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Fluoxetine and cancer risk: insights from *drosophila melanogaster* epithelial cell assay

Abstract

Depression is a growing public health issue, and fluoxetine is the most widely prescribed antidepressant. Despite its extensive use, data regarding its high-dose genotoxicity remains scarce and divergent. This study evaluated the toxicity and carcinogenic potential of different fluoxetine concentrations in epithelial cells of *Drosophila melanogaster.* The methodology utilized a survival assay with third-instar larvae under chronic treatment with fluoxetine (0.125 to 2 mg/mL). Carcinogenicity was assessed through the Epithelial Tumor Detection Test, using trans-heterozygous progeny for the *warts* tumor suppressor gene *(mwh+/+wts)*. Data were statistically evaluated using the Chi-square Test. Toxicity results demonstrated that survival is inversely proportional to concentration, as only the 2 mg/mL dose significantly reduced survival (40%) compared to the negative control (85%). In the tumor assay, concentrations up to 1 mg/mL showed no significant differences from the control, indicating a lack of carcinogenicity at low doses. However, the 2 mg/mL concentration caused a statistically significant increase in tumor induction, yielding 80 tumors across 41 flies. In conclusion, fluoxetine exhibits a strictly dose-dependent toxicogenic profile. The carcinogenic effect at 2 mg/mL probably does not result from direct DNA interaction but might be related to severe oxidative stress triggered by mitochondrial dysfunction and intracellular calcium dysregulation, which overwhelm cellular repair systems and induce apoptosis which is supported by previous literature.

Keywords: SSRIs, genomic instability, depression

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Introduction

According to the Pan American Health Organization, depression is an increasingly common problem in the population, ranking as the second leading cause of death among young people aged 15 to 29.[1] Among the various types of treatment, conventional medicine includes antidepressants in the Selective Serotonin Reuptake Inhibitor (SSRI) class, with fluoxetine being the most widely used today.[2] SSRIs work by blocking the serotonin transporter (SERT) protein channels, thereby increasing serotonin concentration in the synaptic cleft and reducing depressive symptoms.[3] They are called "selective" because they act directly on serotonin reuptake without interfering with dopamine or norepinephrine levels, unlike other drug classes.[4] Fluoxetine, with the molecular formula *N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)-oxy]propylamine* (Figure 1), was the fourth SSRI to enter the global market and the first to be marketed in the United States. Its popularity stems from the fact that it is the only SSRI molecule that exhibits significant clinical activity due to its high lipophilicity, which contributes to its potency, duration of action in the body, and widespread distribution throughout body tissues, as it binds strongly to plasma proteins, particularly albumin.[5] The chemical structure of fluoxetine distinctly features a secondary amino group attached to the terminus of its aliphatic propyl chain. This functional group consists of a nitrogen atom covalently bound to a methyl group and the main alkyl chain. Owing to the lone pair on the nitrogen atom, this amino group imparts basic properties to the compound, causing it to exist predominantly in its protonated, positively charged form at physiological pH. This basicity is pharmacologically vital: it enables the formulation of fluoxetine as a hydrochloride salt to maximize aqueous solubility and oral bioavailability, while the ionized nitrogen establishes critical electrostatic interactions—such as salt bridges with conserved aspartate residues—within the binding pocket of the SERT, driving its potent and selective reuptake inhibition.[6]

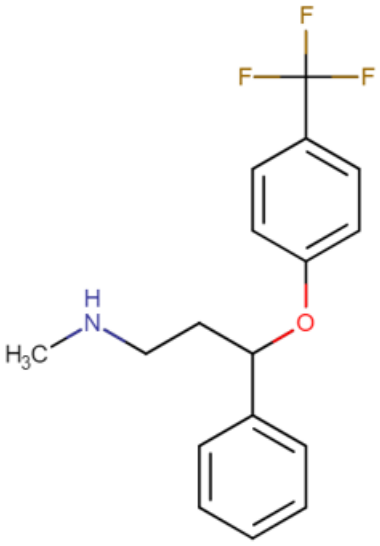

Figure 1 Molecular structure of fluoxetine.

