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Investigation of the Genotoxic Effect of Fluoxetine Hydrochloride in *Drosophila melanogaster*

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ABSTRACT
This study aimed to determine the potential genotoxic effect of fluoxetine hydrochloride (FLX-HCl), an antidepressant commonly used for treating depression, using Somatic Mutation and Recombination Test (SMART). Third-instar *Drosophila melanogaster* larvae transheterozygous for the mutations multiple wing hair (*mwh*) and flare (*flr*^{3}) were chronically fed in a medium containing different concentrations of FLX-HCl (0.1, 0.5, 1, and 2 mg/mL) in the experimental group. Distilled water, 0.1 mM ethyl methane sulfonate (EMS), and 2% dimethyl sulfoxide (DMSO) were used in negative, positive, and solvent control groups, respectively. The survival percentages were calculated by determining the number of individuals surviving when the larvae completed their development in the experimental and control groups. In all application groups, the wings of 40 individuals with both normal and serrate wing phenotypes were examined under a microscope, and genetic changes were evaluated by counting the mutant clones in the wings. The data obtained show that 1 and 2 mg/mL concentrations of FLX-HCl caused toxic effects in *D. melanogaster* individuals. Additionally, FLX-HCl showed a negative genotoxic effect at 0.1 mg/mL concentration, insignificant at 0.5 mg/mL concentration, and positive at 1 and 2 mg/mL concentrations in terms of total mutation evaluation and clone induction frequency in *D. melanogaster* individuals.

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Fluoksetin Hidroklorür'ün Genotoksik Etkisinin *Drosophila melanogaster*'de Araştırılması

ÖZET
Bu çalışmada depresyon tedavisinde yaygın olarak kullanılan bir antidepresan olan fluoksetin hidroklorürün (FLX-HCl) potansiyel genotoksik etkisinin Somatik Mutasyon ve Rekombinasyon Testi (SMART) kullanılarak belirlenmesi amaçlanmıştır. Deney grubunda çoklu kanat kılı (*mwh*) ve flare (*flr*^{3}) mutasyonları için transheterozigot olan üçüncü dönem *Drosophila melanogaster* larvaları, farklı konsantrasyonlarda FLX-HCl (0.1, 0.5, 1 ve 2 mg/mL) içeren ortamda kronik olarak beslenmiştir. Distile su, 0.1 mM etil metan sülfonat (EMS) ve % 2 dimetil sülfoksit (DMSO) sırasıyla negatif, pozitif ve çözücü kontrol gruplarında kullanılmıştır. Deney ve kontrol gruplarında larvalar gelişimini tamamladığında hayatta kalan birey sayıları belirlenerek yaşama yüzdeleri hesaplanmıştır. Tüm uygulama gruplarında hem normal hem de serrat kanat fenotipine sahip 40 bireyin kanatları mikroskop altında incelenmiş ve kanatlardaki mutant klonlar sayılarak genetik değişimler değerlendirilmiştir. Elde edilen veriler, FLX-HCl'nin 1 ve 2 mg/mL konsantrasyonlarının *D. melanogaster* bireyleri üzerinde toksik etkiye neden olduğunu göstermiştir. Ayrıca FLX-HCl, *D. melanogaster* bireylerinde toplam mutasyon değerlendirmesi ve klon induksiyon frekansı bakımından 0.1 mg/mL konsantrasyonunda negatif, 0.5 mg/mL konsantrasyonunda önemsiz, 1 ve 2 mg/mL konsantrasyonlarında pozitif genotoksik etki göstermiştir.

Genetik

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INTRODUCTION

The Organization for Economic Cooperation and Development (OECD) states in its guidelines that the genotoxic effects of the active compounds used in drugs must be tested using model organisms in the drug development process (Anonymous, 2023). Access to information on genotoxicity evaluations of drugs made by drug manufacturers is limited or not possible for many drugs. For this reason, the investigation of the possible toxic effects of drug-active ingredients by independent studies is very essential for human health (Yuzbasioglu et al., 2016). Previous studies performed either in vivo or in vitro showed that drug-active ingredients may have genotoxic effects (Al-Eitan et al., 2020; Khodeer et al., 2020; Álvarez-González et al., 2021; Cheki et al., 2021; Antonopoulou et al., 2022).

