-cooled magnet (WM2) in Chinese High Magnetic Field Laboratory (Hefei, China) • Intensity: 22 T SMF • Duration: 6 days	• Elevated plus-maze test • Open field test • Noninvasive pulse oximetry test • Complete blood count and blood biochemistry test; • H&E staining: Heart, liver, spleen, lung, kidney, and tumor tissues • RNA extraction and RNA-sequencing (RNA-seq)	**SMF** • The antitumor effect of 22 T SMF was 3.6 times greater than that of PD alone • RNA-seq showed SMFs and PD synergistically targeted genes associated with tumor growth, inflammation and neurological diseases
Zhao et al. (2021) [59]	• Osteosarcoma stem cells (OSCs) into tumor-bearing mice	• Exposure to a 0.2–0.4 T SMF using a 16-T superconducting magnet	• ROS detection • H&E Staining • IHC • IF • Western blot • siRNA transfection • TEM • Fe^{2+} detection assay	• The long-term exposure to moderate-intensity SMF did not affect the tumor volume or mass, nor the lung metastasis of K7M2 OSCs • The SMF-treated K7M2 OSCs caused a preference of pulmonary metastasis in tumor-bearing mice

Fe^{2+}: Ferrous Iron; H&E: Hematoxylin–Eosin; HPLC: High-performance liquid chromatography; IF: Immunofluorescence; IHC: Immunohistochemistry / Immunohistochemistry assay; ROS: Reactive Oxygen Species; RT-qPCR: reverse-transcriptase polymerase chain reaction; siRNA: Small Interfering RNA Transfection; sMS: Static Magnetic Stimulation; SMF: Static Magnetic Fields; T: Tesla.

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3.2.4. sMS Combined with Other Interventions

Ten studies reported another type of antitumoral treatment in combination with sMS [27,37,48–52,55–57]. Four out of these studies used cisplatin as the primary antineoplastic treatment, in varying concentrations, ranging from 25 μM to 2 mg/kg [27,49,51,52]. In addition to cisplatin, Chen et al. [50] proposed using the TRPV1 antagonist as an adjunct therapy. Yang et al. [57] used platycodon D at a concentration of 2 mg/kg. Gray et al. [48] and Chen et al. [50] used adriamycin (10 mg/kg) and capsaicin (25, 50, and 75 μM to block TRPV1 channels), respectively. Tenuso et al. used cycloheximide (CHX, 10-2 M), H_2O_2 (10-3 M), puromycin (PMC, 10-6 M), heat shock (HS, 43º C), and etoposide [55]. Teodori et al. used etoposide (VP16) or HS as apoptosis inductors [56]. On the other hand, Sun et al. associated SMF with the transforming growth factor β1 (TGF-β1), which is a key factor promoting proliferation, migration, and epithelial-mesenchymal transition (EMT) in glioblastoma (GBM) [37]. EMT may play a crucial role in tumor invasion and drug resistance.

3.2.5. Outcome Assessments in sMS Studies

The most frequently observed test in the selected articles was related to cell viability, in which the MTT assay was found in 8 articles [25,26,49–52,55,58]. To validate the hypothesis of magnetic stimulation as a possible antineoplastic treatment, the second most frequently performed test was the assessment of cell death by apoptosis assay by Hoechst 33342 or/and propidium iodide (PI) and Annexin V/fluorescein (FITC) [25,26,50,53].

Rodent investigations reveal a consistent pattern of assessments, including Hematoxylin and Eosin (H&E) staining of tumor tissues, tumor growth, animal behavior, and body weight [48,54,57,59]. Yang et al. [57] conducted more comprehensive testing pertaining to biochemistry and RNA sequencing (RNA-seq).

To evaluate the potential impact of sMS and cellular mechanisms, intracellular Ca2+ concentration [50,55,56] was employed to elucidate cell signaling and modulation of apoptosis; production of reactive oxygen species (ROS) such as DCFH-DA (dichlorodihydrofluorescein diacetate) [51]; mitochondrial mass (MitoTracker Red) to evaluate oxidative stress as cell damage [26], membrane lipid peroxidation [51]; related to lipid membrane damage; and analysis of late cell autophagy as a mechanism of cell survival [26]. Furthermore, electron microscopy (TEM and SEM) was employed for detailed observation of morphological and ultrastructural changes at the subcellular level, including cell shape and membrane surface [49,51,55]. As molecular mechanisms evaluated, Western blot analysis was performed for epithelial-mesenchymal markers such as N-cadherin, β-catenin, and matrix metalloproteinase-2 (MMP-2), as well as Bax and Bcl-2 [37,50,53].

