# An overview of Sodium Selenite-induced cataract in experimental animals

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## Abstract: -

Cataract is the most common cause of blindness worldwide. It is caused by the clumping of proteins in the eye's lens, which makes the lens cloudy. The most common disorders causing distance vision impairment or blindness among these billion individuals are cataract (94 million), refractive error (88.4 million), age-related macular degeneration (8 million), glaucoma (7.7 million), and diabetic retinopathy (3.9 million). As life expectancy rises, more people are developing cataracts, especially in low-income countries where access to surgery is limited. Cataract surgery is safe, but it can have some risks, such as retinal detachment. Therefore, there is a need for low-cost, therapeutic alternatives to managing cataracts.

The lens possesses a complex system of antioxidants that protect the lens proteins from damage. Depletion and/or failure of this antioxidant system, the lens proteins can damaged, leading to the development of cataracts. Scientists have been trying to develop new treatments for cataracts using a variety of methods, including in vitro (in a test tube), ex vivo (in an animal organ or tissue), and in vivo (in a living animal).

This review will focus on understanding and exploring the toxicological properties, and safety concerns in sodium selenite-induced cataracts. This study also explores the mechanisms of sodium selenite-induced lens opacification are highlighted

**Keywords: -** Cataracts, lens opacification, lens crystallin, sodium selenite

# 1. Introduction: -

Cataracts, a leading cause of preventable blindness worldwide, are characterized by the degeneration of the lens, resulting in opacification and impaired or blurry vision [1].
The WHO's 2019 World Vision Report shows that around 2.2 billion people are visually impaired [2]. One billion of these individuals have a visual impairment that could have been prevented or remains unaddressed. The most common disorders causing distance vision impairment or blindness among these billion individuals are cataract (94 million), refractive-error (88.4 millions), age-related macular degeneration (8 millions), glaucoma (7.7 millions), and diabetic retinopathy (3.9 millions). Presbyopia (826 million) is the most prevalent cause of near vision impairment [3].

The occurrence of cataracts experiences a rapid rise beyond the age of 40, with a notable prevalence shift from 3.9% in individuals aged 55–64 to a substantial 92.6% among those aged 80 and above [4,5]. Epidemiological models predict a twofold increase in the prevalence of cataract cases in the United States by 2050, from 24.4 million to 50 million cases[6].

Extensive epidemiological investigations have identified prevalent risk factors for cataracts, encompassing advancing age, tobacco use, exposure to ultraviolet (UV) rays, female gender, use of steroids, diabetes, and a high body mass index [7,8]. The prolongation of lifespans on a global scale is poised to escalate the prevalence of cataracts, particularly in economically disadvantaged countries with limited access to surgical interventions. Consequently, there is a pressing need to explore cost-effective pharmacological alternatives for addressing this condition [9].

### 1.1. Types of Cataractogenesis and Symptoms

Cataracts are categorized based on both the origin of the disease and the specific location of the opacity within the eye's anatomy. The etiological classification of different types of cataracts, as summarized by Dennis *et al*. (2015) [10], is presented in Table 1.

The presence of a lens opacity might not necessarily lead to noticeable symptoms and could only be identified during regular eye examinations. A gradual and painless decline in vision among elderly individuals is commonly indicative of cataract development.

