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Review Article
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NAFLD ASSOCIATED WITH FLUOXETINE WITH ITS PROBABLE MANAGEMENT: A REVIEW

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ABSTRACT
Non-alcoholic fatty liver disease is a major global health related linked to severe metabolic abnormalities. However, effective pharmacological therapies remain restricted. Based on a recent meta-analysis, NAFLD affects 32% of the adult population worldwide. The global incidence of NAFLD is estimated to be 47 cases per 1,000 peoplewhich is greater among males (40%) than females (26%). Drug induced liver injury is commonly caused by Amoxicillin-clavulanate,Azithromycin, Acetaminophen, Methotrexate, Atorvastatin, Ticlopidine and fluoxetine. Selective serotonin receptor inhibitor(fluoxetine)after prolonged therapy shown Non-Alcoholic fatty liver disease (NAFLD).This study focused on evaluation of various natural products for their therapeutic potential.The results suggested that natural compounds displayed promising hepatoprotective benefits, potentially reducing liver damage and increasing liver function through various pathways such as oxidative stress, mitochondrial dysfunction and inflammation. Further research in this area could lead to beneficial preventive and therapeutic strategies for patients suffering from NAFLD due to fluoxetine.

Keywords: *Non-alcoholic fatty liver disease, Fluoxetine,Drug induced liver injury, Inflammation and oxidative stress.*

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INTRODUCTION

Drug-induced liver damage is a common liver condition that can range from a temporary modest increase in liver enzymes to fulminant liver failure further leads to death. Drug-induced fatty liver disease accounts for approximately 2% of all cases, confirming that a it is a rare manifestation of harmful chemicals and this leads to development of DILI. This can lead to a progression to non-alcoholic steatohepatitis, fibrosis, and cirrhosis [1].

Direct liver injury is caused by drugs or chemicals that are naturally harmful to the liver. The probability of damage is proportional to the degree of drug administration and is reliably reversible, therefore liver injury can be predicted.

DILI is an unusual and potentially deadly adverse reaction. For some medications, DILI is dose-dependent and predictable. For others medicines, DILI is idiosyncratic and difficult to anticipate [2].

DILI, defined as damage to the liver or biliary system induced by the use of hepatotoxic medicines, is the primary cause of acute liver failure in world of western. A considerable number of commonly used medicines may cause liver damage. DILI has historically been characterised as direct dosage dependent, idiosyncratic, and indirect damage [3].

DILI is commonly caused by Anti-microbial (Amoxicillin-clavulanate, Azithromycin), Anti-inflammatory (Acetaminophen), Anti-cancer (Flutamide, Methotrexate), Hyper-lipidemic (Atorvastatin), Anti-coagulant (Ticlopidine), Anti-convulsant (Carbamazepine), and Psychiatric (Paroxetine, Fluoxetine) frequent causative drugs of DILI [4].

Fluoxetine

Fluoxetine was described in journal in 1974 as a 5-HT)-uptake inhibitor and was emerging class of antidepressant medications known as selective serotonin-reuptake inhibitors, which were initially launched in the United States. These have since become the most frequently prescribed antidepressants [5]. (3-(p-trifluoromethyl phenoxy)-N-

methyl-3 phenylpropylamine, as fluoxetine HCl; Lilly (LY) 110140) was initially reported in a scientific journal in 1974 [6]. Depression is one of the most frequent neuropsychiatric illnesses, affecting 300 million people. Depression is second largest cause of disability by 2020, posing a significant social and economic burden on modern society according to WHO. Tricyclic antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors are among the medications now used in clinical practice to treat depression [7].

Long-term antidepressant medication is frequently used to treat major depressive disorder and other neuropsychiatric illnesses. However, Fluoxetine (SSRI) is a first-line drug for managing depression and other neuropsychiatric disorders. Long-term use of this medication induces NAFLD [8].

Incredibly, fluoxetine has been linked to increased peripheral serotonin synthesis. Emerging data shows that serotonin has a role in the progression of non-alcoholic fatty liver disease.

The long-term use of SSRIs in both kids and adults has been linked with elevated weight gain, dyslipidaemia, and new-onset type 2 diabetes. It is possible that SSRI used throughout pregnancy can cause same metabolic disturbances in subjected to offspring. A study found that male offspring exposed to an SSRI prenatally had an increased risk of being overweight.