4. Discussion

Advancements in MS protocols have yielded results in various domains over the years. The efficacy of neuromodulatory techniques has been evaluated in the management of brain tumors due to their capacity to influence specific neuronal activity within the central nervous system (CNS). Specifically, rMS has been shown to modulate cell signaling pathways that can suppress cell proliferation and tumor progression, including neuroblastoma, by negatively regulating signaling pathways such as Wnt/β-catenin, and by inducing apoptosis [43]. On the other hand, high-frequency rMS can increase cell proliferation in neuroblastoma, demonstrating specificity dependent on the parameters of stimulation employed. Furthermore, rTMS has been demonstrated to induce a transient disruption of the blood-brain barrier, facilitating the delivery of anti-cancer drugs (such as IGF-Trap) to the brain [47]. This is a significant advantage for brain tumor treatment. Nevertheless, initial investigations employing rMS as a treatment for cancer yielded a series of nonsignificant outcomes concerning cellular viability, assessed by MTT assay as the standard methodology. Two studies used the B16-BL6 murine melanoma cell line (in vitro) and C57BL/6J mice inoculated with the same cell line while employing distinct stimulation protocols [45,46]. It was shown rTMS induces

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suppression of tumor growth, extensive areas of necrosis, and an increase of TNF-α levels after 3 and 7 days of stimulation, revealing that it can influence molecular and cellular mechanisms [46].

Corroborating this hypothesis, Lee et al. investigated changes in the expression of BDNF, GDNF, NT-3, and PDGF, as well as cellular proliferation, in immortalized mouse neuroblastoma cells subjected to low- (0.5 Hz) and high-frequency (10 Hz) rMS [44]. The levels of these biomarkers were significantly elevated in the high-frequency group (10 Hz) compared to both the non-stimulated and low-frequency groups (0.5 Hz). Additionally, this study indicated that the expression of Akt and ERK was markedly increased in the high-frequency stimulation group, while low-frequency stimulation reduced it compared to the control group, demonstrating that rMS alters the expression of signaling pathways [44]. It is important to note that ERK and Akt are associated with neurotrophic and growth factors that promote cell survival and proliferation [60]. Consequently, these results provide compelling evidence that different frequencies of rMS modulate the expression of growth factors and influence neuroblastoma cell proliferation in distinct manners [44].

In the in vivo model, low-frequency rMS also exhibited promising results. Jo et al. conducted a study and demonstrated that the tumor exhibited continuous progression in the sham group, whereas the group treated with rMS displayed a markedly slower growth rate, comparable to that observed in the group treated with temozolomide (TMZ), a chemotherapeutic drug. The immunohistochemical analysis revealed reduced cell proliferation, evidenced by lower Ki-67 expression and H&E staining in tumors from the rMS- and TMZ-treated groups [43]. In the same study, in the in vitro experiment, the authors demonstrated that N2a neuroblastoma cells subjected to low-frequency rMS (0.5 Hz) at an intensity of 18 mT for 10 minutes daily over three consecutive days exhibited a significant decrease in cell proliferation, as demonstrated by the CCK-8 assay and the diminished colony formation observed in the CFA assay [43]. To further investigate the role of the analyzed Wnt/β-catenin signaling pathway in the rMS response, both an agonist and an antagonist of this pathway were employed. Downregulation of genes and proteins associated with the Wnt/β-catenin pathway, including WNT3a, WNT5a, β-catenin, DVL1, and LEF1, was observed following treatment with low-frequency rMS. The Wnt pathway antagonist produced effects similar to those of rMS, suppressing cell proliferation and promoting apoptosis, whereas the agonist reversed the inhibitory effects of rMS. This way, it was possible to suggest that low-frequency rMS induces apoptosis and inhibits cell proliferation in neuroblastoma, at least in part, through downregulation of the Wnt/β-catenin signaling pathway [43]. In conclusion, this study provides robust evidence of the potential of low-frequency rMS as a new neuroblastoma treatment approach, establishing the basis for future research and perspective for clinical applications of this technique in cancer therapy.

Recently, the same research group [23] demonstrated that low-frequency rTMS (0.5 Hz) exhibits effective tumor-suppressive properties against glioblastoma by inhibiting proliferation and invasion, and promoting apoptosis via multiple molecular pathways. In tumor spheres in vitro, magnetic stimulation decreases the activation of EGFR and EphA2 receptors. Western blot analysis revealed apoptosis induced by downregulating ERK/JNK/p38 and PI3K/AKT/mTOR pathways, while transcriptome assessment showed a marked reduction in the expression of FLNA and FLNC genes (in vitro and in vivo), both linked to the cytoskeleton and cell mobility. The reduced tumor growth was confirmed by magnetic resonance imaging and bioluminescence, which correlated with a decrease in FLNA and FLNC in mice. The tumor's invasiveness by downregulating the expression of MMP2 and MMP9 indicates that low-frequency rMS not only inhibited cell proliferation but also induced apoptosis in the neuroblastoma model [23]. It is important to note that the results from sMS studies are conflicting; while some indicate that stimulation significantly decreases cell viability [53], others report no significant antitumoral effects using stimulation alone [50,52,58]. These results point to how different protocol standards can produce different outcomes, making sMS a less reliable treatment option than rMS.

