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Comparative Effect of the Antioxidants Resveratrol and *Mangifera indica* L. (Sapindales: Anacardiaceae) Extract on *In vivo* Clastogenicity Induced by Extremely Low-Frequency Electromagnetic Fields

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Abstract: It is known that non-ionizing radiation in the range of extremely low-frequency electromagnetic fields (ELF-EMFs) causes indirect DNA damage by generating reactive oxygen species and free radicals. Therefore, research on antioxidant radioprotective agents has been developed. Many such agents are free-radical scavengers and antioxidants, including dietary compounds. Recently, evidence has shown that resveratrol, a natural phytoalexin mainly extracted from grapes, exhibited various biological activities, including radioprotection against several types of radiation. In the present study, we compared the radioprotective effect of resveratrol with the stem bark extract of *Mangifera indica* L. with antioxidant potential. We demonstrated that resveratrol significantly ($p < 0.05$) inhibited the *in vivo* clastogenic effect of 2.0 mT ELF-EMFs by the micronucleus test, compared with *M. indica*, which did not show radioprotection alone.

Key words: Resveratrol, *Mangifera indica*, mango, radiation protection, clastogenic effect, extremely low-frequency electromagnetic fields, micronucleus.

Introduction

Current technologies may become a source of radiation pollution, particularly from extremely low-frequency (50 Hz to 60 Hz) electromagnetic fields (ELF-EMFs). This pollution is often more potent than any natural source of electromagnetic fields or radiation. The harm caused by ELF-EMFs is still uncertain due to a lack of definitive evidence. However, enough investigations have demonstrated the negative influence of ELF-EMFs in several models of mammals and lower organisms, including bacteria, nematodes, insects like fruit flies, and amphibians (Redlarski et al. 2015). We recently demonstrated that an *in vivo* exposure to ELF-EMFs at 2.0 mT and 60 Hz of frequency induced a clastogenic effect in mammalian cells (Heredia-Rojas et al. 2017, Heredia-Rojas et al. 2018a,b) even though they possess a weak amount of energy to directly produce any DNA breakage or fragmentation (Luceri et al. 2005). In this case, an indirect effect involving oxidative stress has been

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proposed as a mechanism of clastogenesis (Zhang et al. 2017). Since the 1970s, oxidative stress has been associated with various pathologies. In this regard, many studies have shown the protective benefits of antioxidants in cells and animal models (Schmidt et al. 2015, Xu et al. 2017). Among these antioxidants, 3,5,4'-trihydroxystilbene (resveratrol), which is a natural phytoalexin produced by numerous plants in response to several stressors, has been evaluated to prevent a large number of pathophysiological conditions with promising results (Kuršvietienė et al. 2016, Nawas et al. 2017). Furthermore, resveratrol has been proven to possess anti-genotoxic potential (Attia 2012, Hedayati et al. 2013, Türkez & Şişman 2012, Abraham et al. 2016), indicating that this polyphenol may prevent genetic damage. In this regard, we have previously shown that resveratrol significantly reduced the *in vivo* frequency of bone marrow micronuclei (MN) induced by exposure to 2.0 mT ELF-EMFs (Heredia-Rojas et al. 2020).

The present study aimed to compare the radioprotective effect of 3,4′,5-trihydroxy-trans-stilbene, 5-[(1E)-2-(4-hydroxyphenyl)ethenyl]-1,3-benzenediolresveratrol (resveratrol) with a *Mangifera indica* L. (mango) aqueous extract, labelled as QF-808 and further named Vimang. This mango extract has shown potent antioxidant properties (Pardo-Andreu et al. 2005; Pardo-Andreu et al. 2006; Pardo-Andreu et al. 2008) and has also been tested as a radioprotective agent (Jagetia & Balinga 2005, Jagetia & Venkatesha 2005, Carsten et al. 2008) in several study models with acceptable results. More recently, it has been shown that polyphenol-rich fraction from mango has a radioprotective effect (Kondapalli et al. 2014, Naresh et al. 2015, Jabin et al. 2023).

Materials and Methods

Experimental animals

We used sexually mature 12-week-old male Balb/c mice (25g to 30g) raised in our breeding colony. They were kept in a pathogen- and stress-free environment at 24° C, under a light-dark cycle (light phase, 06:00–18:00 h), and given water and food *ad libitum*. After a 10-day quarantine period, they were randomly distributed into experimental and control groups. All animal procedures were developed following University Animal Care and Use for Research Protocols, which are based on the National Guidelines for Ethics and Biosafety under the General Law of Health for issues regarding Health Research (Ministry of Health, Mexico).