SSRIs inhibit serotonin uptake in CNS synaptic clefts, which is connected to their antidepressant effect. Current evidence includes panic, bipolar illness, obsessive-compulsive disorders, major depressive disorders, and bipolar illness with extra medication. It is available in numerous dose levels ranging from 10 to 40 mg under the brand name Prozac.

Fluoxetine inhibits cytochrome P450 (2D6) and various isozymes, potentially causing interaction of medicines. Prolonged usage of fluoxetine, while clinically acceptable, can lead to side effects such as anxiety, insomnia, nausea, and diarrhoea. metabolic issues, sexual dysfunction and Liver disease [9].

Generation of free radicals leads damage to the liver. Supplementary, inflammation in tissue is also caused by overproduction of superoxide, hydroxyl, and several non-radical species like Hydrogen Peroxide (H_2O_2), along with excess phagocyte production, which might lead to damage to tissues [10].

SSRIs are taken by up to 10% of pregnant women. Children exposed to SSRIs in pregnancy have a higher likelihood of being overweight, indicating that foetal exposure can affect long-term metabolic alterations [11].

It is already shown in rats that foetal and neonatal exposure to the SSRI antidepressant fluoxetine resulted in metabolic changes. Non-alcoholic fatty liver is characterised by high hepatic triglyceride levels in body [12].

A recent research found that Fluoxetine caused liver toxicity and found that different stages of damage and inflammation in liver. Drug administration leads to oxidative stress. Long term use of drug may induce variety of undesirable symptoms such as nervousness, insomnia, feeling nauseated, bloating, physiological abnormalities sexual impairment and NAFLD [13].

EPIDEMIOLOGY

The latest data available which indicates that antidepressant drugs has risen by 34.8% over the last 6 years from 61.9 million to 83.4 million in 2025.

According to figures published by the NHS(BSA), the number of persons prescribed antidepressants increased from 7.87 million to 8.32 million in 2025.

Antidepressant drugs which are prescribed out of those the number of SSRI prescription is risen by 35.2% from 33.3 million items to 45.0 million in 2025.

It was discovered that 36% of the population with lean-NAFLD and non-obese-NAFLD had NASH **[14].**

Certain neuropathophysiological conditions cause this redox balance to be disturbed which results in oxidative stress. After neuronal injury, the excessive generation of free radical also contributes to the progression of secondary injury. Reactive nitrogen species (RNS), Highly reactive free radicals and primarily ROS, destruct the DNA, proteins, and membranes of the cell, which sets off a self-propagating inflammation in the cascade of events. Under oxidative stress conditions, dysfunctional mitochondria are thought to be a major mediator in progressive neurodegeneration.

NAFLD

A range of progressive disorders, including simple steatosis, steatohepatitis (NASH), fibrosis and cirrhosis, are included in NAFLD Lastly is characterized by hepatic inflammation and hepatocellular carcinoma (HCC), which is the hepatic manifestation of metabolic syndrome. NAFLD is also cause of liver disease around world and characterized as the presence of hepatic steatosis without hepatocellular damage, such as hepatocyte ballooning or fibrosis [15].

It is the most prevalent chronic liver disease globally, and it is strongly linked to oxidative stress. Lipid metabolism disruptions cause hepatic lipid accumulation, affecting several ROS generators such as mitochondria, endoplasmic reticulum, and NADPH oxidase [16]. This development is linked to insulin resistance, which is significantly associated with the metabolic syndrome, which includes central obesity, diabetes, and hypertension. Previously, increasing intracellular fatty acid concentrations in hepatocytes resulted in steatosis. As a result, multiple complicated interactions between nutritional, lifestyle, and hereditary factors cause necrosis, inflammation, fibrosis, and hepatocellular injury where wide disruption of liver is now due to Drug induced liver injury. Until now, numerous research have established the mechanism connected with insulin resistance, however the mechanisms related to the molecular components have been incompletely characterised [17].

Based on a recent meta-analysis, NAFLD affects 32% of the adult population worldwide. The global incidence of NAFLD is estimated to be 47 cases per 1,000 people, with men having a greater incidence than women proved by the data from the studies the estimated worldwide incidence of NAFLD among adults is 32%, which is greater among males (40%) than females (26%) [18].

