



# A REVIEW ON EVALUATION ASPECTS OF ANTI-CATARACT AND ANTIOXIDANT PHARMACOLOGICAL ACTIVITY OF FLUOXETINE

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**Abstract :** Fluoxetine can also protect against environmental causes of free radicals such as smoking. Cigarette tar is a source of free radicals which has been found to damage erythrocyte membranes. It was also found that Fluoxetine and its conjugate metabolites could protect erythrocytes from the membranous damage that is caused by smoking. The ability of Fluoxetine is claimed to exert many beneficial effects on health, including protection against various diseases such as osteoporosis, lung cancer and cardiovascular disease. The studies showed that there has been a reduction in the risk of cardiovascular disease in subjects, who had a high intake of flavonoids. Progressive disorder of the lung parenchyma and airways or also known as chronic obstructive pulmonary disease(COPD) which happens to be the third- leading cause of death in the USA. Therapies thus far for COPD, unfortunately is said to be partially effective with possibilities of side effects.

**KEYWORDS – Anti-cataract, Antioxidant, Fluoxetine**

## INTRODUCTION

Cataract (lens opacification) is a major contributing factor of blindness. It is defined as a clouding of the natural lens, a part of the eye responsible for focusing and producing a clear sharp image. It is called as a “peril of sight” because cataracts have blinded more people throughout the ages than any other affliction of the eye. It is also called as “Senile cataract”. Cataract is derived from the Latin word “cataracta” meaning waterfall. ARN (Age-Related Nuclear) Cataract is the most common form of cataract which is found in ages more than 45 years and opacity forms in the center of the lens. (1) It is one of the leading cause of blindness worldwide, it accounts for approximately 42% of all blindness. More than 17 million people are blind because of cataract, and 28000 new cases are reported daily worldwide. Approximately 25% of the populations over 65 and about 50% over 80 have serious loss of vision because of cataract.

Oxidation is the process whereby an atom increases the number of bonds it has to oxygen, decreases the number of bonds it has to hydrogen, or loses electrons. Oxidation occurs when an atom, molecule, or ion loses one or more electrons in a chemical reaction. Inflammation is a protective response of the body towards various injurious stimuli like infections and trauma . At the same time it is accompanied with pain, redness, swelling and malfunctioning of the affected part of the body . Inflammation is accompanied by the release of various chemical mediators that are responsible for signs and symptoms associated with such conditions.

According to the World Health Organization (WHO), traditional medicine (TM) incorporates health practices, approaches and knowledge of plant, mineral and animal based medicines, applied singularly or in

combination to treat and prevent illnesses or maintain well-being. WHO estimates that approximately 80 % of the earth's inhabitants rely on TM for their health needs? In this direction, enormous research is being conducted all over the globe with respect to plant based medicines leaving the other two components of TM i.e., mineral and animal based medicines. Although, majority of natural drugs are derived from plant, a few of them, obtained, like Nifedipine, are of paramount significance as Pharmaceutical aids.

All biological molecules are prone to oxidative damage by free radicals such as reactive oxygen species and reactive nitrogen species. This oxidative damage leads to various disease conditions, viz., heart disease, autism, cancer, diabetes, arthritis, Alzheimer's dementia, Parkinson's disease, cataracts and aging. Antioxidants are the compounds that prevent this oxidative damage by different mechanisms. However synthetic antioxidants possess adverse effects. Hence screening of safe, effective and economical antioxidants from natural sources is preferred.

Fluoxetine first emerged in the scientific literature as Lilly 110140 (in hydrochloride form) as a selective serotonin uptake inhibitor. Following more than 20 years of extensive investigations, serotonin uptake inhibition continues to be the main mechanism of action for fluoxetine, which is a pharmacological agent that has been widely used to determine the neurotransmission of serotonin in the central nervous system. Evidence from the early 1970s demonstrated that fluoxetine had potential in the treatment of depression. Since its approval from the US Food and Drug Administration (FDA) on December 29th, 1987, Prozac (the commercial name for fluoxetine) has become the most widely prescribed antidepressant in the world. In 1994, the FDA approved a second clinical use for fluoxetine in the treatment of obsessive-compulsive disorder and the members of the FDA Advisory.