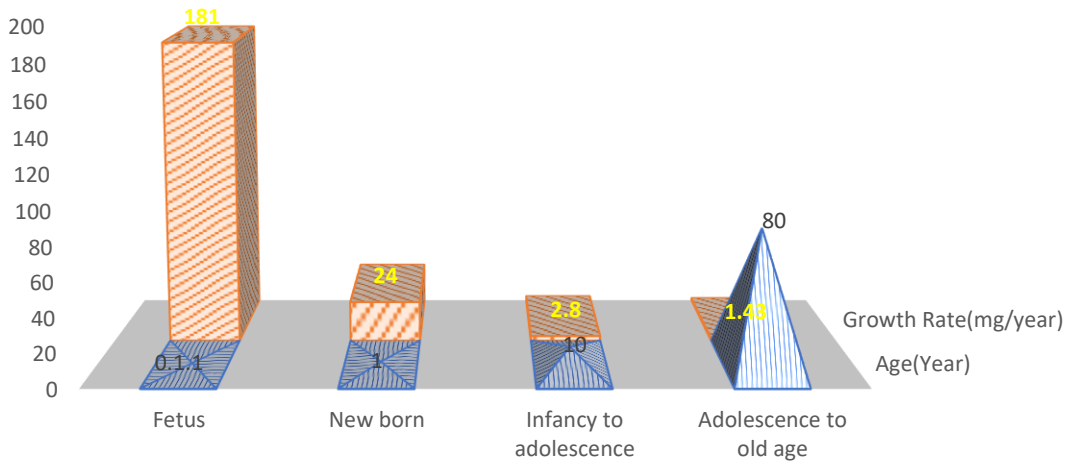
As the lens becomes more opaque over time, the clarity of vision starts to decline. This is accompanied by a decrease in the sharpness of both distant and close-up vision, followed by the perception of blurred sight, a decrease in color perception, and at times, the occurrence of double vision in one eye. The presence of reduced visual clarity and a dim or absent red reflection in the eye indicates the possibility of cataract diagnosis[11].
Table 1. Types of cataractogenesis [10].

| Type of Cataracts | Causes | Vulnerable Population |
|---|---|---|
| Congenital and developmental | Heredity, gestational maldevelopment of lens, maternal malnutrition, radiation, fetal/infantile factors-anoxia, birth trauma, congenital anomalies. | It may occur since birth or from infancy to adolescence. |
| Age-related (Senile) | Senescent changes, dehydration, systemic diseases, smoking, oxidative stress, and lack of essential dietary elements. | Elderly persons, mostly those over the age of 50 years. |
| Traumatic | Some physical damage to the eye lens capsule, penetration of foreign object. | Individuals employed in risky environments like welders and those working in glass furnaces. |
| Complicated | Complications of some chronic inflammatory and degenerative eye diseases. | Individuals with skin conditions, allergies, uveitis, diabetes, emphysema, and asthma. |
| Metabolic | Metabolic disorders such as diabetes mellitus, galactosemia. | Individuals lacking specific enzymes and hormones. |
| Toxic | Certain toxicants and drugs-Steroids, NSAID's. | People on steroid therapy and toxic drugs. |
| Radiation and electrical | Infra-red rays, x-rays, ultra-violet rays, and powerful electric current. | individuals who come into contact with excessive sunlight, artificial radiations, and high voltage. |

### 1.2. Anatomy and Physiology of Lens

To comprehend the disease's underlying mechanisms, it is essential to delve into the anatomy and physiology of the lens. The lens, which is transparent, lacks any direct blood supply [12]. At birth, the lens boasts an equatorial diameter of approximately 6.5 mm, which experiences its most rapid growth between the ages of 2 and 3, reaching dimensions of 7.5 mm and 8.2 mm at 1-2 years respectively. Following this, growth slows down, with an equatorial diameter of 9 mm around the age of 15, stabilizing at an average of 9-10 mm during adulthood. The incremental change throughout each decade of adult life is a mere 1 mm, as detailed in Table 1[13].

**Table 1: Changes in the lens weight throughout life[13]**




| | Fetus | New born | Infancy to adolescence | Adolescence to old age |
|---|---|---|---|---|
| Age(Year) | 0.1 | 1 | 10 | 80 |
| Growth Rate(mg/year) | 181 | 24 | 2.8 | 1.43 |

The anterior part of the lens is coated with a single layer of epithelial cells. These cells not only sustain the lens' metabolic functions but also replicate to generate daughter cells. These offspring cells then migrate and transform into fiber cells [12]. Lens fiber cells constitute over 95% of the lens and are extended to create dense, concentric layers termed "shells." This configuration effectively reduces the gaps between cells (illustrated in Figure 1) [14].