Depression, one of the most common psychiatric disorders in the world, affects approximately 350 million people worldwide (Al-Obaidi & Al-Shawi, 2020). This mental disorder can be seen in people of different age groups, and its lifetime prevalence is estimated to be 16% (Shorey et al., 2022). Although psychotherapy and medication are effective for treating depression, the applicability rate of psychotherapeutic methods is low. As depression rates have increased and drug therapy is the primary method of treating depression, the use of antidepressants has increased recently (Duval et al., 2006).

Fluoxetine (FLX-HCl), one of the widely prescribed selective serotonin reuptake inhibitors (SSRIs) group antidepressants, is used for treating major depression as well as other psychological disorders such as anxiety, obsessive-compulsive disorder, and bulimia nervosa (Rossi et al., 2004; Al-Obaidi & Al-Shawi, 2020). Antidepressants may cause genotoxic damage either directly or indirectly after being metabolized in the liver (Kumar et al., 2020). The active ingredient norfluoxetine is released when FLX-HCl is metabolized. Because FLX-HCl and norfluoxetine inhibit their metabolism over time, they are slowly eliminated from the body and differ from other SSRIs in this respect (Mondal et al., 2013). The prolonged stay of FLX-HCl in the body may increase its toxic effect potential. It has been reported that acute FLX-HCl intoxication causes the death of a patient with a genetic deficiency of the cytochrome-P450 2D6 enzyme involved in the metabolism of SSRIs (Sallee et al., 2000).

Recently, rising rates of depression depending on stress conditions caused by factors such as the COVID-19 pandemic, and worsening of economic and social conditions have increased antidepressant usage by people. Antidepressants are drugs used in long-term treatment, and in some cases, they are administered with other drugs. This situation increases the number of medication patients are exposed to and the possibility of toxic effects that may occur in patients in this way. As for the other drug types, it should be verified that antidepressants do not have serious side effects such as cytotoxicity, genotoxicity, or mutagenicity. For this reason, the determination of the possible toxic effects of antidepressants in humans, especially using in vivo experimental systems, is of great importance.

Although FLX-HCl is an active substance whose toxicity has been examined before being used as an antidepressant drug, studies conducted by independent laboratories show that different findings were obtained from its toxicity assessments. Garayo et al. (2022) reported that no DNA damage occurred in THP-1 cells 6 and 24 h after FLX-HCl (1 and 10 µM) administration and there was no effect on the level of base oxidation induced by $KBrO_3$. In the study evaluating the cytotoxic and mutagenic effects of FLX-HCl in *Allium cepa* and Wistar rats, it was reported that FLX-HCl showed cytotoxicity to *A.cepa* meristem cells, but administration of FLX-HCl by gavage or intraperitoneally to Wistar rats did not cause clastogenic effects (Dusman et al., 2014). Also, in a study conducted in mice and rats, no carcinogenic effect was detected depending on the long-term use of FLX-HCl (Bendele et al., 1992). In contrast, a study investigating the mutagenic potential of FLX-HCl in prokaryotic and eukaryotic cells by performing chromosomal aberrations and Ames tests found that FLX-HCl is mutagenic in human peripheral leukocytes and *S. typhimurium* at the highest doses administered (Cavalcanti et al., 2022). FLX-HCl also showed varying cytotoxic activity on rat spleen macrophages depending on the treatment time and test method. In vivo experiments showed that the drug caused cytotoxicity after single dose and short time exposure. However, no cytotoxicity was detected in long-term in vivo and in vitro experiments (Belowski et al., 2004). Oral administration of 7.2 mg/kg FLX-HCl for 4 weeks induced frequency of micronuclei formation in bone marrow tissue and increased DNA damage in liver and testis tissues of Swiss albino adult male rats (Al-Obaidi & Al-Shawi, 2020). In another study, oral FLX-HCl administration to rats at a higher dose (10 mg/kg day) for a shorter period (7 days) caused the development of

oxidative stress, inflammation, apoptosis, and hepatoxicity (Elgebaly et al., 2018).

