Original Article

Lycopene and L-Carnitine attenuate fluoxetine-induced cytotoxicity and oxidative stress in normal gingival cells: a preliminary analysis

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Abstract

Background & Aims: Fluoxetine-induced cytotoxicity involves multiple mechanisms, including increased production of reactive oxygen species (ROS) and reduced antioxidant capacity by decreasing levels of GSH and buthionine sulfoximine (BSO), which are associated with increased levels of protein carbonyls, malondialdehyde, GST activity, NO and NF-KB levels, and superoxide anions. The purpose of this study was the effect of lycopene and L-carnitine on cytotoxicity and oxidative stress caused by fluoxetine on normal gingival cell line.

Materials & Methods: In this study, 50, 100, and 200 µM concentrations of L-carnitine and lycopene were used as antioxidants to investigate the cellular toxicity caused by fluoxetine and by measuring oxidative stress factors such as ROS and lipid peroxidation (LPO). Statistical analysis was performed using Prism V8 software, and a $p < 0.05$ was considered significant.

Results: The results showed that fluoxetine induced cellular oxidative stress by impairing mitochondrial function. Co-treatment of cells with fluoxetine, lycopene, and L-carnitine effectively inhibited fluoxetine-induced cytotoxicity, scavenged free radicals, and prevented lipid membrane damage ($p<0.05$).

Conclusion: this study demonstrates that fluoxetine can induce cellular damage. Further investigations should be conducted on larger patient populations undergoing longer treatment periods with antidepressants to evaluate their cellular toxicity. The findings also indicate that lycopene and L-carnitine have potent antioxidant effects in mitigating fluoxetine-induced cytotoxicity by scavenging free radicals and preventing lipid membrane damage.

Keywords: Fluoxetine, Cellular Toxicity, Oxidative Stress, Lycopene, L-Carnitine

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Introduction

The drug fluoxetine, also known as Prozac, is a widely used antidepressant medication. It is commonly prescribed for the treatment of depression, obsessive-compulsive disorder, some eating disorders, panic attacks, and premenstrual syndrome. Additionally, fluoxetine is used in the treatment of alcoholism, attention deficit hyperactivity disorder (ADHD),

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borderline personality disorder, sleep disorders, headaches, psychological illnesses, post-traumatic stress disorder (PTSD), Tourette's syndrome, obesity, sexual dysfunction, and phobias (1, 2). The drug selectively inhibits the reuptake of serotonin, resulting in increased levels of serotonin in the extracellular space by binding to the serotonin transporter. Fluoxetine belongs to the family of selective serotonin reuptake inhibitors (SSRIs) and is one of the most widely prescribed drugs for the treatment of depression (3, 4). However, one of the significant side effects of fluoxetine is genetic toxicity resulting from using it. In vivo studies have shown that fluoxetine causes significant genetic damage in bone marrow cells. This damage includes chromosomal breakage, structural abnormalities such as the presence of pieces without centromeres, central fusion of chromosome arms, polyploidy, deletion, and more (5).

Several mechanisms are involved in the cytotoxicity of fluoxetine, including an increase in the production of reactive oxygen species, a decrease in antioxidant capacity with a decrease in GSH and buthionine sulfoximine (BSO) levels, which are associated with increased carbonyl protein levels, malondialdehyde, increased GST activity, increased NO and NF-KB levels, increased superoxide anions, and more (6).

Some studies suggest that the primary source of increased oxidative stress induced by fluoxetine is due to the reaction of superoxide ions with nitric oxide and the production of peroxynitrite. The metabolic pathway of fluoxetine can be explored to find the main source of superoxide anions, where the cytochrome P-450 and NADPH oxidase enzymes are responsible. Moreover, an increase in NO leads to an increase in COX2, which ultimately activates NF-KB (7).

Another factor involved in the toxicity induced by fluoxetine is apoptosis, which occurs through an increase in ROS, intracellular Ca2+ accumulation, decreased MMP, decreased anti-apoptotic ERK1/2 proteins, and an increase in pro-apoptotic JNK and p38 MAPK proteins(8, 9).