Sun et al. [37], employing sMS in U87 and U251 glioma cells aiming at inhibiting the migration and invasion, demonstrated increases in apoptosis, and decreased expression of N-cadherin, β-catenin and MMP-2 proteins, both alone and combined with TGF-β1. Meanwhile, Yang et al. [57],

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using the RNA-seq technique, showed that SMF at high-intensity (22 T) and platycodin D (PD) synergistically target genes associated with tumor growth, inflammation, and neurological diseases. The SMF antitumoral effect was 3.6 times greater than PD alone. Zhao et al. [59] found that moderate (0.2-0.4 T) and prolonged exposure to SMF resulted in the proliferation and tumor sphere formation in K7M2 and MG63 OSCs, promoted the release of ferrous iron (Fe2+), stimulated the production of ROS in OSCs, and triggered the autophagic degradation of ferritin, indicating the activation of microtubule-associated protein in OSCs. In vivo, the application of SMF to tumor-bearing mice did not affect the tumor volume, tumor mass, or pulmonary metastasis of K7M2 OSCs; however, SMF-treated K7M2 OSCs exhibited a propensity for pulmonary metastasis in a mouse model, indicating that SMF may induce metastatic characteristics in OSCs [59]. The study by Strelczyk et al. [54] showed that tumors subjected to sMS were considerably smaller than those in the nonstimulated group, presumably due to inhibit angiogenesis. The combination of sMS with adriamycin also presents tumor regression [48]. Tatarov et al. conducted a thorough analysis of the effects of varying durations of magnetic exposure on tumor growth and viability in mice injected with breast cancer cells [38]. The study involved the injection of the EpH 4-MEK-Bc12 breast cancer cell line in 3 mice groups, and exposed to different durations of SMF (60, 180, or 360 min). The animals were subjected to daily exposure to unipolar half-wave sinusoidal magnetic fields at 100 mT and 1 Hz for up to four weeks. All groups showed tumor growth; however, the group exposed to 360 minutes of stimulation exhibited necrotic tumor tissue and a significant suppression of tumor growth. Mice that were not inoculated with cancer cells but were exposed to magnetic fields showed no histopathological abnormalities in the lung, liver, or skin tissues, leading to the hypothesis that the treatment exhibits cellular selectivity and is not cytotoxic. Zafari et al. [27], using cisplatin-sensitive (A2780) and -resistant (A2780CP) ovarian carcinoma cells, demonstrated that treatment with cisplatin combined with SMF increased the expression of apoptotic genes, specifically the genes CTR1, P53 and P21, and induced necrosis and apoptosis. On the other hand, Medeiros et al. [26] did not demonstrate significant cell death, but reported that sMS can decrease cell autophagy and mitochondrial mass. Other mechanisms analyzed were the increase in the production of ROS and the lipid peroxidation, leading to apoptosis in cancer cells. Kamalipooya et al. [51] used a combined treatment of sMS and cisplatin, and demonstrated that SMF at 10 mT had more effects on the HeLa cell line than in fibroblast cells, sensitizing human cervical cancer cells to cisplatin through ROS accumulation, mostly in HeLa cells. Meanwhile, Teodori et al. [56] and Tenuzzo et al. [55] point to increased intracellular calcium as a mechanism for apoptosis. In summary, the effects of sMS demonstrate enhancing the efficacy of chemotherapy drugs such as Cisplatin [48,49] and Platycodon D [57], and can reduce drug resistance in cancer cell lines [27]. Furthermore, it can also reduce the dose of cisplatin using sMS as an adjuvant [49]. The impact of magnetic fields is frequently specific to cell type and can differ based on the cell condition (normal versus transformed), as demonstrated by Medeiros et al. [25,26]. Kamalipooya et al. [51] also point to a cell-type dependency, focusing on tumor cell lines, introducing the magnetic fields as a possible cancer treatment. Although, the intragenic heterogeneity of cancer constitutes a limiting factor. Moreover, the manner of cells grow (adherence versus spheres in suspension) may potentially affect the effects of magnetic fields. Heng et al. [42] implemented various protocols of iRMS and bRMS to investigate the effects of repetitive magnetic stimulation on the metabolic activity of human colorectal cancer (CRC) and hepatocellular carcinoma (HCC) cells. Although the responses of the examined cell lines, HCT116 (CRC) and HuH7 (HCC), to rMS were largely contradictory; the low-frequency iRMS protocol resulted in a statistically significant decrease of metabolic activity in the HCT116 cells, while it caused a statistically significant increase of metabolic activity in the HuH7 cells, compared to the control groups. The authors suggest that the effects are tumor type- and stimulation protocol-specific, exhibiting nearly different responses based on the frequency and density of magnetic flux [42].