Antioxidants preparation

Resveratrol (≥99% purity) was obtained from Sigma-Aldrich (St. Louis, MO, USA), dissolved in saline isotonic solution at 15 mg/kg [this concentration was selected according to a previous report indicating antigenotoxic effective doses from 6.25 mg/kg to 30 mg/kg (Abraham et al. 2016)], and intraperitoneally (*i.p.*) administrated before radiating. Due to the low solubility of resveratrol in water, it was diluted in saline solution based on the rapid liver polyphenol metabolism and plasma binding to lipoproteins and albumin, which facilitate its entry into the cells (Jannin et al. 2004).

In addition, a stem bark extract of mango was prepared by aqueous decoction for one hour. It was collected in the region of Pinar del Rio, Cuba, with voucher identification code 41722, deposited at the Herbarium of the Academy of Sciences, and kept in the Institute of Ecology and Systematic from the Ministry of Science, Technology and Environment, La Habana, Cuba. The extract was then concentrated by evaporation and spray dried to obtain a fine brown powder named QF-808 and later Vimang, patent number 203/98, Oficina Cubana de la Propiedad Industrial, Havana, Cuba (Núñez-Sellés et al. 2002), as previously reported (Garrido-Garrido et al. 2007). The solid extract was diluted in saline isotonic solution at 15 mg/kg and *i.p.* injected before magnetic field treatment.

ELF-EMF Exposure facilities and measurements

As previously reported, we used a standardised and characterised homemade magnetic field exposure facility (Heredia-Rojas et al. 2017, Heredia-Rojas et al. 2018a). In brief, a coil was prepared by winding 552 turns of enamel-insulated copper wire (1.3 mm diameter), which produced a 13.5 cm radius and 71 cm length cylindrical solenoid. It was connected to step-down and variable transformers and plugged into a 110 V AC source. Animals were placed in the middle of this structure in a homogeneous magnetic field and kept at 25 ± 0.2 °C and 45% humidity. Sham-treated animals were used as negative controls, which were placed in the same room but with the magnetic field device turned off. Magnetic flux density was determined using a Hall-effect probe (Bell FW 6010 Teslameter, Orlando, Fl, USA). In addition, an attached oscilloscope (BK-Precision model 2120, Dynascan Corp., Chicago, IL) was used to monitor the resulting field. A 60-Hz alternating sinusoidal magnetic field was then generated. Frequency content was almost pure 60 Hz (< 2% total harmonic distortion), and 0.3 µT and 20 µT values were observed for background magnetic

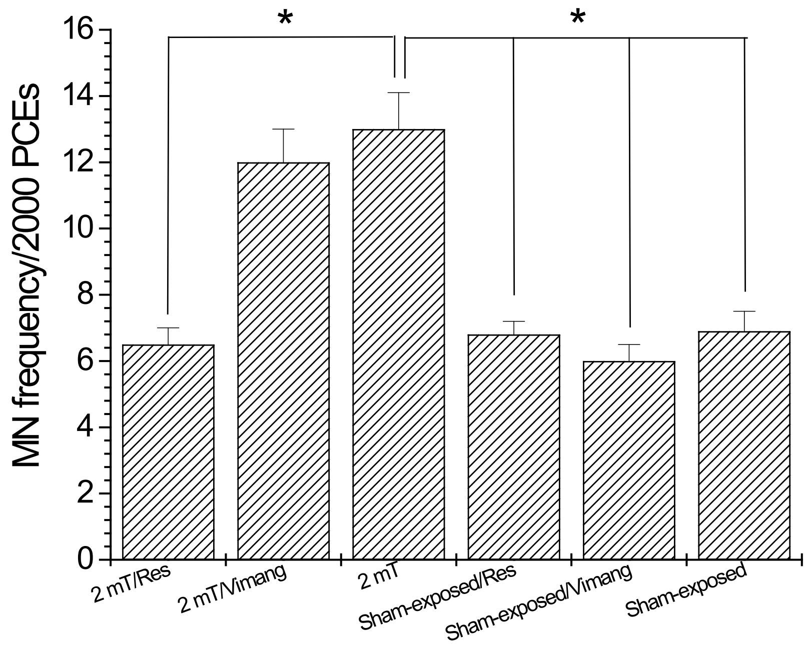

Fig. 1. Effect of resveratrol (Res) and mango extract (Vimang) on mouse bone marrow cells micronuclei (MN) frequency per 2000 polychromatic erythrocytes (PCEs). *$p < 0.05$.

and local geomagnetic fields, respectively. A plastic separator was inserted in the solenoid to place mice in pre-determined zones, where the oscillating magnetic field (rms) value was 2.0 mT to maintain the exposure geometry.