Source: DrugBank.[6]

This drug is metabolized in the liver by the CYP2D6 enzyme, which converts fluoxetine to norfluoxetine. The activity of this enzyme can vary from person to person, leading to variations in the drug's efficacy and side effects.[7] The drug's effects differ when combined with other medications, such as citalopram, codeine, and propranolol, as serum levels of fluoxetine in the body may increase because these drugs inhibit the activity of the CYP2D6 enzyme. On the other hand, fluoxetine in combination with serotonin reuptake inhibitors, such as sibutramine and amitriptyline, can lead to serotonin syndrome,

resulting in cognitive, behavioral, neuromuscular, or autonomic nervous system changes.[2] The lipophilic nature of fluoxetine makes its excretion more difficult, leading to a higher rate of toxicity. In a test conducted on mammalian ovarian cells of the CHO-K1 line, fluoxetine at a concentration of 5 mg/mL caused moderate DNA damage.[8] Furthermore, it was observed that the drug increased the number of cells with chromosomal breaks,[9] while another study revealed that fluoxetine significantly reduced the cell proliferation rate in meristematic cells of *Allium cepa.*[10]

Despite the data above, fluoxetine was not neurotoxic in the development of rats exposed prenatally[11] and did not exhibit any developmental toxicity in rat and rabbit fetuses at maternally toxic concentrations.[12] Thus, high concentrations of fluoxetine demonstrate toxic effects when tested *in vitro*, a finding that was not replicated in *in vivo* experiments, suggesting that fluoxetine is genotoxic, whereas norfluoxetine, its metabolite in the body, is not. However, further studies are needed to assess the genotoxicity of fluoxetine and norfluoxetine, given that the scientific literature on the subject is limited and this drug is widely used not only in the treatment of mood disorders, such as depression and anxiety, but also in weight-loss regimens. Thus, the present study aimed to determine the toxicity of different concentrations of fluoxetine, as well as to evaluate its carcinogenic potential in *D. melanogaster* epithelial cells.

Methodological procedures

Strain maintenance and crossbreeding

The strains were maintained in stock in flasks containing ¼ of a banana-based culture medium (1230 mL of water, 234 g of banana, 37.5 g of biological yeast, 16.5 g of agar, 2 g of methylparaben, and, optionally, 2 mL of antibiotic) until crossing was performed between *mwh/mwh* males and virgin females of the *wts/TM3,Sb*^{1} strain.

Two progenies were generated from this cross: marked trans-heterozygotes *(mwh+/+wts – MH)* and balanced heterozygotes *(mwh+/+TM3, Sb*^{1} *- BH)*; however, in the tumor clone detection assay, only the MH progeny was analyzed. The progeny were distinguished by the expression of the *TM3, Sb*^{1} chromosomal balancer, with phenotypic characteristics observed using a stereomicroscope. Flies carrying this balancer show short, thick body hairs, whereas MH progeny display the wild-type phenotype, characterized by long, thin body hairs Figure 2.

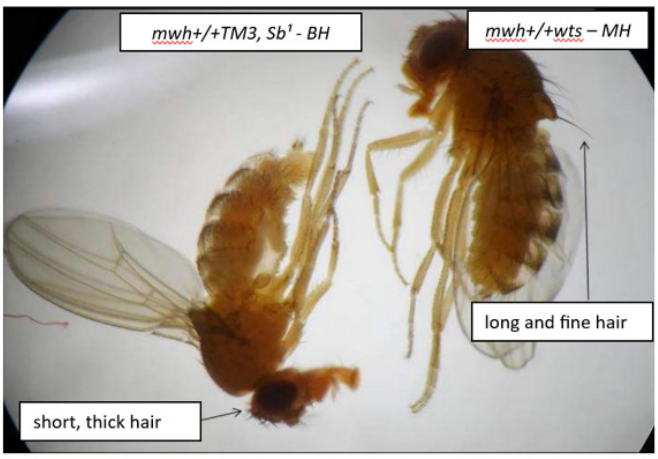

Figure 2 Hair phenotypes on the body of the *D. melanogaster* fly in the different progenies.