NAFLD and it's main associated comorbidity, obesity may be connected with drug-induced liver injury. There is an increasing awareness of risk factors in patients of NAFLD for a variety of medications.

3. INCIDENCE OF NAFLD IN PSYCHIATRIC POPULATIONS

Recent research suggests that patients with bipolar disorder and schizophrenia are more frequently to have metabolic disease of liver, particularly NAFLD could be connected to anxiety, sadness, chronic stress and due to long term of administration of drug. NAFLD and mood problems may have a bi-directional link, similar to liver disease found to be an independent risk factor for developing depression and anxiety.

Risk factors include genetics, psychiatric drugs, socio-economic status, insulin resistance, and inflammation. NAFLD is more common in psychiatric populations due to various factors.

Psychiatric drugs are commonly used to treat children who have mood, behavioural, or developmental issues. Psychiatric medicines are often prescribed in paediatric populations connected with the higher risk of severe metabolic consequences include obesity, diabetes and high cholesterol levels.

Antipsychotics, antidepressants, and medications that stabilise mood have all been linked to an increased emergence and severity of non- alcohol fatty acid in juvenile patients.

Pharmacological of psychotic drugs: Correlation with metabolic liver disease.

Antidepressants, antipsychotics, and mood stabilisers are psychotropic drugs that alter mood and behaviour. SSRI antidepressants and AA medicines have been linked to a higher risk of metabolic illnesses like as diabetes.

AA medicines can lead to sudden stage of obesity and resistance in insulin in both children and adults, providing a considerable metabolic risk. Preclinical investigations utilising relevant doses of AA medicines have shown that insulin resistance, immunological dysfunction, and NAFLD can exist before drug-associated weight gain.

Drugs reduce inflammation in both clinical and preclinical studies while antidepressants like imipramine, desipramine, and fluoxetine affect mitochondrial function. Administration of AA andanti-depressantmedicinesin a patient population exhibiting hyper inflammatory reactions. Chronic oxidative stress and mitochondrial dysfunction of their condition have the possibility to reverse these states.

Excessive liver FFA buildup can lead topro-fibrotic, pro-apoptotic, pro-oxidative, pro-inflammatory signal pathways, which contribute to NASH symptoms such as oxidative stress, inflammation, apoptosis, and fibrosis [13].

4. MECHANISTIC BEHAVIOUR INDUCED NAFLD

4.1 Formation of free radical and oxidative stress in NAFLD

NAFLD, is a contribution of Oxidative stress acting as a "second hit" that promotes the disease. It is primarily linked to early mitochondrial over function, followed by damage and late dysfunction.

Oxidative stress occurs when the production of ROS and capacity of the antioxidant system's to scavenge them disbalances. ROS, such as superoxide anion radicals (O2.) and hydrogen peroxide (H_2O_2), are constantly generated as byproducts of energy metabolism in several hepatocytes.

Oxidative stress is a primary reason of liver injury where lipid excesses the overproduction of oxidants by influencing multiple ROS-generating pathways.

Impaired production of ROS leads to low redox state, which impairs physiological redox signalling. However, when it comes to oxidative stress, high ROS cause Pathological redox signalling causes cellular harm in several illnesses, notably when cellular ROS production switches to more hazardous ROS species [19].

The other major generator of ROS in NAFLD is "cytochrome P450 (CYP) family 2 subfamily CYP2E1, which breaks down FFAs and is activated by them. CYP2E1 executes cycles, discharging electrons into the cytosol and resulting in the production of highly reactive carbonyl free radicals. As a result, oxidative stress may be caused by either excess production of pro oxidant product or improper function of antioxidant system as shown in Figure 01.