Experimental protocol

To evaluate the effect of resveratrol and Vimang extract on magnetic field-exposed animals, the following treatment regimens and control groups (six mice per group) were used: (*a*) mice continuously treated for 72 h at 2.0 mT ELF-EMF and *i.p.* injected with resveratrol, (*b*) 72 h of continuous 2.0 mT ELF-EMF exposure plus *i.p.* administration of Vimang, (*c*) 72 h of continuous 2.0 mT ELF-EMF exposure plus *i.p.* administration of the vehicle (saline isotonic solution), (*d*) sham-exposed mice treated with resveratrol, (*e*) sham-exposed mice treated with Vimang, and (*f*) sham-exposed mice treated with saline alone.

In vivo micronucleus (MN) test

We have used a previously reported MN test homemade magnetic field exposure facility (Heredia-Rojas et al. 2017). We selected the MN assay as a valuable tool for assessing genetic damage induced by various substances. MN serves as an index of gene damage resulting from chromosome breaks, structurally abnormal chromosomes, or spindle abnormalities. The MN assay is widely used to screen for chemicals causing these types of damage (Hayashi 2016). The sample source is erythrocytes from bone marrow and/or peripheral blood cells of animals (usually rodents). Regarding detection, specific staining techniques facilitate the visualisation of micronuclei in polychromatic erythrocytes (PCEs). An increased frequency in micronucleated polychromatic erythrocytes indicates induced chromosome damage, according to the original procedure by Schmidt (1976).

Statistical analysis.

Statistical differences among groups were determined by analysis of variance for normal distributions and the correspondent Tukey test for establishing individual differences. Data normality was calculated by the Kolmogorov-Smirnov test ($p < 0.05$). Results were expressed as grouped mean ± SD of the response of six animals per treatment group. Analyses were performed using the SPSS version 15.0 package.

Results

Figure 1 shows the grouped means of MN frequency after magnetic field exposure in resveratrol and Vimang pre-treated animals, compared with the control groups. A significant ($p < 0.05$) reduction of MN frequency was observed in resveratrol-treated animals exposed to ELF-EMF compared to the untreated control. In contrast, Vimang extract did not protect mice from the clastogenic effect of magnetic fields ($p > 0.05$). In addition, according to our previous reports (Heredia-Rojas et al., 2017; Heredia-Rojas et al., 2018a, 2018b; Heredia-Rojas et al. 2020), a higher MN frequency was observed in the ELF-EMF exposed group without any antioxidant pre-treatment ($p < 0.05$), as expected.

Moreover, to evaluate any direct genotoxic effect of resveratrol and Vimang extracts, sham-exposed animals pre-treated with both substances were compared with sham-exposed ones pre-treated only with the saline vehicle. We did not observe statistically significant differences among these groups ($p > 0.05$) (Fig. 1).

Discussion

Modern technologies, including smartphones and portable computers, represent an important source of electromagnetic radiation. The harm caused is still uncertain since no clear and definitive evidence exists of its negative influence on living bodies. This is despite ELF-EMFs being classified as potentially carcinogenic within group 2B, according to the World Health Organization (2007). In recent decades, we have observed a significant increase in research related not only to the influence of electromagnetic fields and/or electromagnetic radiation on living organisms but also to develop strategies to prevent an over-exposition or alleviate the harmful effects caused by radiation. The present study showed evidence of a radioprotective effect of resveratrol compared to the well-known and patented antioxidant Vimang. Although scarce information on the antigenotoxic effect of resveratrol against the harmful effects of extremely low-frequency radiation at 60 Hz has been reported to date, Zhang et al. (2017) demonstrated that resveratrol may alleviate detrimental effects of long-term occupational exposure to ELF-EMFs on humans that worked in an electrical power plant.