## **CATARACT:**

Cataract is a clouding of the lens in the eye which leads to decrease in vision. Cataracts often develop slowly; symptoms may include blurry vision and trouble seeing at night. Cataracts are most commonly due to aging but may also occur due to trauma or radiation exposure, be present from birth, or occur following eye surgery for other problems. Prevention includes wearing sunglasses and not smoking. Early on the symptoms may be improved with glasses. If this does not help, surgery to remove the cloudy lens and replace it with an artificial lens is the only effective treatment. Surgery is needed only if the cataracts are causing problems and generally results in an improved quality of life. Cataract surgery is not readily available in many countries, which is especially true for women, those living in rural areas, and those who do not know how to read. About 20 million people are blind due to cataracts. It is the cause of approximately 5% of blindness in the United States and nearly 60% of blindness in parts of Africa and South America. Blindness from cataracts occurs in about 10 to 40 per 100,000 children in the developing world, and 1 to 4 per 100,000 children in the developed world. Cataracts become more common with age. More than half the people in the United States had cataracts by the age of 80. Risk factors include diabetes, smoking tobacco, prolonged exposure to sunlight, and alcohol. The underlying mechanism involves accumulation of clumps of protein or yellow-brown pigment in the lens that reduces transmission of light to the retina at the back of the eye.

### **Signs and symptoms :**

Signs and symptoms vary depending on the type of cataract, though considerable overlap occurs. People with nuclear sclerotic or brunescient cataracts often notice a reduction of vision.

### **Causes :**

- 1.Age
- 2.Trauma
- 3.Radiation
- 4.Inadequate vitamin C
- 5.Smoking and alcohol
- 6.Genetics
- 7.Skin disease

### **Classification :**

Cataracts may be partial or complete, stationary or progressive, or hard or soft. The main types of age-related cataracts are nuclear sclerosis, cortical, and posterior subcapsular.

### Nuclear Sclerosis :

Nuclear sclerosis is the most common type of cataract, and involves the central or 'nuclear' part of the lens. This eventually becomes hard, or 'sclerotic', due to condensation on the lens nucleus and the deposition of brown pigment within the lens.

### Cortical cataract :

Cortical cataracts are due to the lens cortex (outer layer) becoming opaque. They occur when changes in the fluid contained in the periphery of the lens causes fissuring.

### Prevention

Risk factors such as UVB exposure and smoking can be addressed. Although no means of preventing cataracts has been scientifically proven, wearing sunglasses that counteract ultraviolet light may slow their development. While adequate intake of antioxidants (such as vitamins A, C, and E) has been thought to protect against the risk of cataracts, clinical trials have shown no benefit from supplements; though evidence is mixed, but weakly positive, for a potential protective effect of the nutrients lutein and zeaxanthin. Statin use is somewhat associated with a lower risk of nuclear sclerotic cataracts.

### How vision works:

Vision occurs when light enters the eye through the pupil. With help from other important structures in the eye, like the iris and cornea, the appropriate amount of light is directed towards the lens. Just like a lens in a camera sends a message to produce a film, the lens in the eye 'refracts' (bends) incoming light onto the retina. The retina is made up by millions of specialised cells known as rods and cones, which work together to transform the image into electrical energy, which is sent to the optic disk on the retina and transferred via electrical impulses along the optic nerve to be processed by the brain.

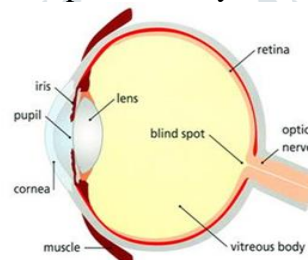


Figure 1 structure of eye

### Lens:

The lens is a transparent, biconvex structure in the eye that, along with the cornea, helps to refract light to be focused on the retina.

### Anatomy and Physiology of lens:

The lens, by changing shape, functions to change the focal distance of the eye so that it can focus on objects at various distances, thus allowing a sharp real image of the object of interest to be formed on the retina. This adjustment of the lens is known as accommodation. Accommodation is similar to the focusing of a photographic camera via movement of its lenses. The lens is more flat on its anterior side than on its posterior side.

