Chapter 3

Cytoprotective Effect of 120 Hz Electromagnetic Fields on Early Hepatocarcinogenesis: Experimental and Theoretical Findings

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Abstract

Carcinogenesis induced chemically produces mutations affecting standard cells' behavior. An electrophilic attack on DNA result as the primary characteristic. Once xenobiotics are administrated to mammals they suffer a metabolic activation in the liver through cytochrome P450 (CYP450) enzymes, converting them to toxic compounds, generating oxidative stress (OS), and bursting electrophiles near the site of oxidation. CYP450 are electron carrier proteins that generate spin-correlated radical pair (RP) intermediaries. An extremely low-frequency electromagnetic field (ELF-EMF) can modulate the spin-flip conversion between singlet and triplet spin states of the RP populations, modifying the product formation during their metabolization. Experimentally, we induce hepatic cancer chemically; we found that ELF-EMF inhibits both the number and area of preneoplastic lesions by more than 50%. Furthermore, theoretically, we develop a quantum mechanical model based on the RP mechanism (RPM) in the Haberkorn approximation to explain the cytoprotective effects of ELF-EMF. Here, we review the status of the action's mechanism of ELF-EMF on our research on early hepatocarcinogenesis.

Keywords: extremely low-frequency electromagnetic fields, quantum mechanics, radical pair model, hepatocarcinogenesis, enzymatic reactions, cytochrome p450

1. Introduction

Cancer is one of the most burdensome illnesses for humans in the present century, representing a significant public health problem, killing more patients than cardiovascular diseases, and provoking an enormous social impact [1]. The disease gives rise to an enormous economic

cost and human sorrow [2]. In the first instance, all cancers can be prevented. However, 70% of worldwide cancer mortality arises in low-income countries and it is predicted that the number of deaths will grow from 5.5 to 8.9 million by 2030 [3]. In general, researchers expect that there will be 21.7 million new cancer patients and more than 13 million cancer deaths, purely from population growth extrapolation [4]. Notwithstanding this, to develop cancer takes many years because this disease is a syndrome of the adult age. The burden of cancer is increasing due to the growing and aging population and because of unhealthy behaviors, such as smoking, alcohol consumption, unhealthy eating, stress, and physical inactivity [5]. Nevertheless, cancer is a slow and devious killer; almost all cancers might be circumvented through prevention, early detection, and treatment [2]. When cancer has been diagnosed, depending on the kind of cancer, treatment involves surgery, radiotherapy, chemotherapy, and immunotherapy, among others, whose success depends on an assortment of factors. Therefore, the development of successful strategies against cancer can be achieved only through an in-depth understanding of the fundamental biological mechanisms that provoke it. With cancer, we are referring collectively to a considerable number of diseases described by an uncontrolled proliferation of genetically altered cells, generating tumors that can metastasize and invade whole organisms, eventually killing the patient [6]. This means that the best knowledge concerning cancer genesis is needed, focusing on preventive and new tailored forms of treatment. This knowledge will be possible through a multidisciplinary effort, where mathematics and physics collaborate with oncologists, molecular biologists, bioinformatics, and many other disciplines to improve the traditional biological method, enriching it with the implementation of new forms and tools of analyses that permit the acceleration of regulatory barriers in health systems that streamline the implementation of new successful therapeutic strategies [7]. In our research group, we have implemented the use of an ELF-EMF to study hepatocarcinogenesis in its early stages to assess its cytoprotective effect, both experimentally and theoretically. We proposed that it is possible to deter the carcinogenic process induced by chemical carcinogens in the early stages during enzymatic procarcinogen activation by CYP450 through the modulation of charge migration in the electron transfer reactions involved in oxidation [8, 9]. This has been achieved by modulating the magnetic sensitivity of short-lived RP intermediaries produced during the catalytic cycle using ELF-EMF. In this chapter, we review the experimental and theoretical findings found by our research group within the context of the current knowledge on the cytoprotective effect of ELF-EMF in the early stages of OS induced by chemical carcinogenesis (ChemCar). We use the term cytoprotection because of the conferred protection that dissuades or modulates, controls, or deviates processes originated from bioactivation of procarcinogens, which avoids or diminishes damage to cells or its molecular components [8, 9]. On the one hand, we describe and discuss the experimental findings of our group on the effect of daily treatment with 4.5 mT (120 Hz) of ELF-EMF. The early stages of OS in rats with chemically induced hepatocarcinogenesis (ChemIndHep) employed the modified resistant hepatocyte model (MRHM) with Fischer rats 344 [10]. Otherwise, as the molecular mechanisms responsible for this effect are still unclear, we developed a quantum mechanical model based on the RPM and the Haberkorn approximation to explain the experimental effects of ELF-EMF on the free radicals produced in the early stages of ChemIndHep [8]. It is plausible to assume that, through the employment of RPM using ELF-EMF, we modulated the RP intermediates involved in free radical generation (as has been reported for other

reactions [11]). Then, directing them towards lower energetic states in such a way that the activation of oxidative products diminished, and the electrophile damage to cells is reduced [9]. Thanks to this multidisciplinary analysis, we can understand the carcinogenic chemical process based on the behavior of charged particles generated during the enzymatic activation of the procarcinogen, that is, when the DNA still has not yet been damaged in the early stages of carcinogenesis [8, 9]. The results of this work allow us to advertise the basis for the design of tailored therapeutic strategies or clinical applications of ELF-EMF as a coadjutant in the treatment of several diseases related to oxidative damage as occurs in cancer [8, 9]. The importance of the use of ELF-EMF-based therapies is precisely their low cost, safety, effectiveness, and their implication on the homeostasis of the biological systems (BS). We can use them in several treatments, such as chronic ulcer healing [12–14], diabetic foot treatment [15], epilepsy treatment, and vascular permeability in the rat brain [16], among others. In the scientific literature, they have been employed in many fields, and the older applications were in the bone regeneration. However, with the problem that concerns us, we can find many examples. (1) Cells of human colon adenocarcinoma exposed to ELF-EMF of 1.5 mT (1 Hz) during 360 min, diminishing in growth [17, 18]. (2) PC-12 cells exposed to ELF-EMF of 50 Hz at several intensities and durations show a decrease in the proliferation rate and their morphological differentiation [18, 19]. (3) Patients with a mean age of 60 years and with stage IV tumors were enrolled in a pilot study. The patients were exposed for 5 days/week over 4 weeks in two different schedules of exposure: one daily for 20 min (four patients) and one daily for

Table 1. Contents of the chapter.