We have previously reported a potential radioprotective and antigenotoxic effect of resveratrol against a magnetic field exposure (Heredia-Rojas et al. 2020) but extended our research by comparing it's *in vivo* effects with the patented antioxidant Vimang. Our results agreed with those of Türkez & Aydin (2013), who observed an antigenotoxic activity of resveratrol against permethrin (PM) injury in cultured human peripheral lymphocytes, as assessed by chromosome aberrations (CA) and sister chromatid exchange (SCE) tests. Their findings indicated that PM-induced increases in the mean frequencies of CA and SCE were diminished by resveratrol in a concentration-dependent manner, which agrees with the findings of Abraham et al. (2016), who evaluated the *in vitro* and *in vivo* antigenotoxic effects of resveratrol against nitroquinoline-1-oxide (NQO) and mitomycin C (MMC) genotoxins, as assessed in the cytokinesis-block micronucleus test for *in vitro* studies. Regarding *in vivo* assays, resveratrol was tested against the genotoxins diepoxybutane (DEB), MMC, methyl methanesulfonate and procarbazine (PCB) and assessed by mouse bone marrow MN test. In all cases, an antigenotoxic effect exerted by resveratrol was found. On the other hand, concerning resveratrol radioprotective activity, Carsten et al. (2008) reported that gamma irradiation-chromosomal aberration frequencies were reduced by resveratrol in mouse bone marrow cells. Furthermore, cultures of primary human lymphocytes pre-treated with resveratrol showed a significant inhibition of genotoxicity induced by exposure to radioiodine-131 (Hedayati et al. 2013).

We compared this observed resveratrol radioprotective effect with a widely used *Mangifera indica* extract (Vimang) as a well-known antioxidant (Martinez-Sánchez et al. 2003, Pardo-Andreu et al. 2006, Pardo-Andreu et al. 2008) and as a radio-protector (Jagetia & Balinga 2005, Jagetia & Venkatesha 2005, Rodeiro et al. 2014). Moreover, it has been reported that Vimang extract exerts liver protection (Remirez et al. 2005, Rodeiro et al. 2007) and neuroprotection (Campos-Esparza et al. 2009, Lemus-Molina et al. 2009). Clinical trials have been conducted in humans (Santos et al. 2003) with promising results. However, we did not find any radioprotective effect of Vimang against the clastogenic effect induced by magnetic field exposure.

On the other hand, to test the direct genotoxic effects of resveratrol and Vimang extracts, bioassays were conducted by exposing animals to these antioxidants but without magnetic field exposure (sham-exposed mice) and compared with sham-exposed mice injected only with saline vehicle. We did not observe direct genotoxic effects of these substances (Fig. 1). Regarding resveratrol, most scientists recognise that it has low toxicity, as it is well-tolerated in several short-term experiments (Almeida et al. 2009, La Porte et al. 2010, Wong et al. 2011) and some clinical trials have demonstrated that resveratrol is pharmacologically safe (Patel et al. 2011). However, some reports showed genotoxic effects. For instance, an increased frequency of sister chromatid exchanges was observed by Matsuoka et al. (2001) in CHL cells exposed to resveratrol. Similarly, an increased frequency of MN was observed in CHO-K1 cells previously treated with resveratrol (Basso et al. 2013). In contrast, some studies using long-term assays on resveratrol toxicity have indicated an adequate tolerance (Zamora-Ros et al. 2006, Chow et al. 2010). Regarding the potential direct genotoxic effects of Vimang, previous reports showed no toxicity or harmful effects attributed to this extract (Rodeiro et al. 2006, González et al. 2007, Garrido-Garrido et al. 2009). Prado et al. (2015) recently demonstrated that orally treated rats with this mango extract at 250 mg/kg to 1000 mg/kg showed no abnormal clinical signs or haematology alterations compared to the control group.

The observed radioprotective effect exerted by resveratrol against ELF-EMF exposure is explained based on its proven antioxidant potential. It is known that oxidative stress is one of the underlying causes of deleterious effects induced by electromagnetic fields (Yakymenko et al. 2016, Schuermann & Mevissen 2021). Moreover, Zhang et al. (2017) have reported that several biomarkers of oxidative stress are closely related to ELF-EMF exposure in humans. Furthermore, an increased oxidative stress response in workers exposed to ELF-EMFs at 132 kV substations has been reported (Tiwari et al. 2015). Several studies have proposed that oxidative stress induced by ELF-EMFs may lead to DNA damage (Wolf et al. 2005) in a dose-dependent way (Ivancsits et al. 2003). However, how a chemical radioprotector reduces radiation's harmful effects is still unclear. Furthermore, an antioxidant agent may present different protection mechanisms for different systems.

In conclusion, the present *in vivo* study suggests that resveratrol inhibited the genotoxic effect of ELF-EMF exposure compared to the widely used Vimang extract. Moreover, no direct genotoxic effect of resveratrol and Vimang regarding MN frequency in mouse bone marrow cells was observed.

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