Nuclei are present in superficial lens fibers, rendering them metabolically active, whereas deeper fibers, constituting the majority of the lens, lack organelles and exhibit minimal metabolic activity. In the inner regions, fiber cells exhibit a notable expression of soluble crystallin proteins, yet they lack nuclei, mitochondria, endoplasmic reticulum, ribosomes, and other organelles [15]. Lens crystallins, accounting for nearly 90% of mature lens proteins, consist of α-crystallins, β-crystallins, and γ-crystallins in human lenses [16]. The purification of the high-molecular-weight α-crystallin fraction from human lenses resulted in two closely related α-crystallin polypeptides: αA-crystallins and αB-crystallins [17,18].

The α-crystallin proteins constitute as much as 33% of the total protein present in the lens[19]. Nevertheless, the lens primarily contains three γ-crystallins (γC, γD, γS-crystallin) and five β-crystallin polypeptides (βB1, βB2, βB3, βA1/A3, βA4) [20].

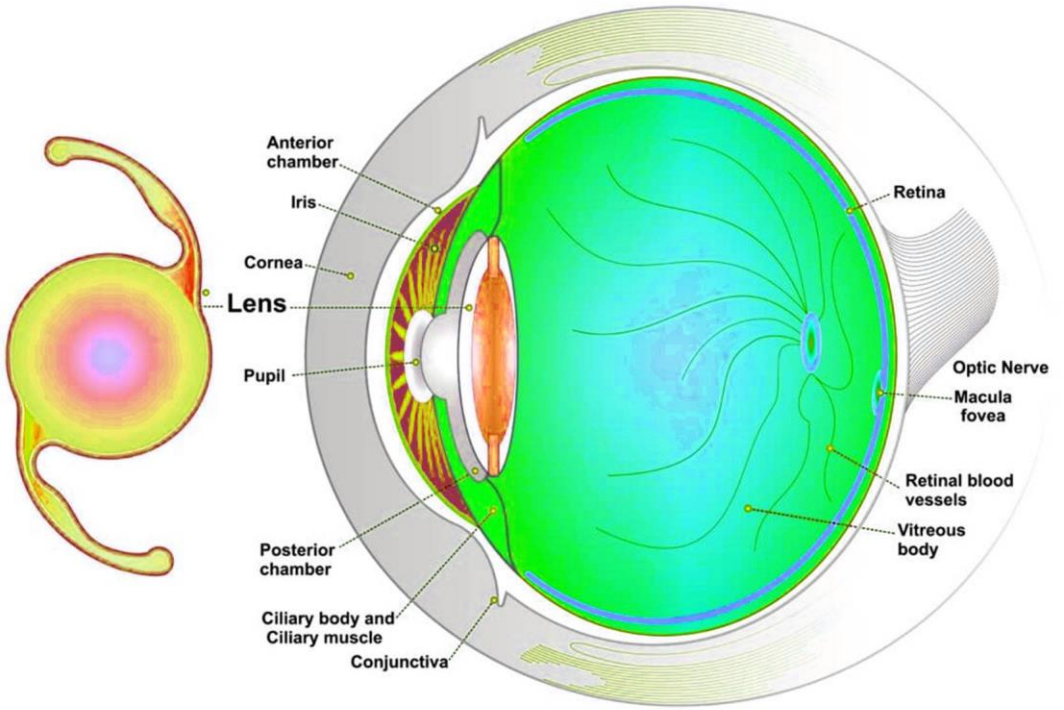



Figure 1 (https://midwesteyecenter.com/lasik-alternatives-and-vision-correction-options/)
Various protective mechanisms within and around the lens play a vital role in maintaining the stability of soluble crystallins. The acetylation of N-terminal residues in β- and γ-crystallins renders these lens proteins inherently resistant to exopeptidases[18]. Additionally, the acetylated N-terminal residues of α-crystallin subunits are sequestered inside high-molecular-weight α-crystallin aggregates, making them inaccessible[21]. This prevents the heat-induced precipitation of β- and γ-crystallins. α-Crystallins also function as molecular chaperones, sequestering misfolded proteins to mitigate widespread protein aggregation[18].