In the literature review, it has been seen that FLX-HCl can cause a positive response in one test but a negative response in another test and may lead to genotoxicity even at low doses. Examining the genotoxic potential of FLX-HCl using various test systems will help to expand our limited knowledge in this field. To reach a more specific conclusion about whether FLX-HCl poses a genotoxic risk, it would be useful to investigate its genotoxicity once again with reliable tests using model organisms. *D. melanogaster* is an important model organism used for genotoxicity determination of many chemical, physical and biological agents (Gunes, 2016; Jiménez et al., 2019; Mishra & Panda, 2021; Teixeira et al., 2021; Véras et al., 2022; Uysal & Celik, 2023). the research evaluating the genotoxic effects of drugs can also be conducted with test systems using *D. melanogaster* (Allgayer et al., 2019; Nagpal & Abraham, 2019; Jajoo et al., 2020). No study investigating the genotoxicity of FLX-HCl in *Drosophila* using Somatic Mutation and Recombination Test (SMART) have been found in the literature. In this context, the current study was designed to evaluate the genotoxic potential of FLX-HCl by examining its mutagenic/recombinogenic effects in *D. melanogaster* using SMART assay.

MATERIAL and METHOD

Genotoxicity Assay

In this study, SMART assay was used to investigate the possible genotoxic effect of FLX-HCl at different concentrations. The SMART method was developed by Graf et al. (1984) based on observing the genotypic changes in wing cells of adult flies with trans-heterozygous phenotype. In this method, information about not only mutagenic effects but also recombinogenic effects of the test substances can be obtained by using special genetic lines.

Drosophila Strains

In experiments, multiple wing hair (*mwh*/*mwh*) and flare (*flr*^{3}/*In* (*3LR*), *TM3 Bd*^{S}) mutant strains of *D. melanogaster* were used. These strains carry genetic markers on their third chromosome: multiple wing hairs (mwh, 3–0.3) and flare (flr3, 3–38.8) (Lindsley & Zimm, 1992). *Drosophila* strains were obtained from Gazi University Gazi Education Faculty Genetics Laboratory. Stock *Drosophila* cultures and treatment groups were kept at 25°C, 40-60% relative humidity during the experiment.

The Experimental Process

In experiments, trans-heterozygous larvae derived from standard cross between 5-day-old *mwh* virgin females and *flr*^{3} males were used. Trans-heterozygous third instar larvae (72 ± 4 h) were collected at 4 h intervals. Larvae were taken from the standard medium and washed, then divided into groups of 100. 1.5 g of the medium was wetted with 5 mL of the test solution at the determined concentration. FLX-HCl was used at 0.1, 0.5, 1, and 2 mg/mL concentrations in the experimental group. 2% DMSO was used to dissolve FLX-HCl when preparing the stock solution. Distilled water was used in the negative control group, 2% DMSO in the solvent control group and 0.1 mM EMS in the positive control group. The doses of FLX-HCl and DMSO administered were determined by the LD_{50} experiments. The dose of EMS was determined based on a previous studies in the relevant literature (Anet et al., 2019). For each treatment, 100 larvae were embedded in the medium and allowed to develop there (Graf et al., 1998). Each dose was repeated three times. Adult individuals emerging from the pupa were stunned with light ether and grouped according to their gender and phenotype under a dissecting microscope. Meanwhile, the number of surviving individuals in each group was determined, and the survival percentage was calculated. Then, the flies were placed in tubes containing 70% ethanol and stored at 4°C until wing preparations were made (Graf et al., 1984). Wing preparations of individuals with normal and serrate wings were made and examined under a microscope, and mutations were classified according to their formation patterns (Graf et al., 1984; Frei & Würgler, 1988; Graf et al., 1998).

Data Analysis

In this study, survival percentage, genotoxicity, and clone induction frequency in *D. melanogaster* individuals were calculated. Whether there were significant differences between survival rates of the control and experimental groups were calculated using the chi-square test. For the evaluation of the possible genotoxic effect of FLX-HCl, the frequencies of each type of spots per individual of an experimental group were compared to a negative control group using a conditional binomial test (Kastenbaum & Bowman, 1970). A binomial test uses sample data to analyze whether the incidence of one level in a binary variable is equal to a specific value. The results obtained were determined as statistically negative, positive, or inconclusive (Frei & Würgler, 1988). The level of statistical significance was accepted as $p<0.05$.

RESULTS

In this study toxicity and genotoxicity of different concentrations of FLX-HCl (0.1, 0.5, 1, and 2 mg/mL) were investigated using *mwh* and *flr*^{3} mutant strains of *D. melanogaster*. This model organism is widely used in genotoxicity studies because it has a genome that exhibits high homology to the human genome and provides the opportunity to obtain reliable data easily

and economically in a short period.