70 min (seven patients). The results showed that patients do not present side effects. Furthermore, this setup evidenced that humans exposed to ELF-EMF with determinate physical characteristics have a safety profile and with excellent tolerability to the treatment [18, 20]. (4) Patients with advanced hepatocellular carcinoma (HCC), stage I/II, were treated with very low levels of EMF modulated at specific frequencies to HCC. The strategy of stimulation was to administer three daily 60 min outpatient treatments until they arrive at disease progression or death. Most patients reported during the treatment the disappearance or diminishing of pain. Four patients presented with a partial response, and 16 patients had stable disease for more than 3 months. This kind of treatment represents a safe and well-tolerated procedure and also provides evidence of the anticancer effect in this type of patient [18, 21]. We follow the distribution of the syntactic themes expressed in **Table 1** for the development of the chapter's content.

2. Carcinogenesis

Carcinogenesis is a slow process categorized by the acquirement over time of accumulated mutations and chromosomal changes caused by impairment in the genome that leads healthy cells to become deregulated [22]. During cancer development, are subjected monoclonal or polyclonal malignant cells [23] to a microevolutionary process [24] accumulating critical mutations in a crucial group of genes involved in cell division, apoptosis, DNA repair, and in other essential genes that control collective cell behavior. However, after some critical mutations in genes that maintain genetic stability in healthy cells, cancer cells turn into the mutator phenotype [25, 26], initiating a cascade of mutations through the genome that produces genetic heterogeneity in tumors [23]. This process provides cancer cells with selective advantages to colonize the patient's organism evading its natural defenses used to handle any cellular attack. Such benefits of neoplastic cells have been called the hallmarks of cancer and include six features: sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis [27]. Transformed cells, then, instead of behaving altruistically and cooperatively, selfishly ignore any regulating signal and proliferate in an uncontrolled way forming tumors, invading organs and tissues, and spreading throughout the organism, colonizing it.

2.1. ChemCar

ChemCar is a multistep process initiated by the electron attack to nucleophilic tissues or molecules, such as DNA, producing mutations that lead normal cells to become unregulated, proliferate, and then turn malignant [8, 9, 28]. Metabolic activation of procarcinogens produces highly reactive chemical species that yield to the overproduction of reactive oxygen and nitrogen species (ROS, NOS), which cause damage to DNA and other biomolecules [29, 30]. The current mutation theory of carcinogenesis considers it to be a complicated process that broadly consists of three phases or stages: initiation, promotion, and progression (for a review see [31–33]). Chemical carcinogens may act together or in sequence to initiate or promote

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carcinogenesis. The initiation stage is characterized by an irreversible dose-dependent genetic change that predisposes normal cells to evolve into a malicious and immortal state [27]. During initiation, cells are induced to proliferate, but not differentiate [33], inheriting mutations and thus producing initiated daughter cells. In the promotion stage, the initiated cells are clonally selected to expand through an increase in cell proliferation or by a decrease in cell death, the so-called apoptosis process [30]. Although promoter stimuli do not interact directly with the DNA, they can be damaged indirectly by OS, and gene expression can be altered by epigenetic mechanisms. Nevertheless, it is considered that promotion is a reversible stage because the elimination of the promoter produces regression in cell proliferation maybe by apoptosis [33]. Lesions in both initiation and promotion stages are yet to be considered as preneoplastic ones or benign neoplasias [32]. However, in the irreversible third state, they are transformed into malignant lesions, i.e., progression. Cell proliferation independent of stimulus characterizes this stage: faster growth, invasion, metastasis, and morphological, biochemical, and metabolic changes in transformed cells [33].

2.2. Carcinogens

There exist a few different mediators that cause cancer, such as biological and physical types, but cancer induced by chemical agents is more frequent [34]. There are a lot of substances or their mixtures identified as carcinogens in the environment, in the diet, in workplaces, in homes, in cosmetics, in the chemicals employed for food production, and even in drugs for human therapeutic use [35]. It has been considered inclusive that cancer could be prevented just by identifying potentially carcinogenic chemicals and eliminating their subsequent human consumption [32]. However, such a practice does not avoid that patients have another kind of cancer. For this reason, search knowledge concerning the chemical and biological mechanisms of cancer development, mainly at very early stages, will contribute to our better understanding of the true nature of this perplexing sickness [8, 9]. Also, it will offer opportunities to generate better strategies to tackle neoplasia or to interrupt the process [32]. It is known that the earlier the detection and treatment of cancer, the better the probabilities of control, prevention, and cure because treatment will be more effective when cancer cells have not yet invaded nearby tissues or metastasized through the body [8, 9, 36]. Furthermore, it is best to interrupt carcinogenesis as soon as possible, maybe in the preneoplastic stages or, even more, at very early stages when carcinogens or by-products of their metabolism have not yet confronted the DNA. In this manner, it could be possible to prevent the progression of the sickness to the invasive terminal stage. The scenario to be considered to identify what mechanisms are needed to be stabilized, arrested, or even reversed [37] should be based on the correct approach to the chemoprevention field in a multidisciplinary study. Cancer research can involve physics and mathematics using physical, natural, synthetic, or biological agents, and mathematical tools of analyses and simulation in computers to reverse, suppress, or prevent either the initial phases of carcinogenesis or the progression of the premalignant cells to invasive sickness [38]. We use ELF-EMF together with quantum mechanics models to assess cancer. Chemical carcinogens are classified into two groups: (1) direct-acting or primary carcinogens and (2) indirect-acting or procarcinogens [8, 9, 39]. Direct-acting carcinogens are compounds sufficiently reactive and electrophilic that they interact directly with DNA forming adducts and chromosome breakage,

fusion, deletion, missegregation, or nondisjunction that lead to genomic damage. Conversely, procarcinogens do not interact directly with the genome until they are metabolically activated, producing genotoxic electrophilic metabolites or ROS. We consider that an essential critical point is the process of activation of chemical procarcinogens in which the proper enzymatic reaction of the substrate produces electrophiles and ROS [8, 9]. CYP450 is responsible for these enzymatic reactions. CYP450 is a family of proteins that share common mechanisms of activation of procarcinogens that result in OS [30, 40]. A particular event in ChemCar is the very origin of reactions in cascades, intermediates, and products, which constitute the insult to cells after procarcinogens have been incorporated into the organism [8, 9]. Thus, downregulation of ROS and NOS could contribute to the prevention of cancer initiation [38].