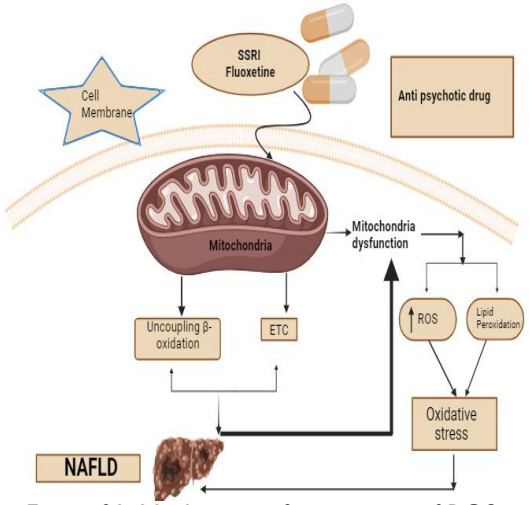

Figure 01: Mechanism of generation of ROS

Dysfunction of mitochondria

Mitochondria, responsible for lipid metabolism and a major source of ROS, lead a important role in the pathophysiology of NAFLD. Once the Mitochondrial β-

oxidation produces one molecule of acetyl-CoA every cycle. The tricarboxylic acid cycle converts acetyl CoA into nicotinamide adenine dinucleotide and the FADH2 in its hydroquinone state.Those molecules are then oxidised, liberating electrons to the mitochondrial respiratory chain and generating ATP [20].

The oxidative surge further degrades mitochondrial function, creating a vicious cycle of ROS formation from inadequate respiration which further affects the respiratory chain. Mitochondria produce ATP, generate ROS, and regulate apoptosis. The transition from NAFLD to NASH is characterised by mitochondrial dysfunction [21]. NASH patients experience a gradual decline in antioxidant capacity due to decrease of antioxidant molecules and oxidative inhibition of antioxidant enzyme activity (e.g., superoxide dismutase, catalase). This can lead to decreased activity and expression of antioxidant enzymes, as seen in cirrhotic-stage NASH patients.

The proportion of energy and fat in hepatic cells is determined by mitochondrial activities, which include beta oxidation of free fatty acids (FFAs), electron transport, ATP synthesis, and reactive oxygen species [22].

Abnormalities in mitochondria alter the balance between prooxidant and antioxidant processes, resulting in anrise in non-metabolized fatty acids in the cytosol as a consequence of the blockade of fatty acid beta-oxidation and the subsequent activation of production of ROS.

Excess FFAs entering mitochondria as a result of increased intake or insulin resistance, even if they lower FAA cytosolic levels, may enhance the permeability of the inner mitochondrial membrane. This reduces the membrane potential and ATP synthesis capacity, impairing mitochondrial function and increasing ROS generation as shown in Figure 02.

The rise in fatty acid oxidation, which causes an increase in electron flux in the electron transport chain (ETC), may cause "electron leakage" (due to a decrease in the activity of ETC complexes), resulting in a direct reaction between electrons and oxygen and the production of ROS [23].

The main reason of ROS in NAFLD is “cytochrome P450 CYP2E1, which metabolises FFAs, is an important generator of ROS in NASH. CYP2E1 executes ineffective cycles, releasing electrons to the cytosol and producing extremely reactive carbonyl free radicals [24].

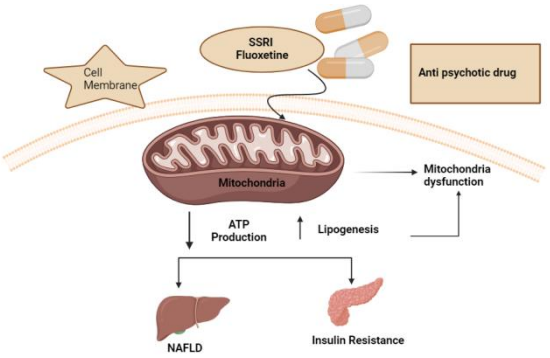

Figure 02: Mechanism of mitochondrial dysfunction

Inflammation in Liver

NAFLD is a pro-inflammatory disorder that requires inflammation to grow and progress. Inflammation causes increased formation of inflammatory factors from both extrahepatic (e.g., adipose tissue, gut) and hepatic locations, with Kupfer cells producing pro-inflammatory cytokines primarily.

The clinical and experimental studies in NAFLD indicate that liver inflammation and insulin resistance are linked to altered hepatic mitochondrial energy, such as abnormal ATP homeostasis, increased fatty acid oxidation, and ROS production.

Long-term illnesses like obesity and diabetes cause systemic inflammation, which contributes to both psychiatric problems and NAFLD. The link between inflammation and metabolic liver illnesses (NAFLD/NASH) is both causal and reciprocal, demonstrating immunological metabolic disease.