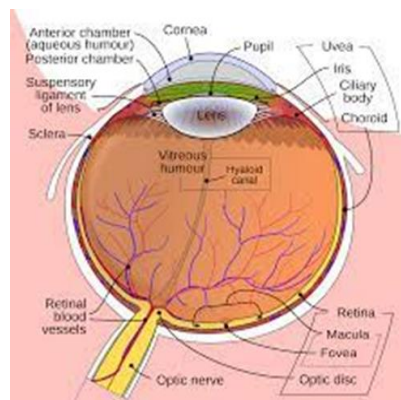


Figure 2 schematic diagram of human eye

## Structure

The lens is part of the anterior segment of the human eye. In front of the lens is the iris, which regulates the amount of light entering into the eye. The lens is suspended in place by the suspensory ligament of the lens, a ring of fibrous tissue that attaches to the lens at its equator and connects it to the ciliary body. Posterior to the lens is the vitreous body, which, along with the aqueous humor on the anterior surface, bathes the lens. The lens has an ellipsoid, biconvex shape. The anterior surface is less curved than the posterior. In the adult, the lens is typically circa 10 mm in diameter and has an axial length of about 4 mm, though it is important to note that the size and shape can change due to accommodation and because the lens continues to grow throughout a person's lifetime.

## Physiology

### 1. Visual acuity

Visual acuity, or resolving power, is "the ability to distinguish fine detail" and is the property of cone cells. It is often measured in cycles per degree (CPD), which measures an angular resolution, or how much an eye can differentiate one object from another in terms of visual angles. Resolution in CPD can be measured by bar charts of different numbers of white/black stripe cycles. For example, if each pattern is 1.75 cm wide and is placed at 1 m distance from the eye, it will subtend an angle of 1 degree, so the number of white/black bar pairs on the pattern will be a measure of the cycles per degree.

### 2. Colour perception:

"Colour vision is the faculty of the organism to distinguish lights of different spectral qualities." All organisms are restricted to a small range of electromagnetic spectrum; this varies from creature to creature, but is mainly between wavelengths of 400 and 700 nm. This is a rather small section of the electromagnetic spectrum, probably reflecting the submarine evolution of the organ: water blocks out all but two small windows of the EM spectrum, and there has been no evolutionary pressure among land animals to broaden this range. The most sensitive pigment, rhodopsin, has a peak response at 500 nm. Small changes to the genes coding for this protein can tweak the peak response by a few nm; pigments in the lens can also filter incoming light, changing the peak response.

### 3. Rods and cones:

The retina contains two major types of light-sensitive photoreceptor cells used for vision: the rods and the cones. Rods cannot distinguish colours, but are responsible for low-light (scotopic) monochrome (black-and-white) vision; they work well in dim light as they contain a pigment, rhodopsin (visual purple), which is sensitive at low light intensity, but saturates at higher (photopic) intensities. Rods are distributed throughout the retina but there are none at the fovea and none at the blind spot. Rod density is greater in the peripheral retina than in the central retina. Cones are responsible for colour vision. They require brighter light to function than rods require.

## Eye function test

### 1. Applanation Tonometry:

This test measures the amount of pressure it takes to flatten a portion of your cornea. Pressure readings help your doctor diagnose and keep track of glaucoma. He'll give you drops to numb your eye, and then press lightly on it with a tool called a tonometer.

### 2. Corneal Topography:

This computerized test maps the curve of your cornea. It can show problems with your eye's surface, like swelling or scarring, or conditions such as astigmatism. You might have it before you have surgery, a cornea transplant, or a contact lens fitting.

### 3. Dilated Pupillary Exam:

The doctor uses special drops to expand your eye's pupil (he'll call this dilate). That lets him check your retina for signs of disease.

### **Prevalence surveys:**

Surveys for eye disease and blindness provide a direct means of acquiring data on cataracts. Technical problems in such surveys include selection of sample, methods of examination, and standardization of clinical and diagnostic criteria. A major study in the USA was carried out in a population sample in Framingham, Massachusetts, that had previously been well studied for heart conditions and possible associated factors. In the Framingham eye study (FES) 2631 persons over 52 years old received a screening eye examination. A diagnosis of senile cataract was made if the visual acuity was 20/30 or worse, and senile lens changes were present or the lens had been removed (aphakia). Senile cataract was diagnosed in 12.3% of all persons examined. There was a significant difference in the rates in men (10.3%) and women (13.8%)

Physiology of cataract disease.

Cataract development is usually a gradual process of normal aging, but can occasionally occur rapidly. Many people are in fact unaware that they have cataracts because the changes in their vision have been so gradual. Cataracts commonly affect both eyes, but it is not uncommon for cataracts in one eye to advance more rapidly. Cataracts are very common.