Source: Morais.[13]

Toxicity Test (Survival Assay)

In this study, the concentrations evaluated were selected using a survival assay. To this end, eggs from the crossbreeding were collected over na 8-hour period in vials containing a culture medium based on agar (4%) and biological yeast supplemented with sucrose. After 72 ± 4 hours, third-instar larvae were washed with water and collected using a fine-mesh sieve. The larvae were then subjected to chronic treatment (approximately 48 hours).

The treatment was conducted in vials containing 1.5 g of mashed potatoes (Yoki® Alimentos S.A.) and 5 mL of different concentrations of fluoxetine (test) and doxorubicin (positive control). To select the concentrations, statistical comparisons of survival rates were performed using the chi-square test for independent samples (significance of 5%).

Epithelial tumor assay (Tumor Clone Detection Assay)

Two mutant strains were used in this test: (1) *multiple wing hairs (mwh, 3-0,3)* strain; (2) *warts (wts, 3-100)* strain—*wts, [1] in [1] kni [ri-1] p [p] wts [3-17]/TM3,SB [1]*. The *warts* strain carries a *wts* marker on chromosome 3, which is maintained in hemizygosity in the presence of the TM3,Sb^{1} chromosomal balancer. The wts marker, when expressed in the wild-type state, acts as a tumor suppressor gene. Deletion of this gene and expression of the recessive allele lead to the formation of cell clones that are considered highly invasive, resulting in the development of epithelial tumors in the fly's body and appendages Figure 3.

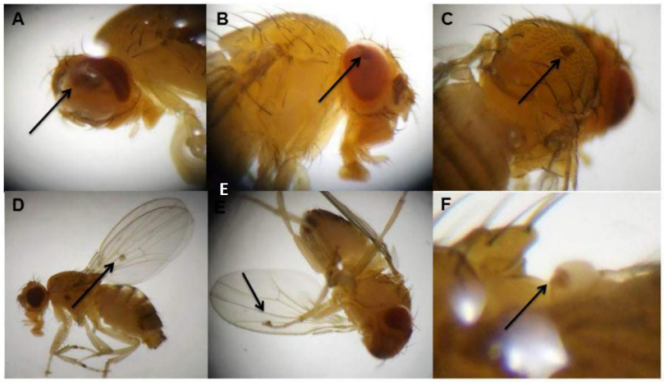

Figure 3 Tumor expression in *D. melanogaster*. Tumor in the head (A), tumor in the eye (B), tumor in the body (C), tumor in the wing (D), tumor in the leg (E) and tumor in the halter (F).

Source: Morais[13]

The incidence rates of epithelial tumors observed in individuals treated with different concentrations of fluoxetine were statistically compared with the incidence rates of epithelial tumors observed in flies treated with distilled water (negative control) using the chi-square test with a significance level of 5%. The chi-square is calculated based in the frequency of tumours observed in each treatment. The frequency of tumors was meticulously recorded utilizing a stereomicroscope, with the specimens being examined while submerged in glycerin. Each part of the fly, including its body and appendages, underwent individual analysis. Following this, the data were organized and categorized based on the respective treatment groups.

Results and discussion

Fluoxetine is a prototypical drug in the class of Selective Serotonin Reuptake Inhibitors (SSRIs), widely indicated for the treatment of Major Depressive Disorder, Obsessive-Compulsive

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Disorder, Bulimia Nervosa, and Panic Disorder. One of its main pharmacokinetic characteristics is the long half-life of its active metabolite (norfluoxetine), which ranges from 7 to 9 days and helps minimize the symptoms of abrupt discontinuation, although it requires careful monitoring for drug interactions mediated by the hepatic CYP2D6 enzyme. The cytochrome P450 (CYP450) complex is an enzymatic system crucial for the biotransformation of xenobiotics. The main isoenzyme involved in this process of fluoxetine clearance is CYP2D6, although other isoforms, such as CYP2C9, CYP2C19, and CYP3A4, also contribute secondarily to its elimination and pharmacokinetics. The hepatic metabolic process is characterized by a saturable oxidative demethylation pathway, converting the original molecule into its major clinically relevant metabolite.[14]