Inflammation in hepatocytes and insulin resistance in NAFLD are associated with changes in mitochondrial energetics, such as ATP homeostasis, increased fatty acid oxidation, ROS production, and lipid peroxidation as shown in Figure 03. Lipid peroxidation triggers inflammatory signals and to the development of NAFLD. Insulin resistance is thought to be the fundamental driver of NAFLD pathogenesis, and insulin resistance causes liver damage. Steatosis, excessive amount of fatty acid, and lipotoxicitycause hepatic susceptibility due to inflammation and oxidative stress [13].

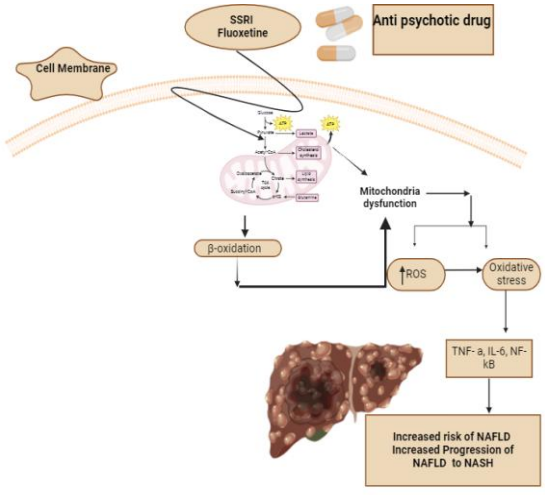

Figure 03: Mechanism of Inflammation in liver

PROBABLE MANAGEMENT OF DRUG INDUCED NAFLD

Various therapeutic agents have been investigated for the probable management of fluoxetine-induced NAFLD, which is connected with insulin resistance, oxidative stress, mitochondrial dysfunction, inflammation, and hepatic lipid accumulation, Antioxidants such as Vitamin E, resveratrol, and quercetin protect hepatocytes from oxidative damage, while herbal compounds like *Curcuma longa*, baicalin, and silymarin exhibit hepatoprotective and anti-inflammatory effects. Metabolic regulators including omega-3 fatty acids, carnitine, and genistein improve lipid metabolism and insulin sensitivitythereby reducing hepatic fat accumulation. Additionally, hesperidin, silibinin, and stilbenes may help prevent hepatic fibrosis and cellular injury. Blueberry extracts and probiotics further improve mitochondrial dysfunction and gut–liver axis imbalance associated with fluoxetine-induced hepatic damage. Thus, these compounds may serve as promising adjunctive therapeutic approaches for the management of fluoxetine-induced NAFLD as shown in table 01.

Table 01: Probable Management of Drug Induced NAFLD

SNO.	FUTURE THERAPEUTIC LEAD COMPOUND	SOURCE	MODE OF ACTION	REFERENCES
1.	Olive oil and leaf extract	Leave of olive	Attenuates hepatic oxidative stress and inflammatory cytokine production while preventing hepatocyte apoptosis and lipid peroxidation	**[21]**
2.	Baicalin	*Scutellariabaicalensis* herb	Enhances antioxidant defence mechanisms and suppresses inflammatory mediators to restore hepatic function and reduce liver injury	**[23]**
3.	Genistein	soybeans	Regulates lipid metabolism and insulin signalling pathways, thereby reducing hepatic fat accumulation, inflammation, and fibrosis	**[25]**
4.	Dandelion	Leave of dandelion	Exhibits hepatoprotective effects through antioxidant scavenging activity and suppression of pro-inflammatory pathways	**[26]**
5.	Astaxanthin and β-Cryptoxanthin	microorganisms and marine organisms (Crayfish, Chum salmon, (*Haematococcus*algae, *Paracoccus* bacteria)	Improves mitochondrial function, suppresses oxidative stress and inflammatory signalling, enhances insulin sensitivity, and inhibits hepatic fibrogenesis.	**[27]**
6.	Curcuma longa L extract	flowering plant	Modulates fatty acid uptake and inhibits hepatic lipogenesis, thereby reducing intracellular lipid accumulation	**[28]**
7.	Blueberry juice and probiotic tablets	Blueberry	Ameliorates oxidative stress and mitochondrial dysfunction through regulation of SIRT1-mediated cellular signalling	**[29]**
8.	Vitamin D	Fish oil	Regulates immune and inflammatory responses, improves insulin sensitivity, and reduces progression of hepatic steatosis	**[29, 31, 32]**
9.	Vitamin E	vegetable oil and nuts	Acts as a potent lipid-soluble antioxidant that protects hepatocytes against oxidative damage and cellular injury	**[33]**
	Carnitine	Avocado, beef	Enhances mitochondrial β-oxidation of	**[34, 35]**