2.3. Metabolization

Usually, drug metabolism is the process of biochemical transformation using drug metabolism enzymes (DME) of xenobiotics, i.e., exogenous compounds introduced into organisms. The organs and tissues of animals have a diversity of DME that protects the body against both potential harmful substances from the environment (xenobiotics) and certain substances produced by the organism itself (endobiotics) [41]. Detoxification reactions comprise three phases and enzymes: phases I and II consist of metabolization reactions and enzymes, and phase III consists of transporters involved in efflux mechanisms [42]. Enzymes of phase I participate in reactions of conversion, mainly involving oxidation, reduction, and hydrolysis. These are classified as oxidoreductases (such as CYP450 monooxygenases, flavine monooxygenases, cyclooxygenases, and alcohol dehydrogenase) and hydrolases [33, 43]. Conversely, enzymes of phase II participate in reactions of conjugation and inactivation of chemical carcinogens and include transferases. Altogether, enzymes of both phases occurring independently, sequentially, or simultaneously transform xenobiotics into polar water-soluble and excretable metabolites [41]. In mammals, the metabolism of exogenous chemicals is carried out mainly in the liver, the primary site in which CYP450 enzymes are present [44]. Although procarcinogens tend to be chemically stable, they are metabolized in the liver by CYP450, a phase I enzyme, which detoxifies typically xenobiotic compounds. The activity of detoxifying enzymes in phase I is critical for carcinogenic activation of xenobiotics, while the activity of enzymes of phase II is essential for xenobiotic neutralization [45].

2.4. The catalytic cycle of CYP450

During the catalytic cycle of procarcinogen activation carried on by CYP450, short-lived spin-correlated RP intermediates are produced, which can either recombine or continue the catalytic process. The cycle initiates at resting state with the enzyme in the ferric form where a water molecule is implemented as the sixth ligand to iron in the active site. The ferric state of the resting enzyme has its five valence electrons occupying its orbitals, equilibrating the low-spin and high-spin state [46]. CYP450 at the beginning has ferric iron predominantly in the low-spin state. The substrate induces conformational changes displacing the water molecule from the distal axial coordinate position of the heme iron. This fact results in iron displacement from the porphyrin plane, which makes the heme a better electron sink and triggers electron

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transference [46], changing the oxidation/reduction potential in the spin state of the heme iron from the low-spin form towards the high-spin form, which is a better electron acceptor. Thus, the electron donor, which could be an iron/sulfur protein or a flavoprotein, reduces the high-spin iron(III) heme to the high-spin iron(II) state. This intermediate compound has a singlet ground state and is a resonating mixture of the ferrous and ferric forms. This conjugation requires that the dioxygen will be in a singlet state so that the empty orbital of the oxygen can mix with the second occupied orbital of the iron [46]. It is transferred in the oxygen from the activated CYP450, that is, compound I, to the heteroatom of the substrate. It has been described in the general catalytic mechanism as an odd-electron process, which involves the transfer of one electron or hydrogen atom to generate an intermediate complex that collapses by recombination [47].

3. Experimental findings

3.1. Hepatocarcinogenesis

Hepatocellular carcinoma (HCC) is one of the public health enemies in low-income countries like Mexico and Brazil. It represents the fifth cause of death in the economic stage of man and ninth in women [48]. Therefore, it is important that HCC is properly understood. HCC is induced by several factors: environmental, infectious, nutrimental, metabolic, and endocrine. Certain factors such as chronic infection with hepatitis B and C, aflatoxin exposure, excessive consumption of alcohol, tobacco, and polysaturated meat consumption can also increase risk [49]. In fact, HCC is associated with liver cirrhosis and chronic hepatitis. Hepatocarcinogenesis is a complex multifactorial phenomenon that appears with loss of heterozygosity, somatic mutation, methylation, and functional inactivation [49]. The disease has a poor prognosis despite the pathophysiological advances and treatments. Chronic liver disease has an initiation point with intrahepatic inflammation promoting the dysregulation of cellular signaling pathways, triggering cell proliferation, and expanding malignant cells [50]. During this stage OS and metabolic disorders appear.

3.2. Nrf2 transcriptional factor + ELF-EMF

The Nrf2 (nuclear factor erythroid 2-related factor 2) transcription factor offers essential protection to cells against OS, binding antioxidant response elements and detoxifying enzymes such as glutathione *S*-transferase A2 and NADPH quinone oxidoreductase [51, 52]. In normal conditions, Nrf2 is found in cytoskeletal protein Keap1 (Kelch-like ECH-associated protein 1). However, when ROS and electrophiles are present, it is dissociated from Keap1, translocating Nrf2 to the nucleus, activating cytoprotective genes that participate in the electrophile conjugation and the excretion of xenobiotics. Since Nrf2 activates phase I and II enzymes, it can be considered as a target for cancer chemoprotection [53]. However, in recent studies, the beneficial antioxidant activity of Nrf2 has been extended to protect cancer cells, since excessive Nrf2 activity provokes mutations in NFE2L2 or Keap1, avoiding chemotherapy efficiency [52, 54, 55]. Another study gave evidence of Nrf2

activation in cancer [56]. Despite the enormous benefits and therapeutic chances offered by the use of Nrf2, however, the regulatory mechanisms involved at the molecular level are still not completely clear. Furthermore, ELF-EMF induces the activation of the antioxidant pathway of Nrf2, associated with the protective effect induced by the administration of 3-nitropropionic acid, which causes neurotoxicity [57], showing that ELF-EMF mitigates oxidative damage [58, 59]. For this reason, it is crucial to implement other useful tools to gain knowledge concerning carcinogenesis.

3.3. Experimental setup

We induce experimental hepatocarcinogenesis through the use of diethylnitrosamine (DEN) when it is hydroxylated by the CYP450 isozymes in the liver, employing an alkylation mechanism to bioactivate it, and reacting with DNA, causing ethylation in their bases, which are called DNA adducts. When those interrupt the base pairing, they provoke mutations and activation of proto-oncogenes such as ras and inhibition tumor suppressor genes such as p53, generating HCC [60]. In our experimental setup in Ref. [10], where MRHM was implemented to generate ChemIndHep, it was found that provoking the rapid proliferation of altered hepatocytes formed preneoplastic lesions in the rat liver to assess the effects of ELF-EMF on hepatocarcinogenesis. The results indicate that applying periodically an ELF-EMF was possible for achieving the modulation of the magnetic-sensitive short-lived RP intermediaries produced during the catalytic cycle. Such daily treatment with ELF-EMF (4.5 mT (120 Hz)) inhibits more than 50% of the number and area of preneoplastic lesions in rats through reduction of cell proliferation and without altering the apoptosis process. The general idea is straightforward: modulate, applying ELF-EMF, the potentially harmful products yield of the reaction by competitive kinetics of RP selective reactions [8], which give the role of a molecular motor to the enzymatic protein. Whose provision of catalyzing electrons to the reaction, is executed when through the substrate of CYP450 are metabolized the xenobiotics that participate in the ChemIndHep [9]. During the implementation of MRHM, the rats were administered a single necrotic dose of DEN (200 mg/kg b.w., i.p.). Seven days later, over 3 consecutive days, the rats were administered 2-acetylaminofluorene (20 mg/kg b.w., orally), after which they were subjected to a two-thirds partial hepatectomy. We employed three groups of six rats (normal control group (NC), sham-exposure group (CT), 120 Hz ELF-EMF group (CTF)) and the biochemical and molecular evaluations were performed under blind conditions.