The main metabolite produced by this biotransformation is norfluoxetine. Like fluoxetine, norfluoxetine acts as a selective serotonin reuptake inhibitor with a potency equivalent to that of the parent drug. The great pharmacological significance of norfluoxetine lies in its exceptionally long biological half-life, which ranges from 7 to 9 days (in contrast to the 2 to 4 days for fluoxetine), ensuring the persistence of therapeutic and biological effects in the body even after temporary or accidental discontinuation of the medication.[14,15]

In addition to acting as substrates, fluoxetine and norfluoxetine function as potent inhibitors of the CYP2D6 enzyme itself, a phenomenon known as autoinhibition. This strong inhibitory property reduces the metabolic capacity of the CYP450 complex with respect to other concomitantly administered drugs that depend on the same clearance pathway. Clinically, this mechanism is primarily responsible for complex drug interactions, elevating plasma concentrations of co-administered substrates and altering cellular and systemic responses in experimental and clinical models.[15]

In this study, the concentrations used to assess tumor induction were selected following a survival test. To this end, the percentages of individuals treated with different concentrations of fluoxetine were compared with the negative control (Table 1). To conduct the test, 20 larvae were transferred to the vials for each treatment, and statistical analysis was performed using the chi-square test. According to the data obtained, it can be observed that the relationship between survival and the concentrations evaluated is inversely proportional; that is, the higher the fluoxetine concentration, the lower the survival rate. Given the above, only the treatment with fluoxetine at a concentration of 2 mg/mL significantly reduced (x^2 calculated = 30.368) the survival of the individuals when compared to the negative control (Table 1).

Table 1 Survival rate (%) of *D. melanogaster* adults following treatment of third-instar larvae with different concentrations of fluoxetine and calculated chi-square values. *Values considered different from the negative control

Treatments	Survival Rates (%)	X^2 calculated
Controle Negativo (Água Destilada)	85%	-
Fluoxetina 0,125 mg/mL	80%	3.612
Fluoxetina 0,25 mg/mL	80%	3.612
Fluoxetina 0,5 mg/mL	80%	3.612
Fluoxetina 1 mg/mL	85%	2.476
Fluoxetina 2 mg/mL	40%	30.368*
Controle Positivo (Doxorrubicina) 0,250 mg/mL	50%	19.97*

In a previous study using Chinese hamster ovary cell cultures, the genotoxic effect of fluoxetine was shown to be the most damaging to human leukocytes when compared to sertraline and clomipramine.[16] Similarly, toxicity was observed at high concentrations but was modulated when combined with vitamins A and C.[8] On the other hand, the absence of toxicity at concentrations equal to or less than 1 mg/mL is consistent with several mutagenicity assessment studies in other biological models. Studies using the chromosomal aberration test in human leukocytes and bacterial assays with *Salmonella typhimurium* have demonstrated the non-genotoxicity of fluoxetine at low concentrations.[17]

The use of *D. melanogaster* in the tumor clone detection assay is based on individuals heterozygous for the *warts (wts)* tumor suppressor gene, allowing the identification of tumors based on the loss of heterozygosity in somatic cells. In this assay, exposure to carcinogens can result in genetic events that lead to the inactivation of the remaining functional allele, resulting in the formation of cell clones with unregulated growth.[18] These tumor clones are primarily observed in epithelial tissues such as the wings, exhibiting abnormal cell growth. Thus, the method allows for the evaluation of the carcinogenic potential of substances through the induction of tumors in multicellular organisms.