Lycopene is a red pigment found in many fruits and vegetables. It is a potent antioxidant that reduces oxidative damage to DNA and, as a result, decreases cancer risk, including prostate and breast cancer. Recent epidemiological studies have shown that a lycopene-rich diet reduces the risk of chronic diseases such as cancer and heart disease. The antioxidant activity of lycopene has been extensively studied and has been shown to neutralize free radicals in cell cultures and animal models. Moreover, experimental evidence indicates that lycopene has the ability to quench oxygen radicals, nitrogen dioxide, thiol, and sulfonyl radicals (10).

L-carnitine is derived from two amino acids, lysine and methionine, and plays a critical role in ATP production through beta-oxidation of long-chain fatty acids in mitochondria. Recently, L-carnitine has received special attention due to its antioxidant properties and protection under various pathological conditions (11). L-carnitine also helps reduce the effects of free radicals (12). The antioxidant system comprises three enzymes: glutathione peroxidase, catalase, and superoxide dismutase. L-carnitine can protect these enzymes against oxidative damage and is also very effective in modulating age-related changes (13).

The objective of this research was to investigate the possible benefits of Lycopene and L-Carnitine in lessening fluoxetine-induced oxidative damage and cytotoxicity in gingival cells.

Materials & Methods

All materials and reagents were prepared from Sigma Company in laboratory grade.

Preparation of gingival cell lines:

Cellular preparation of gingival cell (Primary Gingival Fibroblast; Normal, Human, Adult (HGF) PCS-201-018™) was obtained from the Pasteur Institute's cell bank. The cells were cultured in DMEM-

F12 medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. They were then incubated at 37°C with 5% carbon dioxide and sufficient humidity to reach the logarithmic growth phase (14, 15).

Drug Toxicity Test by MTT:

The MTT assay was used to assess drug toxicity by testing the cell viability. The MTT test is a colorimetric method that measures the conversion of yellow tetrazolium salt or MTT reagent to purple formazan crystals, which is an indicator of live cells. For this study, normal cells without any substances were used as the negative control, while cells treated with fluoxetine were used as the positive control. HGF cell line was cultured on a 96-well plate with 105 cells per well. After 24 hours of incubation at 37°C, the cells were treated with single doses of 200, 100, and 50 µg/ml of L-carnitine and lycopene along with a single dose of fluoxetine. After 48 hours, the surviving cells were evaluated by the MTT assay. A volume of 100 microliters of MTT solution was added to each well, and after 4 hours of incubation at 37°C, the medium was removed. Then, 100 µl of DMSO solution was added to each well, followed by measuring the absorbance intensity at 570 nm using an ELISA reader(16, 17).

Measurement of ROS:

ROS measurement was performed by detaching the cells from the 96-well plate using trypsin and resuspending them in a respiratory buffer. Then, the cells were treated with DCFH-DA reagent for 15 minutes at 4°C and the excitation wavelength were measured at 312 nanometers and the emission wavelength was measured at 420 nanometers using a flow cytometer (18, 19).

Measurement of Lipid Peroxidation:

Lipid peroxidation was measured using the thiobarbituric acid method. In brief, 2.0 mL of cell suspension was mixed with 1.0 mL of TBA reagent containing 5.0 N HCl, 15% trichloroacetic acid (TCA), and 3.0% TBA. The mixture was then incubated in a water bath for 30 minutes, cooled down, and then 2.0 mL of n-butanol was added. After vigorous shaking, the mixture was centrifuged at 3500 rpm for 10 minutes, and the n-butanol layer was separated for measurement at a wavelength of 532 nanometers to calculate the TBARs values from the standard curve(18, 20).

Statistical Analysis:

All statistical calculations for genetic comparison were performed using Prism Ver.8 software. One-way analysis of variance and the corresponding post-test (Tukey-Kramer multiple comprehension test) were used to compare the data, and the graphs were plotted using the same program.