3.4. Experimental results

DNA fragmentation through a calorimetric TUNEL system kit found that daily treatment with ELF-EMF did not induce apoptosis in the altered hepatocytes or caspase-3 activation, showing that ELF-EMF interferes with altered cell cycle continuity and DNA synthesis induced by ChemIndHep. This analysis also was used to detect the endogenous peroxidase activity, showing an essential diminishing in the numbers and areas of glutathione-*S*-transferase-positive (GST-P) liver foci and preneoplastic liver lesions in rats (**Figure 1**). To evaluate the

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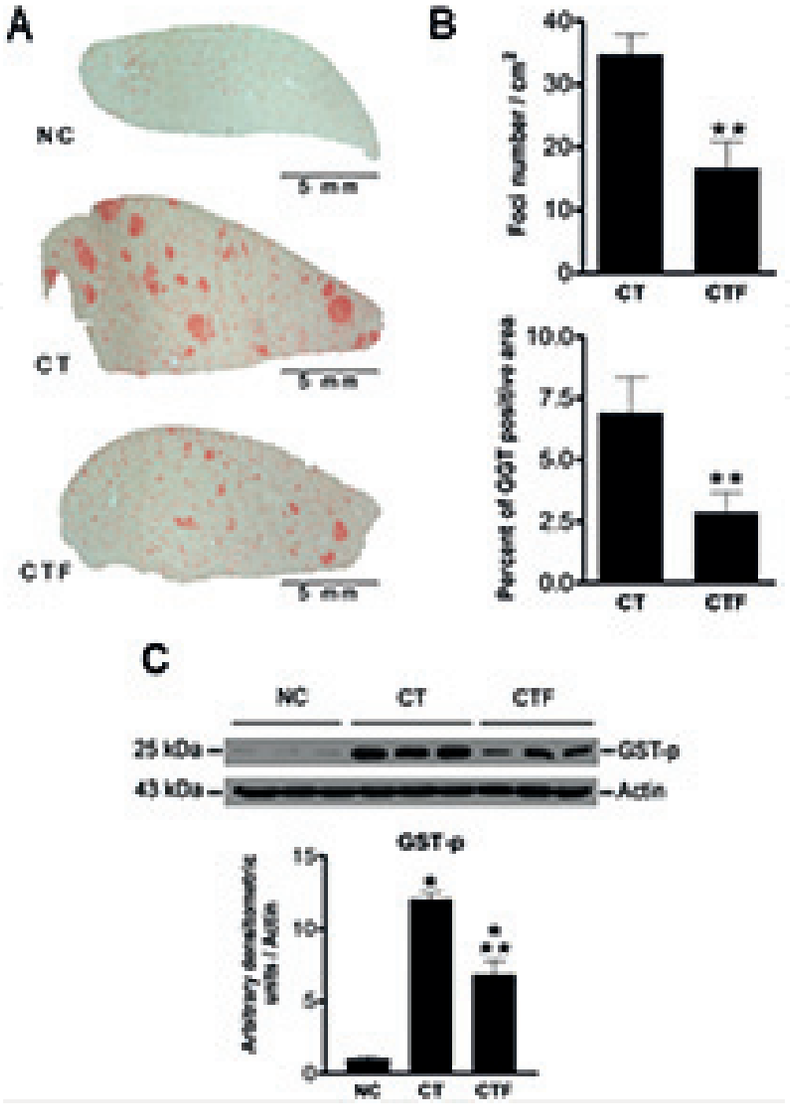

Figure 1. Effect of ELF-EMF exposure on GGT-positive lesions and GST-P expression. (A) Representative liver sections of the NC group, CT group, and CTF group. Scale bars, 5 mm. (B) Quantification of the foci number/cm^2 and percent of the GGT-positive area. (C) Western blot analysis for GST-P expression. GST-P was normalized with actin expression used as the loading control. The expression of NC was adjusted to one in the densitometric unit scales. Statistically different from *NC and **CT, $P < 0.05$. Data are expressed as the mean ± SEM; $n = 6$ for each group (of reference [10]).

effect of ELF-EMF on cell proliferation, immunohistochemical analysis of protein expression of the cell cycle such as PCN, Ki-67, and cyclin D1 were also performed. PCNA participates in replication and DNA reparation, a fundamental process for the cell cycle. Otherwise, Ki-67 is a specific replication marker of the cell cycle, which does not include the G_0 phase. Summarizing, the daily application of 120 Hz ELF-EMF affects the ChemIndHep process participating in the reduction of protein expression of PCNA, Ki-67, and cyclin D1. Their participation does not induce apoptosis; however, it regulates cellular homeostasis inhibiting the development of preneoplastic lesions.

4. Theoretical findings

Currently, it is known that both permanent magnetic field (MF) and ELF-EMF interact with BS at all levels [61]. Nonetheless, there still does not exist precise molecular mechanisms for which ELF-EMF can support their therapeutic use, although much research has been performed and reported of several effects on BS [9]. One of the most common reports is that an external MF can considerably affect the rates of chemical reactions (ChemReac) in BS. Involving free radicals affects the probability of transition between the singlet (S) and the triplet spin state (T), $S \longleftrightarrow T$, generally in the RP [62, 63]. Hyperfine interaction (HypInt) is responsible for control of the spin-flip conversion $S \longleftrightarrow T$ spin states of the RP modifying it by the application of an external MF [9]. Physically, there exist four orders of magnitude between molecules interacting with a geomagnetic field of 50 μT with respect to the vibrational, thermal energy $K_B T$ compared to the strength of a chemical bond, which is 10–100 times smaller [9, 64, 65]. Therefore, adaptive mechanisms to deal with such energies [66] could not be developed, except the geomagnetic field [67], which today as a way of orientation is used [64]. As a result, organisms, considered as complex electrochemical systems, interact in a very complex and subtle way with EMF. Nevertheless, several studies have demonstrated the influence of EMF on BS and diseases, mainly by intensifying the effects of other physical and chemical stressors [61]. In fact, it is possible to verify that static MF [68] or pulsating MF [69] can affect chemical systems and free-radical reactions in BS [70]. For enzymatic reactions, in 1994 Harkins and Grissom reported the MF effect on coenzyme B_{12}-dependent ethanolamine ammonia lyase in vitro activity as evidence of the RPM [9, 71]. When it is used at a low frequency, the effects of weak MF on BS were revised by Liboff [72] using ideas concerning cyclotron frequency resonances. Using vibrational modes by Lednev [73], and the Zeeman levels by Blanchard et al. [74], hyperfine interactions with a one-proton model were treated by Haberkorn and Michel-Beyerle [75], among others [9]. Therefore, the absence of a convincing molecular mechanism is the reason why there exists a significant unconformity in the research community with respect to the existence of certain MF or ELF-EMF effects (MFE or ELF-EMFE) on BS and ChemReac. In this respect, the RP intermediaries simultaneously created, with a spin state correlated is the key. These MF-dependent particles are controlled by a weak MF $(\leq K_B T)$ thanks to their spin correlation, which is far away from the thermal equilibrium. Thus, the RPM seems like the most plausible way to investigate the MFE or ELF-EMFE on the reactivity of ChemReac [64, 65] in BS. A notable example of MF on BS is the photosynthetic reaction center of proteins in which light absorption permits RP formation due to the electron transfer steps [64, 65]. An exceptional case is a report about MFE on the enzymatic synthesis of adenosine triphosphate in cells to control enzymatic deoxynucleic (DNA) synthesis in cell proliferation by Buchachenko [76]. After all, phosphorylation is of vital importance for the function of BS. There exist three sources of irreproducibility of MFE: the presence of paramagnetic metal ions [77], the existence of catalyzing metal ions [76], and kinetics and RP spin dynamics [9, 78]. Besides, there is extensive fundamental and clinical accumulated evidence regarding the effectiveness of ELF-EMF in therapeutics and clinical benefits, and in the significant modulation of molecular and cellular function [61].