To evaluate the toxic effect of FLX-HCl, whether there was a significant difference between the survival rates of the individuals in the control and experimental groups was evaluated with the chi-square test. The results are given in Table 1. No significant difference in the survival rates was detected between the solvent and negative control groups. This indicates that 2% DMSO can be used as a solvent in experiments. As a result of the comparison of survival rates between the negative control and experimental group, it was found that 0.1 and 0.5 mg/mL concentrations of FLX-HCl produced no statistically significant changes. However, increases in groups treated with 1 mg/mL and 2 mg/mL concentrations of FLX-HCl were detected statistically significant (Table 1). This result can be interpreted as 1 and 2 mg/mL concentrations of FLX-HCl have toxic effects in *D. melanogaster* individuals.

Additionally, the possible genotoxic effect of FLX-HCl at different concentrations was investigated by the SMART assay using mutants of *D. melanogaster*. The findings obtained from the analysis of normal and serrate-winged individuals are given in Table 2.

Table 1. Survival rates of individuals in the control and experimental groups
Çizelge 1. Uygulama ve deney gruplarında bireylerin hayatta kalma oranları

Test material	Concentration	Survival rate (%)	p
Distilled water	-	98	-
DMSO	2%	85	0.92
FLX-HCl	0.1 mg/mL	80	1.82
	0.5 mg/mL	74	3.34
	1 mg/mL	72	3.97*
	2 mg/mL	65	6.68***

*p<0.05 ; ***p<0.001 (compared to control)

Table 2. The summary of SMART results of normal and serrate winged individuals
Çizelge 2. Normal ve serrat kanatlı bireylere ait SMART sonuçları

T	C	N	Small single spots (1-2 cells) (m=2)			Large single spots (>2 cells) (m=5)			Twin spots (m=5)			Total *mwh* spots (m=2)			Total spots (m=2)			CIF
			No	Fr.	D	No	Fr.	D	No	Fr.	D	No	Fr.	D	No	Fr.	D	
Normal wings (*mwh/flr*³)																		
EMS (mM)	0.1	80	58	0.73		5	0.06		1	0.01		63	0.79		64	0.68		2.97
Distilled water	-	80	20	0.25		2	0.03		1	0.01		23	0.29		23	0.29		1.17
DMSO (%)	2	80	25	0.31	i	2	0.03	i	1	0.01	i	27	0.34	-	28	0.35	-	1.38
FLX-HCl (mg/mL)	0.1	80	25	0.31	i	2	0.03	i	0	0	i	27	0.34	-	27	0.34	-	1.38
	0.5	80	28	0.35	i	4	0.05	i	0	0	i	32	0.40	i	32	0.40	i	1.64
	1	80	45	0.56	+	2	0.03	i	0	0	i	47	0.59	+	47	0.59	+	2.41
	2	80	52	0.65	+	2	0.03	i	2	0.03	i	56	0.70	+	56	0.70	+	2.87
Serrate wings (*mwh/TM3*)																		
EMS (mM)	0.1	80	62	0.78		4	0.05					66	0.83		66	0.83		3.38
Distilled water	-	80	25	0.32		1	0.01					26	0.33		26	0.33		1.33
DMSO (%)	2	80	28	0.35	-	3	0.04	i				31	0.39	-	31	0.39	-	1.59
FLX-HCl (mg/mL)	0.1	80	26	0.33	-	3	0.03	i				29	0.36	-	29	0.36	-	1.49
	0.5	80	33	0.41	i	4	0.05	i				37	0.46	i	37	0.46	i	1.90
	1	80	48	0.60	+	1	0.01	i				49	0.61	+	49	0.61	+	2.51
	2	80	57	0.71	+	2	0.03	i				59	0.74	+	59	0.74	+	3.02

T: Treatment, C: Concentration, N: Number of wings, No: Number of clones, Fr: Frequency, D: Statistical evaluation according to Frei & Würgler (1988) procedure, +: positive, -: negative, i: inconclusive, m: multiplication factor, probability level, CIF: clone induction frequency, $\alpha = \beta = 0.05$.