Results

As evident from the Figure 1 and Table 1, fluoxetine at an IC50 concentration of 40.26% inhibited the growth of normal cells. Exposure of these normal cells to lycopene at concentrations of 200 µg (micrograms) resulted in a 75.79% inhibition of growth, while at a concentration of 100 µg, the inhibition was at 51.80%, and at 50 µg, it was at 45.21%. This suggests that lycopene can mitigate the toxicity caused by fluoxetine and enhance the growth of normal cells. Moreover, the data shows that growth increases with increasing concentration. On the other hand, exposure of normal gingival cells to L-carnitine at the lowest concentration of 47.45% and at the highest concentration of 75.61% has increased the growth of normal cells.

From a statistical perspective, there is a significant difference between the fluoxetine group and the groups treated with 100 and 200 µg of lycopene, with p-values of <0.001 and <0.0001, respectively. Statistically, compared to the fluoxetine group, all L-carnitine concentrations have a significant difference.

Table 1: Mean and standard deviation of different treatment groups, MTT test

	control	*Fluoxetine*	*Licopen 50*	*Licopen 100*	*Licopen 200*
Mean	101.2	40.26	45.21	51.80	75.79
Std. Deviation	2.160	1.393	3.116	1.324	2.231

	control	Fluoxetine	L-carnitine 50	L-carnitine 100	L-carnitine 200
Mean	101.2	40.26	47.45	64.17	75.61
Std. Deviation	2.160	1.393	1.224	1.652	4.176

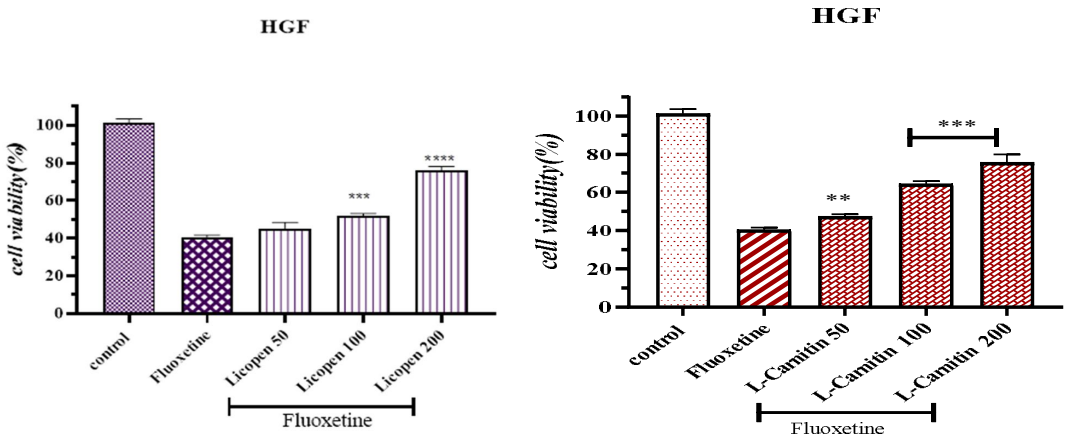

Fig. 1. Effect of lycopene and L-carnitine on fluoxetine-induced cytotoxicity in normal gingival cell line

**P<0.01, *** p<0.001 , **** P < 0.0001: significant compared to the positive control group

The effect of lycopene and L-carnitine on the amount of ROS produced by fluoxetine-induced normal gingival cells:

The administration of Fluoxetine at an IC50 concentration of 63.41% has been found to induce the generation of reactive oxygen species (ROS) in normal cells. However, exposing normal cells to Lycopene and L-carnitine at concentrations ranging from 55.86% to 43.30% and 58.17% to 31.58%, respectively, has been observed to reduce ROS production in these cells.

Statistical analysis shows that there was a significant difference between the effects of fluoxetine and the concentrations of 100 and 200 micrograms of both Lycopene and L-carnitine on reducing ROS production.