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4.1. Fundamental facts

Facing our limited knowledge and using the available information, we reported the cytoprotective effect of 120 Hz ELF-EMF on early ChemIndCar during the enzymatic procarcinogen activation of CYP450 by quantum measurements in Refs. [9, 79]. We proposed that when CYP450 metabolizes the xenobiotics used in the experimental setup to ChemIndHep [10], the enzymatic proteins act as a molecular motor providing a catalyzing electron that interacts with the RP formed during the OS generated when the substrate of the enzyme is oxygenated [9]. Since metabolization is carried on in the liver, the hepatocytes are in contact with the enzymatic protein as in a thermal bath and with a Gibbsian distribution, interacting with the RP as a harmonic oscillator [9]. Employing quantum measurements concepts, we argue the way in which the MF modulates the singlet spin population to diminish the preneoplastic lesion observed during ChemIndHep. The completely formed system between RP and electronic configuration of hepatocytes interacting through the HypInt alters the quantum spin state removing the spin prohibition and giving rise to the appearance of new reaction products. These products in our case result in spin selectivity plus HypInt, affecting the magnetic properties, which impact on the so-called initiated hepatocytes that later become the preneoplastic lesion to study.

We explained that on the formation of the OS was involved through the administration of xenobiotics in the MRHM, an electron transfer, and the MF modulates those in the current Haberkorn approach [9, 79, 80]. The allowed electrophilic reactions that appear in the enzymatic reactions do not require a change of spin because the spin total is zero. Those spin-forbidden reactions, involving paramagnetic participants, can combine their spins freely in any electronic configuration, but it does not mean that all configurations have a chemical reaction [9, 79]. The electron spin gives origin to the MFE, the magnetic isotope effect, and induces nuclear chemical polarization. We use the fact that according to angular momentum conservation, which is a fundamental and universal principle, all ChemReac are spin selective. This means that only those ChemReac that satisfied such a rule are allowed in the product formation. Magnetic interaction is the masterpiece that controls and accelerates the ChemReac. Nevertheless, it is many orders of magnitude less than coulomb energy. However, it has the responsibility of changing the electron spin state through the interchange energy of the channels of spin allowed and prohibited, controlling chemical reactivity [81]. The MFE act over the enzymatic DNA synthesis killing cancer cells [76]. We use the RPM because it controls life at the molecular level [9, 82–84]. We use the fact that a combination of weak static and pulsating EMF can affect radical concentration in a ChemReac [85], modifying the population of nuclear and electron spin states, their energy levels, and the RP alignment of their magnetic moments. Such changes can modify the BS [9]. Also, we use the experimental findings concerning the significant modulation of catalase, CYP450, and inducible nitric oxide synthase activity in myelogenous leukemia cells [86] to reaffirm our idea with respect to the effect of ELF-EMF on the enzymological system. A more critical step is the activation of xenobiotics whose interaction produces OS in the form of electrophiles and ROS [30, 40]. The main protagonist in our approach are the so-called RP, short-lived intermediates that participate in almost all reactions in solution in a correlated way. The RP can recombine or participate in other ChemReac. They

are responsible for a few phenomena such as chemical polarization of electrons and nuclei, and the influence of static and pulsating MF [9, 79]. An RP can decay by recombination, or pull apart the radical by diffusion, or react with other radicals. One of the properties of RP is that recombination probability depends on spin multiplicity, and it varies during RP lifetime. Such variations, as an interesting detail, are manifested as dynamic quantum oscillations, the so-called quantum beats between (S, T) spin states of the RP. The quantum beats modulate the probability of appearance of some reaction channels of the RP that at the time affect the MFE. By studying these quantum beats, one can reveal valuable information concerning the structure, reaction, molecular, and spin dynamics of RP [9, 63, 79, 87]. The RP spin correlation is formed in the coherent state, which oscillates between the S and T spin state, an oscillation that depends on the spin Hamiltonian operator parameters (see references [8, 9] for details), in particular that of the HypInt. The period of the oscillation on organic radicals is in the range of nanoseconds, making RP recombination a plausible test that suggests that small EMF affects BS [9, 88].

4.2. The model

ChemReac can be seen as a physical process involving a set of regrouping atoms with the rearrangement of electronic shells of reacting participants, giving place to the generation of new molecular structures called reaction products. The new ways of controlling ChemReac have their basis on the selectivity of spin, a process involving the spins of molecules, electrons, and nuclei of all participants. For this reason, the rate of spin-selective processes is dependent on MF, which alters the spins of the participants, changing partially or wholly the spin selectivity [9, 89, 90]. Thus, to reveal the interaction to explain the cytoprotective effect of ELF-EMF in CYP450, we must define the conditions where the quantum measurement is performed. The first condition is that all quantum states participating in the hepatocytes-RP system in the enzymatic reaction are singlets, because of their high reactivity. The second condition is during the enzymatic procarcinogen activation of CYP450 when the xenobiotics are metabolized, in which appear the RP when is generated the OS. The RP intermediaries are produced in this step, and they are responsible for the insult to hepatocytes, which become the future preneoplastic lesions after to finish the ChemIndHep. The third condition is daily MF stimulation during all ChemIndHep. Nonetheless, the spin evolution of RP is driven by the MF through the HypInt and their reactivity is controlled by spin dynamics, converting non-reactive triplets into reactive singlets through quantum measurement. We showed the way in which the MF modulates the charges in migration evaluating the recombination probability to exemplify. In this respect, when the RP interacts with another electrons' spin, this interaction acts as a catalyst, increasing the recombination probability and accelerating the $S \longleftrightarrow T$ interconversion [9, 90, 91].