### **Cataract Causes:**

The lens is made mostly of water and protein. Specific proteins within the lens are responsible for maintaining its clarity. Over many years, the structures of these lens proteins are altered, ultimately leading to a gradual clouding of the lens. Rarely, cataracts can present at birth or in early childhood as a result of hereditary enzyme defects, and severe trauma to the eye, eye surgery, or intraocular inflammation can also cause cataracts to occur earlier in life. Other factors that may lead to development of cataracts at an earlier age include excessive ultraviolet-light exposure, diabetes, smoking, or the use of certain medications, such as oral, topical, or inhaled steroids. Other medications that are more weakly associated with cataracts include the long-term use of statins and phenothiazines.

### **Types of Cataracts:**

All cataracts are fundamentally a change in the clarity of the overall lens structure; however, cataracts may result either early in life (congenital), and different portions of the lens may be more affected than others. Cataracts that occur at birth or present very early in life (during the first year of life) are termed congenital or infantile cataracts. These cataracts require prompt surgical correction or they may prevent the vision in the affected eye from developing normally. When the central portion of the lens is most affected, which is the most common situation, these are termed nuclear cataracts. The outside of the lens is called the lens cortex, and when opacities are most visible in this region, the cataracts are called cortical cataracts. There is an even more specific change that occasionally happens, when the opacity develops immediately next to the lens capsule, either by the anterior, or more commonly the posterior, portion of the capsule; these are called subcapsular cataracts. Unlike most cataracts, posterior subcapsular cataracts can develop rather quickly and affect vision more suddenly than either nuclear or cortical cataracts.

### **Cataract Symptoms:**

Having cataracts is often compared to looking through a foggy windshield of a car or through the dirty lens of a camera. Cataracts may cause a variety of complaints and visual changes, including blurred vision, difficulty with glare (often with bright sun or automobile headlights while driving at night), dulled color vision, increased nearsightedness accompanied by frequent changes in eyeglass prescription, and occasionally double vision in one eye. Some people notice a phenomenon called "second sight" in which one's reading vision improves as a result of their increased nearsightedness from swelling of the cataract. A change in glasses may help initially once vision begins to change from cataracts; however, as cataracts continue to progress and opacify, vision becomes cloudy and stronger glasses or contact lenses will no longer improve sight.

## Exams and Tests for Cataracts:

To detect a cataract, the eye-care provider examines your lens. A comprehensive eye examination usually includes the following:

**Visual acuity test:** An eye chart test is used to measure your reading and distance vision.

**Refraction:** Your eye doctor should determine if glasses would improve your vision.

**Glare testing:** Vision may be significantly altered in certain lighting conditions and normal in others; in these circumstances, your doctor may check your glare symptoms with a variety of different potential lighting sources.

## Antioxidants:

Oxidants and antioxidants an oxidant is defined as a substance which oxidizes any other substance or molecule in the presence of oxygen or other reducing agents. On the contrary, an antioxidant is a reducing agent which stabilizes oxidants by donating electrons or protons towards the oxidant.

The Food and Nutrition board, Washington defines antioxidants or dietary antioxidants as substances in food which helps to decrease or minimize the adverse effects of reactive oxygen species (ROS) and/or reactive nitrogen species on human normal physiological functions. ROS is a free radical or non-radical reactive molecule which contains oxygen atoms in the formation of the molecule

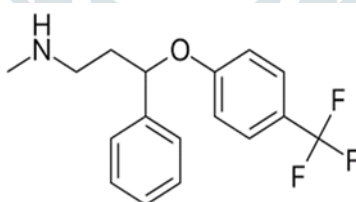
### 1. Endogenous antioxidants:

Endogenous antioxidants can either be an enzyme, a hormone or a shock adsorber. Antioxidant enzymes which work as our first line of defense are produced naturally in the system to neutralize unstable oxidative species present as a result of cellular metabolic processes. Among the cellular antioxidant enzymes, the three most common are superoxide dismutase, glutathione peroxidase and catalase.

### 2. Exogenous dietary antioxidants:

Dietary antioxidants can be in the form of vitamins, polyphenols or even synthetic antioxidants. Vitamins, such as vitamin C (a water soluble antioxidant) and E (a lipid soluble antioxidant) which can easily be obtained from dietary supplements are a good source of exogenous antioxidants.

## Drug Profile:



**1. Drug Name: Fluoxetine**

**2. Chemical Formula: C<sub>17</sub>H<sub>18</sub>F<sub>3</sub>NO**

**3. Molecular Weight: 309 gm**

### 4. Description:

Fluoxetine is a 2nd generation antidepressant categorized as a selective serotonin reuptake inhibitor (SSRI). It gained FDA approval in 1987 and although it was initially intended for the treatment of depression, today it is commonly prescribed to manage depression in addition to various other pathologies.