Table 2: Mean and standard deviation of different treatment groups, ROS test

	control	Fluoxetine	Licopen 50	Licopen 100	Licopen 200
Mean	11.19	63.41	55.86	48.86	43.30
Std. Deviation	1.008	3.001	3.497	1.297	2.527

	control	Fluoxetine	L-carnitine 50	L-carnitine 100	L-carnitine 200
Mean	11.19	63.41	58.17	42.98	31.58
Std. Deviation	1.008	3.001	1.389	3.763	1.969

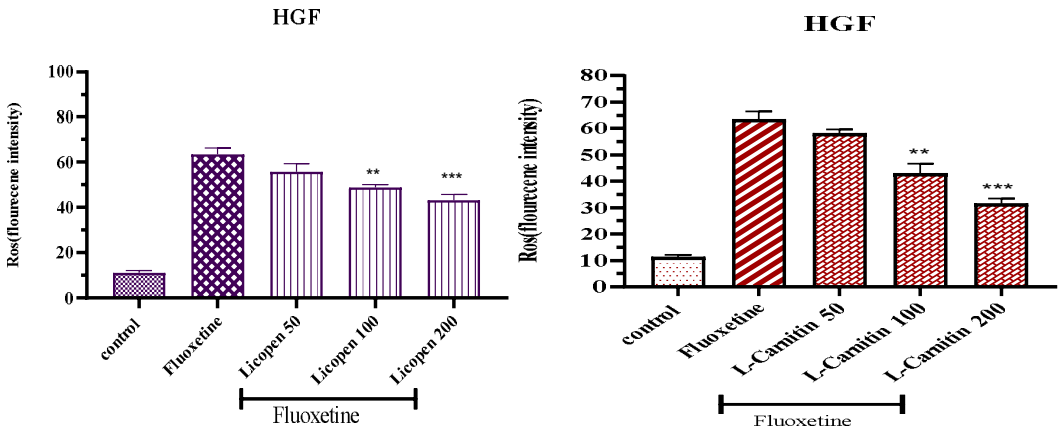

Fig. 2.: The effect of lycopene and L-carnitine on the amount of ROS produced by fluoxetine-induced normal gingival cells

**P<0.01, *** p<0.001 : significant compared to the positive control group

The effect of lycopene and L-carnitine on the amount of MDA produced by fluoxetine-induced normal gingival cells:

In the presence of fluoxetine at an IC50 concentration, LPO production was increased by 52.73% in normal cells. However, exposure of normal cells to different concentrations of lycopene (200, 100, and 50 micrograms) resulted in a decrease in LPO production by 29.50%, 36.74%, and 43.46%, respectively. Moreover, when normal cells were exposed to carnitine at a concentration of 50 micrograms, LPO production decreased by 46.52%. At concentrations of 100 and 200 micrograms, LPO production decreased by 34.54% and 23.46%, respectively. All differences in concentrations between Lycopene and L-carnitine-treated cells and the fluoxetine group were statistically significant.

Table 3: *Mean and standard deviation of different treatment groups, MDA test*

	control	*Fluoxetine*	*Licopen 50*	*Licopen 100*	*Licopen 200*
Mean	15.58	52.73	43.46	36.74	29.50
Std. Deviation	2.435	1.696	3.414	2.870	1.886

	control	Fluoxetine	L-carnitine 50	L-carnitine 100	L-carnitine 200
Mean	15.58	52.73	46.62	34.54	23.46
Std. Deviation	2.435	1.696	3.629	4.072	1.699