Among the main advantages of using *D. melanogaster* in this assay are its low cost, ease of maintenance in the laboratory, short life cycle, and high sensitivity to genotoxic agents.[19] Furthermore, there is a high degree of evolutionary conservation between *D. melanogaster* and humans regarding cell cycle control pathways; for example, the wts gene encodes a protein homologous to human kinases involved in the regulation of cell proliferation, which is essential for controlling tissue growth.[20] This functional similarity lends great relevance to the assay, aiding in the screening of compounds with carcinogenic or even antitumor potential.

The likely mechanism underlying fluoxetine toxicity in *D. melanogaster* cells involves a multifactorial pathway that goes beyond simple blockade of the serotonin transporter, characterized by the induction of oxidative stress and the dysregulation of intracellular calcium homeostasis. At high concentrations, the drug promotes massive efflux of calcium ions from the endoplasmic reticulum into the cytoplasm, in addition to blocking voltage-gated sodium channels. This cytoplasmic calcium overload compromises mitochondrial integrity, triggering the excessive production of reactive oxygen species (ROS) that damage lipids, proteins, and cellular DNA. As a direct consequence of this cytotoxic cascade, apoptotic pathways are activated, which explains the chromosomal breaks detected in somatic genotoxicity tests, as well as severe delays in larval development and acute physiological dysfunctions, such as dose-dependent cardiac arrest in the biological model.[15]

The investigation of the genotoxic potential of fluoxetine in somatic cells of *D. melanogaster* reveals a strictly dose-dependent toxicity profile, as demonstrated by the Somatic Mutation and Recombination Test (SMART). At concentrations equivalent to human therapeutic levels or low environmental exposures (between 0.1 and 0.5 mg/mL), the drug does not exhibit significant mutagenic or recombinogenic activity, indicating that the organism's cellular repair systems are able to mitigate any stress without inducing changes in the somatic cells of the imaginal discs. However, when exposed to high, acute concentrations (1.0 and 2.0 mg/mL), the somatic cells of the fruit fly show a significant increase in the frequency of mutant clones, which constitutes a positive result for genotoxicity and genomic damage in this biological model.[21]

This duality of effects underpins the discussion in the ecotoxicological and neuropharmacological literature regarding the

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safety limits of the molecule. The mechanism by which fluoxetine induces DNA damage at saturating doses goes beyond the blockade of the serotonin transporter and is linked to secondary cytotoxic effects such as the blockade of ion channels and the dysregulation of intracellular calcium homeostasis. This ionic overload promotes mitochondrial dysfunction and consequent severe oxidative stress; the accumulation of reactive oxygen species directly attacks nitrogenous bases, generating breaks in DNA strands that exceed the capacity for cellular repair and result in the somatic mutations described.[15,21]

The comparison of toxicity between fluoxetine and its main active metabolite, norfluoxetine, in biological models such as *D. melanogaster*, is initially based on the similarity of their primary mechanisms of action. Both molecules act as potent inhibitors of the homologous serotonin transporter, blocking the reuptake of this neurotransmitter and increasing its availability in the synaptic cleft. However, in toxicity assays, norfluoxetine often exhibits pharmacodynamic potency that is slightly greater than or equivalent to that of the parent drug in modulating receptors and ion channels, which exacerbates neurochemical, developmental, and behavioral disturbances in the affected organism.[15]

The critical difference in the severity of chronic toxicity lies in the pharmacokinetic properties and metabolic persistence of norfluoxetine. While fluoxetine is progressively biotransformed by cytochrome P450 isoenzymes, the norfluoxetine metabolite has a significantly prolonged biological half-life and greater lipophilicity, which hinders its clearance and promotes bioaccumulation in cellular tissues. In organisms with rapid life cycles, this inability to eliminate the compound quickly causes norfluoxetine to act as a persistent toxic agent, causing more damage than the acute and temporary effects of isolated exposure to fluoxetine. The continuous presence of the metabolite stimulates the prolonged efflux of calcium ions from the endoplasmic reticulum into the cytoplasm, triggering sustained mitochondrial dysfunction and the consequent overproduction of ROS.[15] Unlike fluoxetine, whose cellular stress declines as it is metabolized, norfluoxetine sustains oxidative damage to membranes and DNA over extended periods, inducing higher rates of apoptosis and somatic genotoxic damage in the model.