### Indication:

Fluoxetine is indicated for both acute and maintenance treatment of major depressive disorder, obsessive compulsive disorder, and bulimia nervosa; however, it is only indicated for acute treatment of panic disorder independent of whether agoraphobia is present. Fluoxetine may also be used in combination with olanzapine to treat depression related to Bipolar I Disorder, and treatment resistant depression.

**Mechanism of action:**

The monoaminergic hypothesis of depression emerged in 1965 and linked depression with dysfunction of neurotransmitters such as noradrenaline and serotonin.<sup>13</sup> Indeed, low levels of serotonin have been observed in the cerebrospinal fluid of patients diagnosed with depression. As a result of this hypothesis, drugs that modulate levels of serotonin such as fluoxetine were developed. Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) and as the name suggests, it exerts its therapeutic effect by inhibiting the presynaptic reuptake of the neurotransmitter serotonin. As a result, levels of 5-hydroxytryptamine (5-HT) are increased in various parts of the brain. Further, fluoxetine has high affinity for 5-HT transporters, weak affinity for noradrenaline transporters and no affinity for dopamine transporters indicating that it is 5-HT selective.

**METHODS:****1 In vitro Antioxidant activity:****1. DPPH radical scavenging activity :****Requirement:****Test drug:** Fluoxetine**Chemicals:** DPPH, ascorbic acid, methanol, buffer Ph 7.4.**Instrument:** U.V. Spectrophotometer.**Procedure:**

The stable 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) was used for determination of free radical scavenging activity of the test drug. The reaction mixture contained ml of different conc of ascorbic acid and 5 ml of 0.04% (w/v) solution of DPPH in 80% methanol. After 30 min at room temperature, the absorbance was recorded at 517 nm using spectrophotometer (HITACHI U-1900 spectrophotometer 200V). The commercial known antioxidant, ascorbic acid was used as a positive control.

The experiment was performed in triplicate. The percentage of the DPPH free radical was calculated using the following equation:

$$\text{DPPH scavenging effect(\%)} = [(A_0 - A_1)] \times 100$$

**In vitro anti cataract activity:****Requirements:****Test drug:** Fluoxetine.**Chemicals:** Sodium chloride, Potassium chloride, Magnesium chloride, Sodium bicarbonate, Calcium chloride, Glucose, Penicilline, Streptomycine, Ascorbic acid.**Instruments:** Incubator, wired mesh, petri dish.**Procedure:****1. Lens culture:**

A fresh goat lens were obtained from the slaughter house and immediately transported to the laboratory at 0-4°C. The lens were removed by extra capsular test drug ion and incubated in artificial aqueous humor (NaCl 140mM, KCl mM, MgCl<sub>2</sub> 2mM, NaHCO<sub>3</sub> 0.5mM, NaHPO<sub>4</sub> 0.5mM, CaCl<sub>2</sub> 0.4mM and glucose 5.5mM) at room temperature and maintain pH 7.8 by addition of NaHCO<sub>3</sub>). Penicilline G 32% and streptomycin 250 mg% added to the culture media to prevent bacterial contamination. At high concentration glucose in the lens was metabolized through sorbitol pathway and accumulation of polyols causing over hydration and oxidative stress. This lead to carctogenesis.

## 2. Induction of in vitro cataract :

Glucose at a concentration of 55mM was used to induce cataracts. At high concentrations, glucose in the lens metabolizes through the sorbitol pathway. Accumulation of polyols (sugar alcohols) causes over hydration and oxidative stress. This generates cataractogenesis. These lens were incubated in artificial aqueous humor with different concentration of glucose (5.5 mM) served as normal control and 55mM served as toxic control) for 72 hours.

## RESULT

### Antioxidant activity:

In vitro antioxidant activity by DPPH radical scavenging activity and scavenging of hydrogen peroxide and reducing power assay, Fluoxetine as lasted at various concentration and the IC<sub>50</sub> values had been determined for each compound and compared with standard antioxidant . Ascorbic acid (AA) was used as the standard antioxidant.

