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Ginkgo biloba Extract: A Preliminary Study on Its Radiomitigative Potential Using the Conventional Dicentric Chromosome Assay

Silva[a,c*], J. C. G.; Silva[b,c], C. V. B. G. S.; Mendes[c], M. E.; Lopes[d], I. M. S. S.; Melo[c,d], A. M. M. A.; Lima[c], F. F.

[a] Postgraduate Program in Energy and Nuclear Technologies, PROTEN, Universidade Federal Pernambuco, UFPE, 50740-540, Recife, PE, Brazil.
[b] Postgraduate Program in Biological Sciences, PPGCB, Universidade Federal Pernambuco, UFPE, 50740-570, Recife, PE, Brazil.
[c] Centro Regional de Ciências Nucleares do Nordeste, CRCN-NE, 50740-437, Recife, PE, Brazil.
[d] Department of Biophysics and Radiobiology, Universidade Federal de Pernambuco, UFPE, 50670-420, Recife, PE, Brazil.

*Correspondence: julio.gsilva@ufpe.br

Abstract: Radioprotectors and radiomitigators can be substances of natural or synthetic origin that, once administered to the human body, are capable of preventing, protecting against, or reducing damage caused by radiation. This study aimed to assess the radiomitigating potential of *Ginkgo biloba* extract by examining the frequency of dicentric chromosomes in irradiated human lymphocytes. Blood samples were obtained from a healthy volunteer. One sample was left in the laboratory as a control, and the others were irradiated in a ^{60}Co source at a dose of 2 Gy and incubated in test concentrations of *Ginkgo biloba* extract (0.025 and 0.05 µg/ml) according to a standard protocol. Complete metaphases were analyzed, and the frequencies of alterations were statistically evaluated to verify the radiomitigating potential of *Ginkgo biloba* extract. The ANOVA and Tukey tests revealed a statistically significant difference between the groups treated and untreated with Ginkgo biloba exposed to 2 Gy of radiation ($p < 0.05$), indicating that both concentrations tested were able to reduce the damage. In this *in vitro* study, *Ginkgo biloba* extract was able to reduce the frequency of dicentric chromosomes in irradiated human lymphocytes, with a concentration of 0.025 µg/ml standing out.

Keywords: Ionizing radiation, cytogenetic dosimetry, dicentric, *Ginkgo biloba* extract.

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Extrato de *Ginkgo biloba*: Um estudo preliminar sobre seu potencial radiomitigador usando o ensaio convencional de cromossomo dicêntrico

Resumo: Radioprotetores e radiomitigadores podem ser substâncias de origem natural ou sintética que, uma vez administradas ao corpo humano, são capazes de prevenir, proteger ou reduzir danos causados pela radiação. Este estudo teve como objetivo avaliar o potencial radiomitigador do extrato de *Ginkgo biloba* examinando a frequência de cromossomos dicêntricos em linfócitos humanos irradiados. Amostras de sangue foram obtidas de um voluntário saudável. Uma amostra foi deixada no laboratório como controle, e as outras foram irradiadas em uma fonte de ^{60}Co na dose de 2 Gy e incubadas em concentrações de teste do extrato de *Ginkgo biloba* (0,025 e 0,05 µg/ml) de acordo com um protocolo padrão. Metáfases completas foram analisadas, e as frequências de alterações foram avaliadas estatisticamente para verificar o potencial radiomitigador do extrato de *Ginkgo biloba*. Os testes ANOVA e Tukey indicaram diferença estatística entre os grupos tratados e não tratados com *Ginkgo biloba* expostos a 2 Gy de radiação ($p < 0,05$), demonstrando que ambas as concentrações testadas foram capazes de reduzir os danos. Neste estudo *in vitro*, o extrato de *Ginkgo biloba* foi capaz de reduzir a frequência de cromossomos dicêntricos em linfócitos humanos irradiados, com destaque para a concentração de 0,025 µg/ml.

Palavras-chave: Radiação ionizante, dosimetria citogenética, cromossomos dicêntricos, extrato de *Ginkgo biloba*.