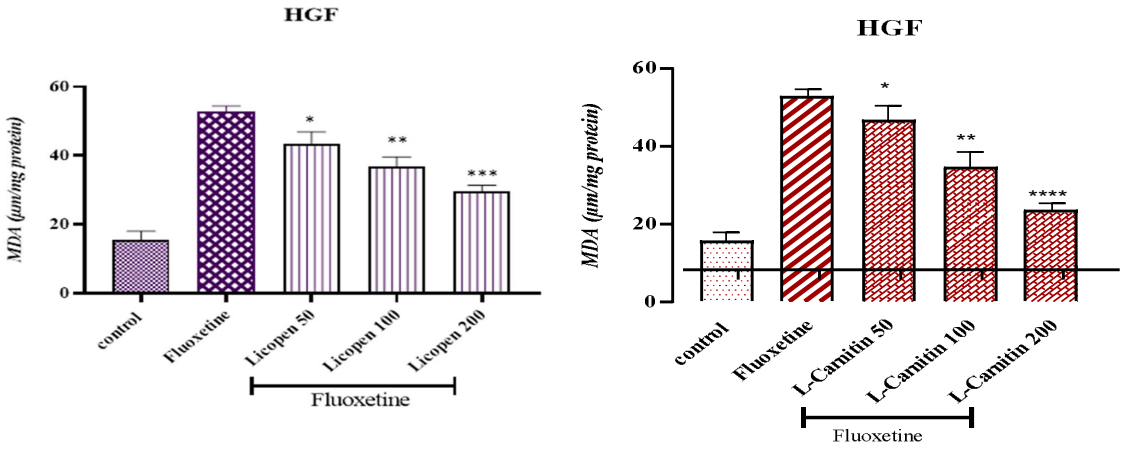

Fig. 1. The effect of lycopene and L-carnitine on the amount of MDA produced by fluoxetine-induced normal gingival cells

*p<0.05, **P<0.01, *** p<0.001, **** p<0.0001 : significant compared to the positive control group

Discussion

In a study, it was suggested that fluoxetine induces concentration-dependent cellular toxicity, making it highly selective for the treatment of human colorectal, breast, and ovarian cancers (1). Another study demonstrated the involvement of unlikely p53 activation due to fluoxetine, indicating the expression of an apoptotic pathway dependent on p53 in human colorectal cancer cells HCT116 (2). Previous studies have shown that fluoxetine induces apoptosis, ultimately leading to the mitochondrial membrane dysfunction in liver cancer cells (3). Some primary pathways of genotoxicity caused by fluoxetine can be found in its metabolic pathway, where the main sources of increased superoxide anions are cytochrome P-450 and NADPH oxidase enzymes. Furthermore, increased NO leads to increased COX2 and ultimately NF-KB (4, 5).

Other factors involved in the toxicity of fluoxetine include the induction of apoptosis through increased ROS, intracellular Ca2+ accumulation, decreased MMP, anti-apoptotic protein ERK1/2 reduction, and pro-apoptotic proteins JNK and p38 MAPK increase (3, 6). Multiple mechanisms are involved in fluoxetine-induced cytotoxicity, including increased production of reactive oxygen species, reduced antioxidant capacity with decreased GSH and BSO-L levels associated with increased protein carbonylation, malondialdehyde, increased GST activity, increased NO and NF-KB levels, increased superoxide anions, and more (4, 21, 22). A study has shown that fluoxetine induces autophagy and ultimately reduces cell growth in normal breast cells (7).

In one study, a high level of intracellular ROS production was observed in Hep3B cells treated with fluoxetine. Additionally, the results showed that fluoxetine reduces MMP in Hep3B cells (3). In a study, it was stated that fluoxetine reduces the rate of cell division in all cell lines treated with this drug. Moreover, the cytotoxic effects were only observed at the highest fluoxetine dose (2.0 milligrams per milliliter), resulting in cell death or inhibition of cell division(8). Fluoxetine induces oxidative stress by increasing free radicals and causing harmful changes in cells (8, 10).

Lycopene is a lipophilic carotenoid hydrocarbon with a red color due to its chromophore with 11 double bonds. Its antioxidant properties are derived from this polymerized structure. Unlike α- and β-carotenes, lycopene is not a provitamin A due to the absence of a β-ionone ring and its non-cyclic structure. After decades of research, lycopene has been found in tomatoes, watermelon, pink grapefruit, papaya, and other fruits. Unlike other carotenoids that are widely distributed, lycopene is mainly found in tomatoes and tomato products (23).

Oxidative stress caused by ROS is associated with aging, carcinogenesis, and cardiovascular diseases. Lycopene can act as an antioxidant through various mechanisms, and the best mechanism is by scavenging free oxygen radicals (O2), which is due to its extensive double bond system (24). In cellular culture, V79 Chinese hamster lung fibroblasts were treated with peroxynitrite to induce DNA strand breakage and protein nitration. It was shown that this effect was inhibited by lycopene at concentrations ranging from 0.31 to 10 micromoles per liter. In another preclinical study, lycopene at concentrations of 0.25 to 10 micromoles per liter reduced oxidative DNA damage caused by estrogen catechol oxidation in lung fibroblasts and plasmid DNA (25). It was found that 81% of the intracellular location of lycopene in prostate cancer cells under treatment with lycopene was in the nucleus. Consistent with this, it has been observed that the protective effects of DNA by lycopene are related to the localization of lycopene in the nucleus (26).