4.2.1. Haberkorn approach

To study the hepatocytes-RP system, we use the information of all parameters employed in the evaluation of MFE, the recombination yield, and the singlet population, which are all included in the Haberkorn approach; this is the most common theory used for spin dynamics studies.

This approach is obtained using the spin density matrix in the framework of the Liouville–von Neumann equation involving the rate at which singlets disappear, called k_S; it is involved in an unnormalized wave function [9, 80] $\|\psi>= c_S e^{-k_S t/2}\|S> + c_T\|T>$. Here the amplitudes for the singlet disappear at the rate $-k_S/2$, provoked by the interaction between RP and a third electron for the electron configuration of the hepatocytes (see reference [9] for details). We have written the evolution of the standard density matrix as [9]:

$$\hat{\rho}_{\text{in}} = \begin{pmatrix} C_S C_S^* e^{-k_S t} & C_S C_T^* e^{-k_S t/2} \\ C_T C_S^* e^{-k_S t/2} & C_T C_T^* \end{pmatrix} \equiv \hat{\rho}_0 \rightarrow \hat{\rho} = \begin{pmatrix} C_S C_S^* \left[1 - e^{-k_S t}\right] & \tilde{\varnothing} \\ \tilde{\varnothing}^{\dagger} & \hat{\rho}_0 \end{pmatrix}. \tag{1}$$

Moreover, to satisfy the unicity of the trace in the density matrix, we include the third electron. Obtaining the so-called reaction products, $\hat{\rho}$, according to the rule of conservation of the number of entities participating, i.e., for the generation of some product population, $\tilde{\varnothing} = (0\ 0)$ is a null vector [9, 79].

4.2.2. Quantum measurements

When we have a ChemReac with only a singlet spin state as in our case, we can consider it as a quantum measurement [80]; the amplitudes for the singlet disappear at the rate of $-k_S/2$ provoked by the interaction of the third spin electron that can be studied. During their evolution, the RP can change their spin multiplicity. Through the use of electron spin resonance spectroscopy (ESR) studies, such spin changes are simply called beats, meaning dynamical quantum oscillation between the $\|S>$ and $\|T>$ spin states of the RP. Using them, we study the behavior of the spin dynamics of RP. A crucial issue here is that RP appears in the coherent state, which permits the oscillations between $\|S>$ and $\|T>$ spin states of the RP, commanded by HypInt. Measured at a quantum level, these beats represent the manifestation of the RP in ESR studies. Tacitly, the beats correspond to $S \leftrightarrow T$ spin-flip transitions generated by HypInt. The behavior of an unpaired electron under MF, or without MF, determines the influence of HypInt so we can measure the MFE. Eq. (1) expresses how singlet disappears at the desired rate k_S. Nevertheless, the off-diagonal terms represent the coherent superposition decaying at a rate of $k_S/2$. This expresses the motion equation for the density matrix with $\hat{H}_{int}$ as the Hamiltonian interaction operator as (see reference [9], for details):

$$\frac{\mathrm{d}\hat{\rho}}{\mathrm{dt}} = -i\left[\hat{H}_{int}, \hat{\rho}\right] - \frac{1}{2}k_S\left(\hat{\rho}\hat{Q}_S + \hat{Q}_S\hat{\rho}\right), \tag{2}$$

where $\hat{Q}_S = \|S><S\|$ is the projection operator for the singlet state. The yield of recombination calculated from the singlet state of the RP can be evaluated by [9]:

$$\Phi_{\mathrm{S}} = \mathrm{k_S} \int_0^{\infty} \mathrm{Tr}\left[\hat{\mathrm{Q}}_{\mathrm{S}}\hat{\rho}(\mathrm{t})\right]\mathrm{dt}, \tag{3}$$

In fact, with Eq. (3), we evaluate the effect of MF on the yields of the diamagnetic products involved, and in those RP that do not participate in the recombination process. Furthermore, in

the exponential approach, the Φ_S represents the effect of all reencounter times for the reencounter probability of a diffusive geminate RP when it describes the time evolution after their formation, and $\tau^{-1} = k_S$ is the average reencounter time when $k_S = k_T$ [9]. We use as an initial condition the fact that the population is born in a singlet state $\|\Psi(t=0) >= \|S >$. The evolution time wave function reads $\|\Psi(t) >= \sum_n A_{P_n}(t)\|P_n > + A_S(t)\|S > + \mathrm{A}_{T_0}(\mathrm{t})\|T_0 >$. In this sense, the quantum measurements [92] give us the formation of products and then the effect of singlets in the hepatocytes with an intensity $\|A_S(t)\|^2$ [9, 79]. With use of the spin-based quantum mechanical model, we perform the calculation of singlet spin population and determine the MFE, obtaining a result of 61% compared with the experimental findings of 56% and 58%. Evaluating the quantum yield for the RP intermediaries in the substrate-product system of the CYP450, it is interesting to illustrate the cytoprotective mechanism, which consists of the diminution of the singlet population, responsible for diminishing the number of initiated cells, and, therefore, the preneoplastic lesion formation. To study the spin population behavior of the system, we diagonalize the interaction spin Hamiltonian in the superstate representation, applying the Lanczos method [9]. Beyond the mathematical model, the biology of the problem concerns the action of the EMF on RP affecting the hepatocytes during the enzymatic procarcinogen activation of the CYP450, precisely modulating the charges that are in migration during the electron transfer reactions generated by the interaction of the CYP450 in their substrate-producing electrophilic species and ROS. The intermediaries generated during this process are the source of the first insult to hepatocytes on their way to becoming preneoplastic lesions in the ChemIndHep protocol. We used three assumptions: (1) the ChemReac are spin selective, (2) ChemReac are nuclear spin selective, and (3) ChemReac are selective with the spin of the electron. Under such circumstances, only the reactions with singlets favored the formation of standard molecules. The reactions with triplet RP are forbidden. Under this outline, the spin of the electron controls the generation of the magnetic spin effects [9]. One of the keys of the model is to consider the role of the enzymatic protein as a molecular motor, catalyzing electrons to the reaction, where the RP is generated into the substrate of CYP450 when it is metabolizing the xenobiotics used in the MHRM. The hepatocytes are in contact with the RP in the liver as in a thermal bath, and we assume a Gibbsian distribution, interacting harmonically with them. This strategy includes the very tough dissipation problem, whose quantization process involves some difficulties. To do this, we employed the Caldera–Legget model [93, 94], which explicitly includes it. We use the path integral method in the Feynman–Vernon functional approach to describe the time evolution of the spin population of the system. Also, we employ the influence-functional technique to incorporate the Brownian motion at any temperature. Thus, our system can be considered close and we can apply the traditional quantization method [93]. We consider conservation of energy, and to give an exact treatment of the quantum dissipation dynamics, we use the hierarchical equation of motion, which is more tractable from a numerical point of view. We use for simplicity, $H_p = \omega_{osc}\hat{b}^{\dagger}\hat{b}$ modeling the ChemRec and consider the thermal bath as a set of harmonic oscillators with equally spaced energy levels at the frequency ω_{osc}. This expresses the complete system to study as $\hat{H}_{Sb} = \sum_{\alpha\mu}\left(\hat{a}_{\mu}^{+}\hat{F}_{\alpha\mu}^{-} + \hat{F}_{\alpha\mu}^{+}\,\hat{a}_{\mu}^{-}\right)$, representing $\hat{a}_{\mu}^{+} \equiv \hat{a}_{\mu}^{\dagger}$ $\left(\hat{a}_{\mu}^{-} \equiv \hat{a}_{\mu}\right)$, the creation (annihilation) operator of the electron in some specified spin-orbit state. Moreover,