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1. INTRODUCTION

Ionizing radiation (IR) has been utilized across various sectors of society, with applications in medicine, including radiology and radiotherapy, in the energy sector through nuclear power generation, in industry for quality control and materials inspection, in agriculture for food irradiation [1–2], and even in product sterilization. However, improper handling of IR can lead to exposure scenarios, such as radiological or nuclear accidents, resulting in damage to the human body [3–4].

Biological systems interact with IR via two primary mechanisms: direct and indirect actions. Direct action involves the interaction of radiation energy with deoxyribonucleic acid (DNA), causing single-strand breaks (SSBs) and double-strand breaks (DSBs). Indirect action occurs through the radiolysis of water, generating free radicals that stabilize by interacting with critical biomolecules, including proteins, lipids, and again, DNA [5].

In radiation exposure incidents, the extent of biological damage is assessed by estimating the absorbed dose using sensitive and specific biological markers that reflect radiation-induced harm. The Dicentric Chromosome Assay (DCA) is considered the gold standard for such analyses, as it is a specific biomarker for IR exposure. Dicentric chromosomes, containing two centromers, result from erroneous homologous recombination repair following radiation-induced DNA strand breaks [6].

Radioprotective and radiomitigating agents are compounds capable of attenuating the biological effects induced by IR. Their effectiveness is related to the timing of administration: radioprotectors are effective when administered before radiation exposure, while radiomitigators act post-exposure [7–8]. Radioprotector substances primarily function by inducing DNA repair pathways, thereby stimulating cell proliferation, while radiomitigators act by scavenging free radicals through antioxidant mechanisms [9-11]. Among commercially

available radioprotectors, only WR-2721 is approved by the U.S. Food and Drug Administration (FDA), although it has a short half-life in the body and is associated with side effects such as nausea, vomiting, and hypotension [10]. In this context, natural products have emerged as promising alternatives, capable of mitigating radiation-induced damage to biological materials with fewer associated side effects [11].

Endemic to East Asia and dating back to the Permian period, qualifying it as a "living fossil," the *Ginkgo biloba* tree exhibits antioxidant, anti-inflammatory, hypoglycemic, and hypotensive properties. It acts by scavenging free radicals and stimulating endogenous antioxidant molecules such as Superoxide Dismutase (SOD) and Glutathione (GSH) [14-17]. It also mediates the inflammatory process by downregulating the expression of tumor necrosis factor alpha (TNF-α) and nuclear factor kappa B (NF-ϰB), while upregulating interleukin-10 (IL-10) [12–14]. Due to these properties, *Ginkgo biloba*-based formulations have shown promising neuroprotective actions, capable of preventing the progression of neurodegenerative diseases [15–16]. These attributes have generated interest in exploring the radiomitigative potential of *Ginkgo biloba* extract.

2. MATERIALS AND METHODS

The experiment was conducted in accordance with procedures reviewed and approved by the Research Ethics Committee for Human Studies of the Health Sciences Center at Universidade Federal de Pernambuco (UFPE), under the Certificate of Presentation for Ethical Consideration (CAAE) No. 39932720.4.0000.5208, as registered on the Plataforma Brasil.

A healthy donor was selected through a clinical anamnesis to ensure that, within the six months before sample collection, the individual had not undergone any treatment involving ionizing radiation or used any illicit substances. Following the signing of an

Informed Consent Form, a 20-ml peripheral human blood sample was collected from the donor. Venipuncture was performed at the Biological Dosimetry Laboratory (LDB – Recife, PE, Brazil) using sterile vacuum tubes containing lithium heparin.

2.1 Irradiation of Donor Blood Sample

Immediately after collection, the blood sample was divided into four 5 mL aliquots, which were further assigned to four experimental groups. Group 1 served as the negative control, receiving neither irradiation nor extract treatment. Group 2 served as the positive control, subjected to irradiation only. Groups 3 and 4 were irradiated samples and subsequently treated with *Ginkgo biloba* extract at concentrations of 0.025 and 0.05 µg/mL, respectively.