In a study, it was found that lycopene protects cells against ionizing radiation damage. This protective effect may be due to the antioxidant property of lycopene and its prevention of the deleterious effects of ROS (27). In cardiovascular studies, it has been observed that lycopene increases the antioxidant activity of enzymes such as SOD, catalase, and glutathione peroxidase in mouse hepatocytes after exposure to ionizing radiation (28). The balance of these enzymes in each specific cell and in the whole body of living organisms is essential for maximum protection against radiation. The results of a study reported that in rats treated with cisplatin, lycopene administration before and after cisplatin treatment increased glutathione enzyme levels (29). Many other studies have reported that carotenoids such as lycopene and beta-carotene reduce the frequency of chromosome damage in cells of some living organisms (30). Antioxidants in the human diet reduce chromosomal damage. For example, in a study, it was found that consumption of tomato derivatives reduced oxidative DNA damage in lymphocytes (31).

In studies, it has been shown that L-carnitine plays an important role in energy production by facilitating the transfer of activated fatty acids (acyl-CoA) into the mitochondrial matrix (13). Carnitine also protects the cell membrane against damages caused by free oxygen radicals. This substance has a specific biological function in scavenging free oxygen radicals and increasing levels of enzymatic and non-enzymatic antioxidants (14). L-carnitine can also help reduce the effects of free radicals (15). The antioxidant system consists of three enzymes: glutathione peroxidase, catalase, and superoxide dismutase. L-carnitine can protect these enzymes from oxidative damage and is very effective in regulating age-related changes (16).

L-carnitine has been widely used as an inducer of oxidative stress in laboratory models. Results show that exposure to 300 micromolar H2O2 for 12 hours resulted in a significant reduction in cell growth and increased LDH leakage in HL7702 cells. L-carnitine at concentrations of 0.1 to 3 millimolar showed no detrimental effect on HL7702 cell growth. However, cell growth was inhibited by 5 millimolar L-carnitine. It is possible that higher doses of carnitine may have adverse effects (17). Results showed that protective

effects of 0.1 to 3 millimolar L-carnitine were observed against H2O2-induced cell growth inhibition. LDH leakage was also dose-dependently inhibited by 0.1 to 1 millimolar L-carnitine. These findings suggest that L-carnitine is capable of reducing cellular toxicity induced by H2O2 in HL7702 cells (18, 19).

MDA, as the final product of lipid peroxidation, is usually used to estimate the level of lipid peroxidation. It has been shown that L-carnitine can prevent many pathological conditions that lead to increased MDA levels due to lipid peroxidation (18, 19). In an article, it was demonstrated that the level of MDA in HL7702 cells increased after exposure to H2O2. However, pretreatment with L-carnitine (0.1 to 1 millimolar) prevented further increases in MDA levels (20).

Based on the information provided, it appears that lycopene and L-carnitine may have a protective effect on the inhibition of cytotoxicity and oxidative stress caused by fluoxetine in the gingival fibroblast cell line. Fluoxetine has been reported to induce cellular toxicity through various mechanisms, including increased ROS production, decreased MMP, and activation of apoptotic pathways. On the other hand, both lycopene and L-carnitine have demonstrated potent antioxidant properties that can scavenge free radicals and protect against oxidative damage.

Conclusion

Similarly, L-carnitine and lycopene have been found to protect cell membranes against damages caused by free oxygen radicals, increase levels of enzymatic and non-enzymatic antioxidants, and reduce the effects of free radicals. Based on these findings, it is plausible that lycopene and L-carnitine could potentially mitigate the cytotoxic and oxidative stress effects of fluoxetine on gingival fibroblast cells, providing a potential avenue for future research into their role as protective agents against the side effects of fluoxetine in this cell line.

Conflict of interest

No potential conflict of interest was reported by the author.

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