Fluoxetine has been extensively studied not only for its therapeutic effects but also for its potential impact at the cellular and molecular levels. Recent studies indicate that, under certain conditions, this drug can induce DNA damage, suggesting a possible genotoxic effect. In human liver cell cultures (HepG2), using the comet assay, it was observed that treatment with fluoxetine causes a significant increase in DNA breaks, and this damage is generally associated with increased intracellular oxidative stress.[22]

The results regarding the assessment of fluoxetine's carcinogenic potential in D. *melanogaster* epithelial cells using the Tumor Clone Detection Assay show a clear correlation between the concentrations tested and the frequency and distribution of the analyzed tumors. At concentrations of 0.125 mg/mL, 0.250 mg/mL, 0.5 mg/mL, and 1 mg/mL, the total number of tumors did not differ statistically from the negative control, which recorded only 17 tumors, as the calculated chi-square values ranged from 0.0093 to 1.911 (Table 2). These values indicate the absence of a carcinogenic effect at these concentrations, a finding supported by previous literature reports[21], and no significant genotoxic effects of fluoxetine were observed in *D. melanogaster* using the wing SMART assay.

Table 2 Frequency of epithelial tumors observed in heterozygous descendants for the wts tumor suppressor gene of *Drosophila melanogaster* exposed to different concentrations of fluoxetine

Treatments	Number of individuals	Total of tumors (tumor frequency)						Total	X^2 calculaded
		Eyes	Head	Wings	Body	Legs	Halters		
Negative Control	59	0 (0)	0.051 (3)	0.034 (2)	0.152 (9)	0.034 (2)	0.017 (1)	17	-
Positive Control	57	0.088 (5)	0.579 (33)	0.561 (32)	1.912 (109)	0.667 (38)	0.053 (3)	220	44.30**
Fluoxetine 0.125 mg/mL	102	0.01 (1)	0.049 (5)	0.029 (3)	0.265 (27)	0.088 (9)	0.039 (4)	49	0.128
Fluoxetine 0.250 mg/mL	101	0.01 (1)	0.089 (9)	0.297 (3)	0.158 (16)	0.039 (4)	0.01 (1)	34	0.0093
Fluoxetine 0.50 mg/mL	62	0 (0)	0.048 (3)	0.032 (2)	0.258 (16)	0.08 (5)	0 (0)	26	0.6
Fluoxetine 1.0 mg/mL	59	0.034 (2)	0.136 (8)	0.153 (9)	0.508 (30)	0.203 (12)	0 (0)	61	1.911
Fluoxetine 2.0 mg/mL	41	0.024 (1)	0.122 (5)	0.195 (8)	0.927 (38)	0,.683 (28)	0 (0)	80	9.59**

**Values considered different from the negative control. Negative control: water; Positive control: doxorubicin (0.250 mg/mL).

On the other hand, treatment with the highest concentration of fluoxetine (2 mg/mL) resulted in a significant increase in tumor induction. At this dosage, 80 tumors were counted in 41 individuals, and the chi-square test revealed that this difference was statistically significant compared to the negative control (Table 2). In in vivo models, the genotoxic effects of fluoxetine can be observed, particularly in aquatic environments exposed to the drug. A study demonstrated a significant increase in the DNA damage index and the frequency of micronuclei following exposure to different concentrations of the drug, indicating possible chromosomal breaks and genomic instability. These results imply that fluoxetine may act as a genotoxic agent in aquatic ecosystems, raising significant environmental concerns.[23] The variation in numerical data between the groups can be attributed to the presence of the wts allele within the population. Each treatment had a varying quantity of this allele, especially since the treatments focused on examining tumor frequency did not involve counting the number of larvae.