The portion of blood corresponding to groups 2, 3, and 4 was transported to a ^{60}Co source (Gammacell 220 irradiator) located at the Department of Nuclear Energy of the Federal University of Pernambuco (DEN–UFPE, Brazil) for irradiation at a temperature of approximately 22 °C. A 4 mm polyethylene build-up material was used to ensure electronic equilibrium of the samples during irradiation. The total administered dose was 2 Gy, selected based on criteria established by the International Atomic Energy Agency [19]. A fraction dose of 2 Gy has been established as a standard in external beam radiotherapy, serving as the reference dose frequently studied in radiation biology, including research on occupational exposure and its potential risks for healthcare professionals working with ionizing radiation.

Following irradiation, the blood samples were incubated at 37 °C for 2 hours to simulate a real-life radiation exposure scenario, allowing sufficient time for DNA repair mechanisms to be activated before sample processing. Subsequently, the irradiated material was treated with Ginkgo biloba extract (Merck/Germany) at predetermined concentrations of 0.025 and 0.05 µg/ml, and blood cultures were prepared for further analysis.

2.2 Cell Viability

Cell viability was determined using the MTT reduction method ([3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide]), according to the (MERCK MTT kit) protocol. After the end of the culture, $1x10^6$ cells/µL were added to 96-well cell culture plates, followed by 10 µL of a 5 mg/mL MTT dye solution in each well. It is worth noting that the test was performed in triplicate for each extract concentration selected for the study. After the exposure time (3 h), the culture medium was removed, and 80 µL of dimethyl sulfoxide (DMSO) was added to each well to solubilize the formazan crystals (resulting from the reduction of the tetrazolium salt, which is reactive to the water-insoluble dye). The plates were gently shaken for 10 minutes, and then absorbance was measured in an ELISA device at 570 nm. The test was performed with extract concentrations of 0.025 and 0.05 µg/ml. Only the effects of extract concentrations that passed the cell viability test were evaluated.

2.3 Lymphocyte Culture

Peripheral blood lymphocyte cultures were prepared in 15 mL Falcon tubes, each containing 4 mL of RPMI 1640 culture medium (Gibco/Thermo Fisher Scientific) supplemented with *Ginkgo biloba* extract (at concentrations of 0.025 and 0.05 µg/mL) for evaluation of its radiomitigative effect. Additionally, 0.5 mL of fetal bovine serum (Gibco/Thermo Fisher Scientific), 0.5 mL of whole blood, 0.1 mL of phytohemagglutinin (Sigma/Aldrich), and 0.6 mL of streptomycin (Sigma/Aldrich) were added to each tube. The cells were incubated for 48 hours, and 0.1 mL of colcemid (Sigma/Aldrich) was added at 46 hours, in accordance with the protocol recommended by the International Atomic Energy Agency [19].

After incubation, the samples were removed from the incubator and centrifuged at 1050 RPM for 10 minutes. Following centrifugation, the supernatant was carefully removed, leaving approximately 0.75 mL of the cell pellet. Approximately 8 mL of potassium chloride (KCl) solution was then added, followed by another round of centrifugation under the same

conditions. The supernatant was removed again, and 8 mL of fixative solution composed of methanol and acetic acid (3:1) was added.

The samples were homogenized and centrifuged once more at 1050 RPM for 10 minutes. This process was repeated until the pellet appeared clear—typically after three washes—after which a final volume of 8 mL of fixative was added.

2.4 Slides Preparation

The pellet containing peripheral blood lymphocytes was resuspended in approximately 1 mL of fixative solution. Cell suspensions were then dropped onto clean glass slides from a height of approximately 1 meter at two separate points. The slides were left to air-dry at room temperature for 24 hours. After drying, the slides were stained by immersion in a 5% Giemsa solution for 7 minutes, followed by air-drying at room temperature.

2.5 Cytogenetic Analysis

Metaphases were analyzed using an optical microscope (Leica DM500/Danaher), initially with a 10× objective lens to locate cells, and subsequently with a 100× lens objective for chromosomal analysis. Viable cells were defined as those containing 46 centromeres, without overlapping chromosomes, and were assessed for unstable chromosomal aberrations (dicentric chromosomes and rings with their respective fragments). A total of slightly more than 100 metaphases per group were analyzed [19].