The thermogradient across the anterior segment of the eye, with its 2°C lower temperature than the core body temperature due to the corneal evaporative cooling and its unique vascular distance, reinforces the stability of crystallins[22]. Moreover, the sophisticated ion homeostasis regulation mediated by Na+/K+ ATPase and Ca2+ ATPase, along with gap junctions and aquaporin channels in the pre-equatorial epithelium, contributes significantly to preserving the structural integrity of lens crystallins[23].

As the majority of the lens is composed of organelle-free inner fibers, metabolic activity is limited, and oxygen levels are reduced in the lens's central region, ultimately promoting the stability of lens proteins. [24]. In fact, reports indicate that the concentration of oxygen in the lens nucleus can be remarkably low, measuring less than 10 µM in mammalian lenses[25].

**Table 2. Crystallins identified in human lens**

| Protein | Size (Da) | Residues | ΔG (kJ/mol) | Gene | Chromosomal location | References |
|---|---|---|---|---|---|---|
| **αA** | 19 909 | 173 | 27 | CRYAA | 21q22.3 | [18] |
| **αB** | 20 159 | 175 | 21 | CRYAB | 11q23.1 | [18] |
| **βA1** | 23 191 | 198 | - | CRYBA1 | 17q11.2 | [19] |
| **βA2** | 21 964 | 196 | - | CRYBA2 | 2q35 | [19] |
| **βA3** | 25 150 | 215 | 58 | CRYBA1 | 17q11.2 | [19] |
| **βA4** | 22 243 | 195 | - | CRYBA4 | 22q12.1 | [20] |
| **βB1** | 27 892 | 251 | 67 | CRYBB1 | 22q12.1 | [20] |
| **βB2** | 23 249 | 204 | 49 | CRYBB2 | 22q11.23 | [18] |
| **βB3** | 24 230 | 211 | – | CRYBB3 | 22q11.23 | [18] |
| **γC** | 20 747 | 173 | 36 | CRYGC | 2q33.3 | [18] |
| **γD** | 20 607 | 173 | 69.4 | CRYGD | 2q33.3 | [19] |
| **γS** | 20 875 | 177 | 43.9 | CRYGS | 3q27.3 | [20] |

**Mechanisms Associated with Cataract formation**

Cataract formation primarily involves two mechanisms. The amino acid tryptophan in the lens absorbs UV radiation, forming N-Formyl Kynurenine. This can combine with 3-OH Kynurenine and riboflavin, acting as photosensitizers. When they absorb light, electrons are released and react with oxygen, forming superoxide anion radicals. These radicals can affect the $Na^+$ $K^+$ ATPase pump in the eye, potentially leading to eye swelling and lens opacification [26].

An additional mechanism involves cysteine oxidation, leading to disulfide bond formation among crystalline proteins. This produces insoluble aggregates, contributing to lens opacity [27]. The loss of transparency in cataract development stems from complex metabolic processes altering the refractive index. During cataractogenesis, Post-translational modifications of lens proteins occur, including oxidation, glycation, and others, promote aggregation, disrupt lens cell structure, and lead to opacification [28].

Apart from this some other pathway such as non-enzymatic glycation, oxidative stress and polyol pathway are also responsible for cataract development [29].

## INDUCTION OF CATARACT:

**Naphthalene induced cataract:** Naphthalene undergoes hepatic oxidation, generating an epoxide, then converts to stable naphthalene dihydrodiol, enzymatically proceeding to dihydroxy naphthalene. Yet, instable at physiological pH, 1,2-dihydroxy naphthalene autooxidizes to 1,2-naphthoquinone and H2O2. [30]**.**

**Glucocorticoid induced cataract:** Glucocorticoid cataract results in the formation of steroid adduct protein, induction of transglutaminase, and reduction of ATPase activity may lead to cataract. Steroid cataracts are produced by the activities of glucocorticoids and progressed by way of production of oxidative stress similar to other types of cataracts [31]**.**

**Selenite induce cataract:** Selenite cataract resembles human cataract in many ways such as vesicle formation, increased calcium, insoluble protein, decreased water–soluble proteins and reduced glutathione (GSH). However, selenite cataract shows no high molecular weight protein aggregation or increased disulfide formation and is dominated by rapid calpain-induced proteolytic precipitation, while senile cataracts may be produced by prolonged oxidative stress[32].