In addition, a previous study, especially with rTMS-coupled IGF-Trap, observed that the anti-tumoral effect was transient, with tumors eventually progressing or developing resistance to treatment over time [47]. These conditions suggest the need to optimize protocols and/or combine

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them with other therapies in order to obtain more sustained results specific to the cell type or disease. This confirms the hypothesis that CRC cell sensitivity to rMS (suppression of their viability by low-frequency iRMS) may depend on the effects of magnetic fields on molecular structures associated with the cell membrane and, to a lesser extent, the effect of the magnetic field on the electron transport chain in mitochondria. In HCC cells, it appears more likely that the effects of rMS on the mitochondrial electron transport chain may be involved in the suppression of viability.

While numerous studies indicate a favorable safety profile for exposure to magnetic fields, the need for systematic long-term toxicological investigations in organs including bone marrow and reproductive systems remains emphasized. The current scoping review categorizes the majority of study categories: high- and low-frequency exposure. In this context, tumor proliferation is the most frequently mentioned outcome, whilst tumor suppression is the second most cited. It is important to note that the studies analyzed in the current review include numerous limitations that affect clarity and usefulness of research. A significant challenge resides in the considerable heterogeneity of the magnetic field parameters (intensity, frequency, duration of exposure and type of modulation) employed across many investigations. This magnetic stimulation protocol heterogeneity complicates the direct comparison of outcomes and the establishment of an "ideal standard" of exposure. The efficacy of any magnetic stimulation approach is dependent on specific factors: cancer nature and location, cell type and metabolic state, besides to exposure parameters such as intensity, frequency, and duration, which are critical and can even reverse the effect (inhibitory versus stimulatory).

5. Conclusions

In conclusion, the current review reveals the intricate relationship between magnetic fields and biological systems, emphasising the necessity for further research to refine treatment protocols, elucidate unraveled mechanisms, and confirm the safety and efficacy of magnetic stimulation techniques. However, these findings suggest the potential of magnetic fields as an adjuvant therapy for cancer, enhancing the efficacy of traditional treatments, like chemotherapy.

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Abbreviations

The following abbreviations are used in this manuscript:

ATP	Adenosine Triphosphate
bRMS	Burst Repetitive Magnetic Stimulation
BDNF	Brain-Derived Neurotrophic Factor
CCK-8	Cell Counting Kit 8
CFA	Colony Formation Assay
CHX	Cycloheximide
CNS	Central Nervous System
CRC	Colorectal Cancer
cTBS	Continuous Theta Burst Stimulation
DCFDA	2′,7′-Dichlorofluorescin Diacetate
EMT	Epithelial–Mesenchymal Transition
FAAS	Flame Atomic Absorption Spectrophotometer
Fe^{2+}	Ferrous Iron
FGF-2	Fibroblast Growth Factor 2
FITC	Fluorescein Isothiocyanate
GDNF	Glial cell line-Derived Neurotrophic Factor
GO	Gene Ontology
H&E	Hematoxylin–Eosin
H′ase III	Heparin Lyase III
HCC	Hepatocellular Carcinoma
HPLC	High-Performance Liquid Chromatography
HS	Heparan Sulfate
IF	Immunofluorescence
IGF-Trap	IGF Signaling Inhibitor
IHC	Immunohistochemistry
IL-2	Interleukin-2
iRMS	Intermittent Repetitive Magnetic Stimulation
iTBS	Intermittent Theta Burst Stimulation
LLC	Lewis Lung Carcinoma
LTD	Long-Term Depression
LTP	Long-Term Potentiation
MDA	Malondialdehyde
MMP-2	Matrix Metalloproteinase-2
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
NIBS	Non-Invasive Brain Stimulation
NSS	Neurological Severity Score
NT-3	Neurotrophin-3
PD	Platycodin D
PDGF	Platelet-Derived Growth Factor
PI	Propidium Iodide
PMC	Puromycin
RNA-seq	RNA sequencing
rMS	Repetitive Magnetic Stimulation
ROS	Reactive Oxygen Species
RT-qPCR	Reverse-Transcriptase quantitative Polymerase Chain Reaction
rTMS	Repetitive Transcranial Magnetic Stimulation
SEM	Scanning Electron Microscope
siRNA	Small Interfering RNA Transfection
SMF	Static Magnetic Field
sMS	Static Magnetic Stimulation
TEM	Transmission Electron Microscope
TBS	Theta Burst Stimulation
TGF-β1	Transforming Growth Factor β1

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TMS	Transcranial Magnetic Stimulation
TMZ	Temozolomide
TNF-α	Tumor Necrosis Factor alpha
TUNEL	Terminal dUTP Nick End-Labeling assay
WM2	Water-Cooled Magnet

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