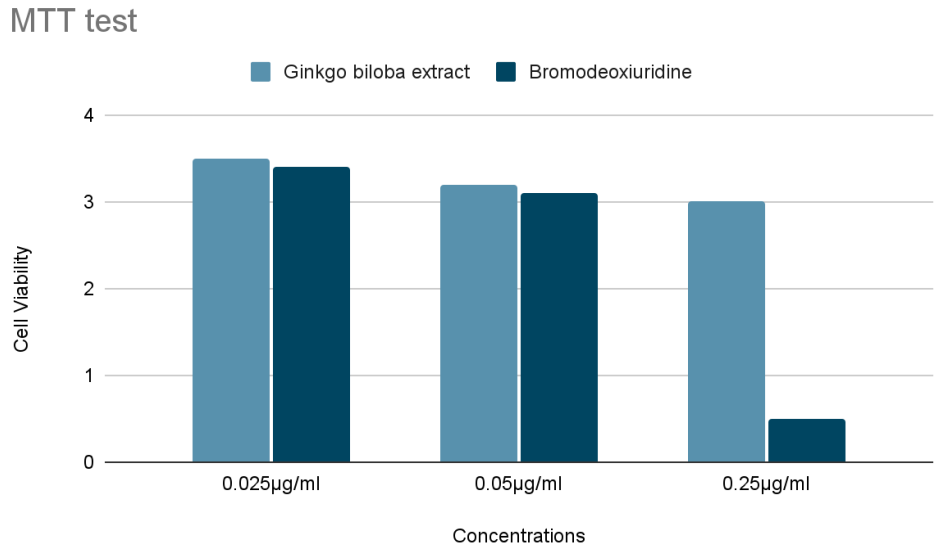
2.6 Statistical Analysis

For statistical analysis, the frequency of cytogenetic alterations was assessed. Analysis of variance (ANOVA) was applied to evaluate the radiomitigative effect by comparing results across the different extract concentrations. Tukey's post hoc test was used to assess pairwise differences between individual samples. Differences were considered statistically significant at p-values < 0.05.

3. RESULTS AND DISCUSSIONS

Cell viability analysis, performed using the MTT assay, revealed that samples treated with Ginkgo biloba extract exhibited higher cell viability compared to samples treated with the cytotoxic agent bromodeoxyuridine at concentrations of 0.025, 0.05, and 0.25 µg/ml. As shown in Figure 1, cell viability decreases as the concentrations of both substances increase. This effect can be understood through pharmacodynamic principles, which suggest that as the concentration of a substance increases, its toxic potential typically increases, within a therapeutic range that ensures treatment safety [23]. In the case of bromodeoxyuridine, the highest concentration (0.25 µg/ml) induced more pronounced cytotoxic effects compared to lower concentrations. In contrast, *Ginkgo biloba* extract showed greater cell viability at higher concentrations, demonstrating its low toxicity to human peripheral blood lymphocytes.

Figure 1: Cell viability obtained by the MTT colorimetric test.



Analysis of dicentric chromosomes was performed by evaluating 781 lymphocyte metaphases, of which 525 metaphases were from control samples and 256 metaphases from test samples (Table 1).

As observed, the frequency of dicentric chromosomes for the negative control (non-irradiated and untreated) remained within the background range recommended by the literature, which is about 1 in every 1000 analyzed cells [19]. The same behavior was observed in the groups treated with Ginkgo extract and non-irradiated, as expected, since dicentrics are specific changes caused by ionizing radiation.

Table 1. Comparison of the frequency of dicentric chromosomes between all groups (controls and irradiated blood treated with *Gingko biloba* extract). **Legend:** *Con*: Concentration (µg/mL); *Y*: Frequency of Dicentrics; *var*: Variance; *var*/*Y*: Variance-to-mean ratio; *u*: *u*-test.