the bath operators $\hat{F}^{-}_{\alpha\mu} = \sum_k t_{\alpha\mu k}\,\hat{a}_{\alpha k} = \left(\hat{F}_{\alpha\mu}\right)^{\dagger}$, whose influence is characterized by bath spectral density functions $J_{\alpha\mu\nu}(\omega) = \pi\sum_k t_{\alpha\mu k}t^{*}_{\alpha\nu k}\delta(\omega - \omega_{osc})$. In our approach such terms are expressed by the reaction operator $\hat{R}_S = \alpha\hat{b}^{\dagger}\hat{N}_{-} + \alpha^{*}\hat{b}\hat{N}_{+}$, representing the spin-selective recombination of the singlet state. To evaluate the recombination process, which is responsible for the time evolution (see details in Ref. [9]), we express the Liouville equation (Eq. 2) in the quantum interaction representation, involving all terms of the system [9] $\frac{d\hat{\rho}_c(t)}{dt} = -i\left[\hat{H}_T + \hat{H}_P + \hat{R}_S, \hat{\rho}_c(t)\right]$, where $\hat{\rho}_c(t) = \hat{U}_0(t,t_0)\hat{\rho}_c(t)\hat{U}_0^{\dagger}$, $\hat{H}_0 = \hat{H}_T + \hat{H}_P$, and $\hat{U}_0(t,t_0) = e^{-i\hat{H}_0(t-t_0)}$ is the evolution operator of the system. Formally, we evaluate all operator quantities involved in the interaction representation. Once we calculate the thermal bath's degree of freedom contributions and apply the detailed balance principle, we arrive at the solution to the Haberkorn approach, $\rho_{SS}(t) = \rho_{SS}(0)e^{-k_S t}$, $\rho_{T_0T_0}(t) = \rho_{T_0T_0}(0)$, $\rho_{ST_0}(t) = \rho_{ST_0}(0)e^{-\frac{k_S}{2}t}$, $\rho_{T_0S}(t) = \rho_{T_0S}(0)e^{-\frac{k_S}{2}t}$, $\rho_{PP}(t) = \rho_{SS}(0)\left(1 - e^{-k_S t}\right)$.

From the last equation, we can present the form in which products are formed. We suppose that in the initial process at $t = 0$, $\rho_{PP}(0) = 0$, there are no damaged hepatocytes. The behavior of the generation of damaged hepatocytes will depend on the initial singlet spin population $\rho_{SS}(0)$, which means that the medium absorbs all that is produced by the enzymatic reaction $\rho_{PP}(t) = -[\rho_{SS}(t) - \rho_{SS}(0)]$ [9].

4.2.3. Results on hepatocytes

We described the effect through the following dynamical mapping [9, 79] $\|S> \|0>_{\text{Hep}} \rightarrow \eta_1\|P> \|\sigma>_{\text{Hep}} + \eta_2\|S> \|0>_{\text{Hep}}$, $\|T_0> \|0>_{\text{Hep}} \rightarrow \|T_0> \|0>_{\text{Hep}}$. When we normalize it, measurement of the generation of some reaction product on the hepatocytes $\|P>$ is represented according to [9, 79]:

$$\hat{\rho}(0) = \begin{pmatrix} \|A_S\|^2 & A_S A^{*}_{T_0} \\ A_{T_0}A^{*}_S & \|A_{T_0}\|^2 \end{pmatrix} \rightarrow \hat{\rho}_n = \beta\begin{pmatrix} \|\eta_1\|^2\|A_S\|^2 & \eta_2 A_S A^{*}_{T_0} \\ \eta^{*}_2 A_{T_0}A^{*}_S & \|A_{T_0}\|^2 \end{pmatrix}, \beta = \frac{1}{1 - \|\eta_1 A_S\|^2}. \tag{4}$$

This fact means that the hepatocytes measure the spin nature of the RP that is participating. The spin state of the hepatocyte changes according to the spin nature of the RP that is interacting. During the measurement process, the S and T_0 components do not change, but the hepatocytes change their spin states according to the RP spin character following the dynamical mapping [9, 79] $\|S> \|0>_{\text{Hep}} \rightarrow \beta_1\|S> \|\sigma>_{\text{Hep}} + \beta_2\|S> \|0>_{\text{Hep}}$, $\|T_0> \|0>_{\text{Hep}} \rightarrow \beta_3\|T_0> \|\chi>_{\text{Hep}} + \beta_4\|T_0> \|0>_{\text{Hep}}$, instituted by the interaction [9, 79]:

$$\begin{aligned}\hat{H}_{in} = &\left\{\eta_S\|S><S\|\right\}\otimes\left[\|\sigma>_{\text{Hep}}<0\| + \|0>_{\text{Hep}}<\sigma\|\right] + \left\{\eta_{T_0}\|T_0><T_0\|\right\} \\ &\otimes\left[\|\chi>_{\text{Hep}}<0\| + \|0>_{\text{Hep}}<\chi\|\right]\end{aligned} \tag{5}$$

where η_S and η_{T_0} give us the strength of the interaction of the hepatocytes with the RP spin character, appearing in the new term, $\beta_3\|T_0> \|\chi>_{\text{Hep}}$, without $\|P>$ states. In this case, the probabilities $\|\beta_1\|^2$ or $\|\beta_3\|^2$ express the appearance of $\|S>$ or $\|T_0>$ spin states, represented by