In a previous study, no significant changes were identified in the bacterial genetic material. On the other hand, changes in chromosomal stability were observed, as clastogenic events were noted.[17] Furthermore, some studies indicate the absence of significant mutations in experimental models, particularly in systems simulating mammalian metabolism, suggesting that genotoxic effects may depend on factors such as concentration, exposure time, and the cell type analyzed[24]. Based on the results found in this study and according to the conditions employed, low concentrations of fluoxetine do not alter genomic stability (Table 2).

In contrast, the carcinogenic effect observed at a concentration of 2 mg/mL may be supported by the evidence of toxicity previously demonstrated, in which *D. melanogaster* individuals treated with high concentrations of this drug exhibited alterations in neuronal and cardiac functions, involving ion channels and modulation of cellular excitability.[15] This disruption in balance and the cellular oxidative

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stress generated by the toxicity of the dose result in genomic damage to the epithelial cells of these individuals. Thus, the carcinogenicity observed in individuals treated with the highest concentration is caused not by the drug's direct interaction with DNA, but because of cellular redox imbalance.

Furthermore, studies show that antidepressants have potential mutagenic and carcinogenic mechanisms capable of inducing genomic damage, either through their metabolites or by direct action on DNA. This potential may stem from the fluorobenzene and nitro groups present in the chemical structure of these compounds. Nitro groups can be converted into nitroso compounds and, subsequently, into alkylating molecules.[25,26] Various adverse effects, such as DNA adducts, strand breaks, and *cross-links*, are caused by DNA alkylation, since alkylating agents are electrolytic compounds that have na affinity for nucleophilic centers in DNA or proteins, leading to the transfer of the alkyl group via covalent bonds.[27,28]

The genotoxicity of fluoxetine also appears to be related to the induction of apoptosis and mitochondrial dysfunction. The increase in markers of early and late apoptosis in cells exposed to the drug supports the hypothesis that DNA damage does not occur directly but is associated with a context of cellular stress. Furthermore, intense production of reactive oxygen species (ROS) can lead to the oxidation of nitrogenous bases, single- and double-strand breaks, and impaired chromosomal integrity, contributing to potential mutations if cellular repair systems are insufficient.[22]

Conclusion

Overall, the results of this study show that the toxicity and carcinogenic potential of fluoxetine in somatic epithelial cells of *D. melanogaster* are strictly concentration dependent. Low and intermediate concentrations, up to 1 mg/mL, preserved genomic stability and survival rates comparable to those of the negative control. In contrast, the highest concentration tested, 2 mg/mL, showed marked cytotoxic and genotoxic effects. This dose-dependent pattern supports the relative safety of fluoxetine at therapeutic levels while highlighting the need for careful evaluation of exposure limits and the acute effects of overdose. Furthermore, a literature-based analysis indicates that the carcinogenic effect observed at the highest dose (2 mg/mL) does not result from direct mutagenicity of the molecule on DNA structure, but rather from a secondary cellular stress cascade. The underlying mechanism involves massive efflux of intracellular calcium and the consequent blockage of ion channels, culminating in mitochondrial dysfunction and overproduction of reactive oxygen species. It is this severe redox imbalance that oxidizes nitrogenous bases and generates chromosomal breaks, overwhelming cellular repair systems and activating apoptotic pathways—processes that explain both the drastic reduction in larval survival and the emergence of tumor clones. Finally, this study reaffirms the effectiveness and feasibility of the *Drosophila melanogaster* model—specifically through the Epithelial Tumor Detection Assay, based on the *warts* tumor suppressor gene—as a robust, sensitive, and highly predictive tool for screening the toxicity and carcinogenicity of xenobiotics. Given the widespread use of fluoxetine in clinical practice and its increasing detection as a contaminant in aquatic ecosystems, the data generated provide crucial theoretical insights into the cellular impacts of this drug, highlighting the need for further *in vivo* and *in silico* studies to more thoroughly monitor its long-term effects.

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None.

Conflicts of interest

The authors declare there is no conflict of interest.

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