Dose (Gy)	Conc. (µg/mL) *G. biloba*	Cells Score	Dic Score	Y	% of damage	Estimated Dose
0	0	113	0	0.00	0%	0
0	0.025	179	0	0.00	0%	0
0	0.05	133	0	0.00	0%	0
2	0	100	17	0.170	15.0%	2.073
2	0.025	142	13	0.092	5.63%	1.192
2	0.05	114	15	0.132	10.53%	1.950

When comparing the untreated irradiated sample and the test samples, it is observed that the frequency of alterations is higher in the sample that was not treated with Gingko extract. Additionally, it was demonstrated that in both tested concentrations of the extract, there was a reduction in the percentage of damage (Table 1). The concentration of 0.025 µg/ml was more prominent, as it was able to reduce damage by 45% compared to the non-irradiated and untreated control sample, as indicated by the frequency percentages (Y).

In the literature, some studies [8, 21-22], which used the same technique to demonstrate possible radioprotective effects, presented frequency behaviors similar to those observed in this study, where the samples treated with substances investigated as radioprotective showed a significant decrease in their frequencies, when compared to the untreated samples (Table 2).

Table 2. Comparison of Dicentric Chromosome Frequencies with Literature. **Legend:** *Y* dic: Frequency of Dicentrics.

	Dose (Gy)	Extract/Drug	Concentration	Y dic.	CI 95% Dic Score
This study	2	*Gingko biloba*	0.0µg/ml	0.170	0.089 - 0.251
			0.025µg/ml	0.092	0.044 - 0.139
			0.05µg/ml	0.132	0.064 - 0.199
[21] MONTORO, *et. al.*, 2005	2	Propolis	0.0 mg/ml	0.28	0.1101 - 0.1551
			1mg/ml	0.15	0.118 - 0.192
[8] DE SIQUEIRA, *et. al.*, 2019	2,5	Quercetin	0.0µM	0.092	0.0654 - 0.1186
			37.5µM	0.028	0.0132 - 0.0428
[22] ALOK, *et. al.*, 2020.	2	Diclofenac sodium	0.0µM	0.15	0.115 - 0.181
			10µM	0.13	0.098 - 0.162
			100µM	0.102	0.074 - 0.130
			1mM	0.06	0.039 - 0.0811

As observed, the studies reflect the same pattern identified in the present work: when comparing treated samples with untreated ones, it is evident that the extracts investigated as potential radioprotector agents demonstrated the ability to reduce intracellular damage. This is evidenced by the decreased appearance of dicentric chromosomes in the treated samples.

Montoro and collaborators reported that a 1 mg/mL concentration of propolis extract exhibited radioprotective properties, achieving a 46% reduction in damage. However, they emphasized the necessity of testing a broader range of concentrations, as well as different radiation types and doses, to determine whether the radioprotective effect is consistent across these parameters.

Siqueira and collaborators evaluated the radiomitigative effect of quercetin, achieving a reduction in damage of approximately 70% at a concentration of 37.5 µM. The authors noted that the observed radiomitigative properties of quercetin highlight the need for further studies to better explore its radioprotective potential.

Alok and collaborators observed that a 1 mM concentration of sodium diclofenac significantly reduced the frequency of chromosomal alterations (60%), outperforming lower concentrations such as 10 μM and 100 μM. Although those lower doses also reduced damage frequencies, their effects were less significant when compared to untreated irradiated samples.

To assess the variability among the samples, means and standard deviations were statistically analyzed using ANOVA and Tukey tests. Statistically significant differences were considered at p-values < 0.05.

The ANOVA test revealed statistically significant differences between irradiated and non-irradiated samples in terms of dicentric chromosome frequencies ($p < 0.05$). These findings were further detailed by Tukey's post hoc test, which showed significant differences ($p < 0.05$) between the irradiated group without *Ginkgo biloba* and the groups treated with 0.025 μg/mL and 0.05 μg/mL. These results indicate that both concentrations of the extract were effective in reducing radiation-induced damage. However, to confirm these findings, additional studies with a larger number of individuals and cells analyzed are needed.

4. CONCLUSIONS

The *Ginkgo biloba* extract has shown indications that it is capable of reducing the formation of chromosomal alterations in human peripheral blood lymphocytes after irradiation with 2 Gy of gamma radiation, especially at the concentration of 0.025 μg/ml. However, to better understand this potential, further studies will be conducted using different types of radiation, absorbed doses, and a larger number of cells analyzed.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

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