10.		extract	fatty acids, improves insulin resistance, and reduces inflammatory liver damage	
11.	Omega-3 fatty acids	alpha-linolenic acid.	Suppresses hepatic lipogenesis, enhances fatty acid oxidation, and reduces oxidative stress and inflammation	**[36]**
12.	Silymarin	milk thistle plant	Stabilize Oxidative stress, Chronic inflammation, Insulin resistance, and works as Hepatocellular protection	**[37, 38, 39]**
13.	Resveratrol	grapes, berries, red wine and nuts.	Stabilize Oxidative stress, Insulin resistance, and Hepatocellular protection	**[40]**
Natural Phenolic Compounds				
14.	Quercetin	Onion, broccoli	↓liver injury ↓oxidative stress (Nrf2, HO-1, NFkB)	**[30]**
15.	Rutin	Buckwheat	↓Oxidative stress (Gpx, plasma MDA) ↓insulin resistance	
16.	Epigallocatechin	Tea	↓hepatic steatosis, ↓Oxidative stress (Gpx, plasma MDA) ↓insulin resistance	
17.	Anthocyanins	Blueberry, black currant	↓hepatic oxidative stress (ROS, GSH)	
18.	Luteolin	Celery and parsley	↓hepatic steatosis, ↓Oxidative stress ↓inflammation (TNF- a)	
19.	Naringenin	citrus fruits	↑ insulin sensitivity ↓obesity	
20.	Hesperidin	Citrus	↓hepatic steatosis, ↓hepatic fibrosis (liver histology)	
21.	Stilibenes (Resveratrol)	Grapes	↓ insulin resistance ↑ insulin sensitivity ↓ obesity	**[41]**
22.	Silibinin	*Silybum marianum*	Decrease liver enzymes ↓ hepatic steatosis ↓ liver oxidative stress (ROS, i-NOS)	
Synthetic Compounds				
SNO.	**SYNTHETIC COMPOUNDS**	**SOURCES**	**MODE OF ACTION**	**REFERENCES**
23.	Bavachinin	Purchased from Chengdu Pufei De biotech company	BVC interacts to the pocket of PCNA, raising its interaction with DNA polymerase delta and the pro-regeneration effect.	**[42]**
24.	ALDH2 activator Alda-1	EMD Chemicals, Gibbstown,	Increased clearance of Aldehydes, and Preserving Mitochondrial respiratory function	**[19]**
25.	Caffeic Acid Phenethyl Ester (CAPE)	Sigma-Aldrich Co,LLC, Germany	TOS and OSI level decreased and PON-1 and TAC increased	**[22]**
26.	Daidzein	(Bio Spectrum Ltd., Seoul, Korea)	↓hepatic steatosis, (PPAR-a, PPAR-)	**[41]**
27.	Pioglitazone	Takeda Chemical Indus triesOsaka, Japan	Attenuate insulin resistance	**[25]**

CONCLUSION

Fluoxetine is a commonly prescribed SSRI used for the treatment of depression, anxiety disorders, obsessive-compulsive disorder, and several other psychiatric illnesses. Numerous Researches found that Fluoxetine is Antidepressant drug but due to prolonged treatment of this drug cause NAFLD. Natural products and plant-derived bioactive compounds have gained considerable attention because of their potent anti-inflammatory, antioxidant, and hepatoprotective properties and this review is focused on these natural products. They can prevent liver damage and serve as a significant source of medicine. Their potential deserves exploration and development. Despite encouraging findings, further preclinical and clinical investigations are required to establish the safety, efficacy, optimal dosage, and mechanism of action of these natural products. Therefore, this leading compound will become promising drugs for treating NAFLD induced by fluoxetine.

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CONFLICT INTEREST

The authors declare that they have no known competing financial interests.

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