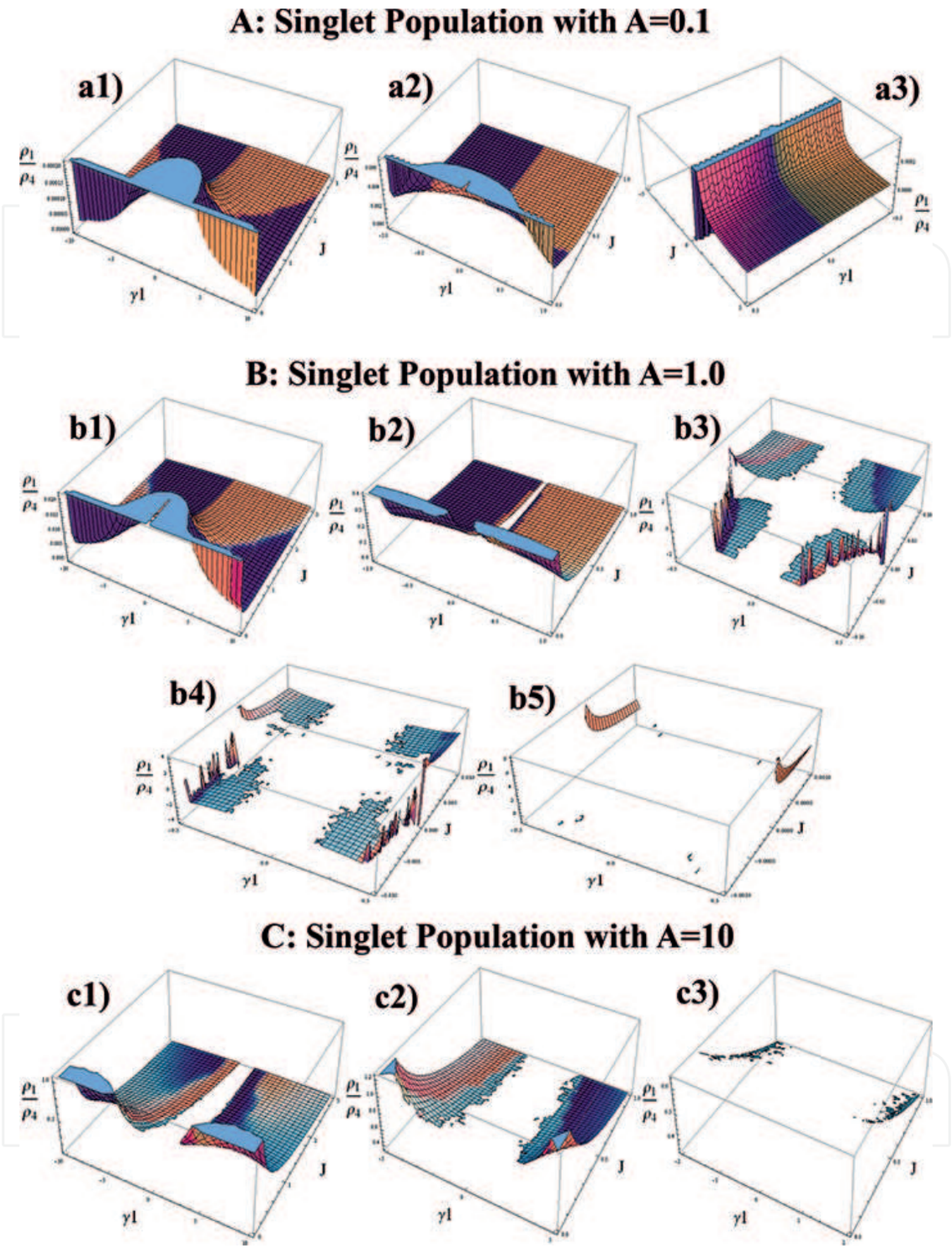

Figure 2. (a) Singlet population normalized with ρ_4 for A (=0.1): With the range of values of (γ_1,J) (a1) [(−10,10), (0,3)], (a2) [(−1,1), (0,1)], (a3) [(−0.5,0.5), (−5,5)]. (b) Singlet population normalized with ρ_4 for A (=1): With the range of values of (γ_1,J) (b1) [(−10,10), (0,3)], (b2) [(−1,1), (0,1)], (b3) [(−0.5,0.5), (−0.1,0.1)], (b4) [(−0,5,0.5), (−0.01,0.01)], (b5) [(−0.5,0.5), (−0.001,0.001)]. (c) Singlet population normalized with ρ_4 for A (=10): With the range of values of (γ_1,J) (c1) [(−10,10), (0,3)], (c2) [(−5,5), (0,1)], (c3) [(−2,2), (0,1)] (from reference [9]).

$\|\sigma>$ and $\|\chi>$ [9]. They measure the fraction of singlets transformed into a reaction product or transformed cell. It is precisely this kind of product formation that changes the electronic configuration of the hepatocytes, as we claim. The result is evident from **Figure 2**, where we note that by increasing the hyperfine coupling constant, A, the singlet population is diminished. Thus, once the hepatocytes interact during δt with the CYP450, they change their spin states through the application of the selective spin operator. For each time interval, δt will apply some dynamical mapping to each new healthy hepatocyte in the tissue $\|0>_{\text{en}}$, incorporating them into the enzymatic reaction that provides catalyzing electrons during the metabolization of xenobiotics [9], $\|\Psi(\delta t)>_{\text{s en}} = \mathbb{U}(\delta t)\|\Psi(\delta t)>_0 = e^{-i\hat{H}_{in}}\delta t\|\phi_0>_{\text{s}}\|0>_{\text{en}}$. Also, neglecting the memory effects due to the previous results with other singlets, which are diminishing as is evidenced by the quantum measurement $\|\beta_1\|^2 = k_S\delta t$, changes the electronic configuration of the hepatocytes when the RP is converted in a reaction product by the recombination kinetics [9, 79].

5. Conclusions

We studied the ChemIndHep experimentally through the use of MRHM. We found that the periodical application with ELF-EMF (4.5 mT (120 HZ)) inhibits by more than 50% the number and area of GST-P liver foci and preneoplastic liver lesions in rats. Through the reduction of cell proliferation and without alteration of the apoptosis process, ELF-EMF interferes with the altered cell cycle continuity and DNA synthesis induced by ChemIndHep. Theoretically, we found that with the use of a 120 Hz ELF-EMF it was possible to achieve modulation of the magnetic-sensitive short-lived RP intermediaries produced by the OS, generated when xenobiotics are metabolized during the catalytic cycle by the CYP450 in the early ChemIndHep. The process of modulation uses the competitive kinetics of the RP selective reactions [71], giving the role of a molecular motor to the enzymatic protein [9]. To achieve this, we studied a quantum mechanics model to describe the interaction of RP/hepatocytes following the typical Haberkorn approach studying the spin dynamics and employing the path integral method and second quantization. The idea of this chapter was to obtain an explanation of the way in which hepatocytes can modify their electronic structure when interacting with the RP, which comes from the enzymatic reaction. Although it is an in-depth mathematical model, the results of our research provide us with further details of the MF's control on BS, specifically in the ChemReac that modulates the electrons in OS (cytoprotective effect) generated in the reactive hepatocytes-RP system in the liver, with the outcome of understanding hepatocarcinogenesis.

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Conflict of interest

The authors declare that they have no conflict of interest.

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