In normal winged (*mwh*x*flr*³) individuals, it was seen that FLX-HCl had a statistically negative result at 0.1 mg/mL concentration, insignificant at 0.5 mg/mL concentration, and positive at 1 and 2 mg/mL concentrations in terms of total mutation evaluation (Table 2). These results show that 1 and 2 mg/mL concentrations of FLX-HCl have mutagenic effects in *D. melanogaster*. The formation of mutant clones is a result of various genetic mechanisms. Mitotic recombination, nondisjunction, point mutations, and

deletions between the *mwh* and *flr*^{3} genes cause the formation of uniform clones. Based on this information, it can be said that the abovementioned genetic changes occurred, and clones were formed in the wings of individuals with *mwh*x*flr*^{3} genotype at 1 and 2 mg/mL concentrations. Clone induction frequencies were also evaluated. It is known that the formation of clones exceeding 2 per 10^5 cells indicates a genotoxic effect (Graf et al., 1994). Therefore, clone induction frequencies at 1 and 2 mg/mL concentrations can be interpreted as FLX-HCl caused genotoxic effects on *mwh*/*flr*^{3} individuals.

When the SMART results of the serrate winged (*mwh*/*TM3*) individuals were examined, it was seen that FLX-HCl had statistically negative results at 0.1 mg/mL concentration, insignificant at 0.5 mg/mL concentration, and positive at 1 and 2 mg/mL concentrations in terms of total mutation evaluation (Table 2). These results show that 1 and 2 mg/mL concentrations of FLX-HCl had a mutagenic effect on the *mwh*/*TM3* individuals. Mitotic recombination does not occur in serrate winged (*mwh*/*TM3*) individuals due to the suppressive effect of the *TM3* chromosome (Kaya et al., 2004). Based on this information, clones were formed in the wings of individuals with *mwh*/*TM3* genotype only because of mutation at 1 and 2 mg/mL concentrations. Additionally, as seen in Table 2, the fact that the frequency of clone formation per 10^5 cells is above 2 at 1 and 2 mg/mL concentrations is evidence that FLX-HCl has genotoxic effect in serrate-winged individuals at these concentrations.

DISCUSSION

The main treatment for depression, the prevalence of which has increased worldwide in recent years, is drug therapy (Duval et al., 2006). FLX-HCl, an antidepressant from the SSRIs group, is among the most commonly prescribed drugs for the treatment of depression and other mental disorders (Garayo et al., 2022). The drugs are biotransformed by enzymatic reactions in the liver to be excreted from the body (Phang-Lyn & Llerena, 2023). Since FLX-HCl and its hepatic metabolite norfluoxetine inhibit their metabolism, their removal from the body takes a long time (Mondal et al., 2013). The long elimination time of a drug is a contributing factor to its toxic effect potential (Garza et al., 2019). In this context, it is important to clarify the toxic effect potential of FLX-HCl. In this study, we aimed to evaluate the potentially toxic and genotoxic effects of FLX-HCl in *D. melanogaster*, a widely used *in vivo* assay system for reliable genotoxicity assessment.

The data obtained from this study revealed that FLX-HCl has a dose-dependent genotoxic effect. Similarly, a study examining the dose-response relationship between acute FLX-HCl treatment and genotoxic effect by Comet assay in rat C6 glioma cell cultures found a dose-dependent increase in DNA damage (Slamon et al., 2001). In another in vitro study, FLX-HCl-induced genotoxicity was investigated in cultured Chinese hamster ovary cells using the Comet assay. The data obtained showed that FLX-HCl had no genotoxic effect at concentrations of 0.2 and 1 µg/ mL. However, the highest dose (5 µg/mL) caused genotoxicity (Lemos et al., 2005).

In the present study, the toxic and genotoxic effects of high FLX-HCl concentrations were evaluated. The data obtained show that FLX-HCl produced both toxic and genotoxic effects by decreasing the percent survival and inducing mutations/recombinations at concentrations of 1 and 2 mg/mL. The literature search identified studies that investigated the toxic effects and toxicity mechanisms of high-dose FLX-HCl administration in model organisms. A study conducted in male Sprague-Dawley rats showed that chronic administration of high doses of FLX-HCl caused aneuploidy and a dose-dependent decrease in mitotic activity (Ustuner, 2010). In a study investigating the mechanisms of toxic effects of high-dose FLX-HCl consumption on model organisms, FLX-HCl was found to increase mortality and slow development at a concentration of 500 µM and to alter heart rate at doses of 10 µM and 100 µM in *D. melanogaster* (Majeed et al., 2015). Our results are consistent with the results of this study, which showed that FLX-HCl induced toxicity in *D. melanogaster* at high doses (10, 100, and 500 µM).