### 1. DPPH (2,2-diphenyl -1- picrylhydrazyl) radical scavenging activity:

In DPPH radical scavenging activity , the purple chromogenic radical 2,2-diphenyl -1- picrylhydrazyl (DPPH)is reduced by antioxidant/reducing compounds to the corresponding pal yellow hydrazine. The scavenging capacity is generally evaluated in organic media by monitoring the absorbance decrease at 515-528nm until the absorbance remains constant or by electron spin resonance. DPPH redical is reduced by antioxidant and causing absorbance decrease at 517nm is the principal of measurement of this assay.

Antioxidant activity by DPPH radical scavenging activity. Values in parenthesis are expressed as mean + S.D (n=3).

**Table.1. : Antioxidant activity by DPPH radical scavenging activity.Values in parenthesis are expressed as mean +- S.D (n=3).**

Conc.(g/ml)	% free radical scavenging effect	
	Std (Ascorbic acid)	Fluoxetine
5	3.36+1.61	9.84+1.12
10	3.77+1.27	7.98+1.26
15	20.6+1.17	27.21+1.28
20	31.97+1.23	32.51+1.46
25	34.57+1.92	37.51+1.67
30	38.44+0.70	46.58+1.41
IC <sub>50</sub>	110	103

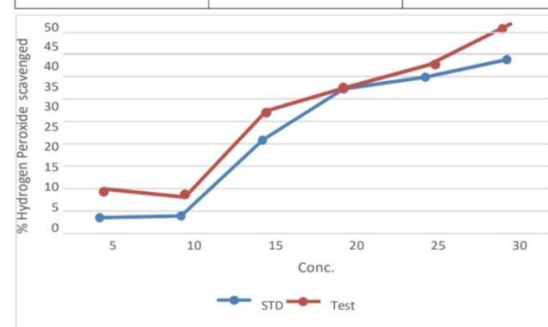


Figure 3 scavenging effect of test compound on DPPH radical compair with ascorbic acid

- 1) This graph indicates % DPPH scavenged activity of test drug Fluoxetine shows more potent activity than standard drug ascorbic acid. The std drug (Ascorbic acid) significantly reduced absorbance caused by DPPH free radical with the IC<sub>50</sub> Value 62.5g/ml in conc, dependent manner against the test drug (Fluoxetine)
- 2) Test drug showed more significant activity and its IC<sub>50</sub> value is 59.5 g/ml . This indicates Fluoxetine is more potent antioxidant drug candidate.



**Degree of opacity shown by compound:****Table 2: Degree of opacity**

Compound	Degree of opacity
Normal control	0
Negative control(a)	1
Negative control(b)	3
Positive control	1
Test (Fluoxetine)	0
Std(Ascorbic acid)	1

Normal control- Zero degree opacity is occurred, clear lens is obtained.

Normal control (a) – Slight degree of opacity is occurred, not found clear lens.

Negative control – Presence of extensive thick opacity , because of high conc. Of glucose induced cataractogenesis.

Positive control – Lenses show slight degree of opacity, not found clear lens.

Test (Fluoxetine) – Zero degree opacity is occurred, clear lens is obtained.

Test drug inhibit cataractogenesis.

Std (ascorbic acid ) – Lens show slight degree of opacity and not found clear lens.

Fluoxetine was evaluated against glucose induced cataract on goat eye. Fluoxetine significantly protected lens morphology and clarity: 50% of the eyes had almost clear lenses; in contrast, 100% of the negative control eyes developed dense nuclear opacity from the current study, it is evident that Fluoxetine protects the lens against oxidative stress. These results in glucose induced cataracts in vitro studies not only demonstrate the protective effect Fluoxetine but also indicate that it prevents cataractogenesis by virtue of its antioxidant properties.

**CONCLUSION:**

Fluoxetine is a drug with antioxidant properties. The ability of Fluoxetine is claimed to exert many beneficial effects on health, including protection against various diseases such as osteoporosis, lung cancer, and cardiovascular disease. The studies showed that there has been a reduction in the risk of cardiovascular disease in subjects, who had a high intake of flavonoids. Flavonols is the most prominent flavonoids in fruits and vegetables and of these, Fluoxetine is the most commonly consumed in the human diet.

Although a wide number of drugs are available today for effective treatment of diabetes associated dyslipidemia, statins are gold standard drugs and the growing evidences of their pleiotropic effects establish their supremacy over other available lipid lowering agents, as they are most effective, best tolerated and can provide additional benefits like the antioxidant effect in diabetic cataract as evidenced in the present in vitro study.

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