FLX-HCl is an agent that prevents the reuptake of the neurotransmitter serotonin into neurons by binding to the serotonin transporter and increasing the extracellular serotonin concentration (Stahl, 1998). Previous studies showed that FLX-HCl interacts with serotonin receptors in *Drosophila* (Neckameyer et al., 2007; Silva et al., 2014). On this basis, studies evaluating the effects of high-dose FLX-HCl in *D.melanogaster* may provide important information to elucidate the acute effects of this drug in humans.

Clinical studies were found in the literature that investigated genotoxicity in patients treated with FLX-HCl. A study conducted with patients receiving antidepressant treatment showed that FLX-HCl had a higher genotoxic effect than sertraline and clomipramine (Draz et al., 2009). Since the elimination of FLX-HCl and its active ingredient norfluoxetine from the body is protracted, it may have a higher genotoxic potential than the other antidepressants. Data from the study conducted by Dundaroz et al. (1999) showed that treatment with FLX-HCl resulted in increased DNA damage in female patients taking the drug for 6-9 months. However, in the study conducted by Panwar et al. (2020), it was reported that eight weeks of treatment with FLX-HCl had an antioxidant effect that reduced oxidative stress-induced DNA damage in male and female patients

diagnosed with major depression. Although drugs have genotoxic effects, it may not be possible to demonstrate their potential genotoxicity in short-term studies. Therefore, long-term patient outcomes are important in deciding whether or not to prescribe drugs.

Drug interaction is another important factor affecting the toxic effect potential of FLX-HCl. Clinical and experimental studies have shown that FLX-HCl has the potential to interact with drugs such as immunosuppressants, antipsychotics, and antidepressants when used in combination and can cause critical health problems and even death in treated patients (Power et al., 1995; Ferslew et al., 1998; Wu & Deng, 2011; Harris & Heil, 2013).

The liver, which is capable of metabolizing toxic compounds and eliminating their harmful effects, is also the target organ for drug toxicity (Castell et al., 1997). Liver damage and changes in serum biomarkers are considered indicators of toxic effects due to oxidative damage. Long-term studies in rats have shown that FLX-HCl causes changes in serum biomarkers, oxidative damage due to free radical formation and histopathological differentiations in the liver (Zlatković et al., 2014; Karimi-Khouzani et al., 2017; Ganguly et al., 2022).

Studies in the literature show that FLX-HCl treatment may have indirect toxic effects on the environment and other living organisms in addition to direct toxic effects in humans. FLX-HCl is not degraded by up to 11% after use and is excreted primarily in the urine. FLX-HCl entering aquatic ecosystems via wastewater has been shown to accumulate in the bodies of aquatic organisms and may cause adverse effects (Gunnarson et al., 2008; Oakes et al., 2010; Schultz et al., 2011). Ecotoxicological studies investigating the toxic effects of FLX-HCl on various aquatic organisms (freshwater planarians, fish, mussels, frogs, zebrafish, and marine rotifers) showed that this compound has embryotoxic, genotoxic, mutagenic, neurotoxic, and cytotoxic effects on these organisms by increasing mortality, DNA damage, the frequency of micronuclei formation, oxidative stress, and morphological changes in cells (Cortez et al., 2019; Ofoegbu et al., 2019; Byeon et al., 2020; Blahova et al., 2021; Orozco- Hernández et al., 2022; Vijitkul et al., 2022).

FLX-HCl is an antidepressant that is increasingly used today. However, current studies have not provided any certainty regarding its genotoxic effects. In the literature, in addition to studies showing that FLX-HCl has no toxic effects, there are also studies showing that FLX-HCl has toxic effects on humans, other living organisms, and the environment. In this study, the potential genotoxic effect of FLX-HCl was evaluated using the in vivo assay SMART. The results of this study support the data available in the literature showing that FLX-HCl potentially has a toxic effect. The data obtained show that FLX-HCl has a genotoxic effect at concentrations of 1 and 2 mg/mL, inducing both mutations and recombinations. *D. melanogaster* is a eukaryotic model organism whose genome has high gene homology with the human genome. Many of the biological and physiological functions at the cellular level have been conserved between mammals and *Drosophila* (Reiter et al., 2001; Strausfeld & Hirth, 2013). In this context, this research contributes to the clarification of the possible genotoxic effects of FLX-HCl in humans by evaluating the genotoxic effect of the drug in a living system with high gene homology to humans.

Statement of Conflict of Interest

The authors have declared no conflict of interest.

Author's Contributions

The contribution of the authors is equal.

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