**Smoke induced cataract:** Cigarette smoke contains trace and heavy metals. The increased metal contents in lens cause lens damage by the mechanism of oxidative stress forming oxygen radicals, via metal catalysed Fenton reaction[33]

**Cataract induced by drugs:** Many drug abusers as well as various toxins may cause oxidative damage and interrupt the lens growth as they bind to sulfahydryl groups, including glutathione peroxidase and $Na^+$ $K^+$ ATPase, along with superoxide dismutase and catalase, which are responsible for the maintenance of clarity of the lens during oxidative stress[34].

**Selenite model of cataractogenesis:**

The sodium selenite cataract model is the most widely utilized experimental paradigm for senile nuclear cataracts in humans, as it partially recapitulates the pathophysiological features of this condition. This chapter will concisely summarize the methodological details of this model and attempt to elucidate the underlying mechanisms of cataract formation induced by sodium selenite[32].

**In vivo Experimental approaches**

Selenite-overdose cataracts in rats are a valuable tool for researchers to studying nuclear cataracts, as they are rapid and easy to produce.

Sodium selenite, a cataractogenic agent widely used in experimental studies since 1978[35], can induce cataracts in suckling rats with a single subcutaneous injection of 19-30 μM/kg body weight at 10-14 days of age, before the critical lens maturation period ends at 16 days [36].

Severe, bilateral nuclear cataracts develop within 4-6 days after selenite injection. Precursor stages include posterior subcapsular cataract (day 1), swollen lens fibers (days 2-3), and perinuclear refractile ring (day 3). Although the model is primarily used to study nuclear cataracts, a transient cortical cataract also develops in 15-30 days after injection, which subsequently resolves within several months. In contrast, the nuclear cataract is permanent [37].

Andreson et al. (1988) observed rapid development of a permanent nuclear cataract within 3-5 days after a single subcutaneous injection of sodium selenite at 30 μM/kg body weight in rats, followed by development and subsequent resolution of a transient cortical cataract 15-30 days after injection.

Selenite cortical cataract formation appears to arise from early epithelial damage that disrupts normal fibrogenesis and ion control, leading to water influx, cellular destruction, and opacity. Remarkably, selenite cortical cataract spontaneously resolves after several months, restoring the epithelium, outer cortex, and mid-cortex to near-normal conditions. The major mechanisms for this resolution likely include (1) extensive proteolysis to remove damaged proteins from the lens and (2) resumption of normal fibergenesis to replace lost fibers.[38]

**Mechanism of cataract formation induced by sodium selenite**

Several biochemical processes occur during the formation of selenite cataracts. These include alteration of epithelial metabolism, accumulation of calcium, calpain-induced proteolysis, crystallin precipitation, phase transition, and cytoskeletal loss[39].

As indicated above, in both experimental approaches, either in vivo or in vitro, sodium selenite manifests its effect on the lens by inducing primarily oxidative stress in lens tissue. However, its exact mode of action is still open to debate.[40] The formation of selenite-induced nuclear cataracts is hypothesized to be initiated by disrupted lenticular Ca2+ homeostasis, reduced ATP content, diminished GSH levels, elevated NADP/NADPH ratio, increased glycerol-3-phosphate, and DNA double-strandc breaks. Elevated Ca2+ activates m-calpain, causing substantial proteolysis of β-crystallin and α-spectrin, leading to lens opacity via phase separation in selenite-induced cataractous lenses. [41,42].

**Safety concerns of Sodium selenite**

Sodium selenite is a colorless, water-soluble salt of selenium. Sodium selenite can exist in two forms: anhydrous ($Na_2SeO_3$) and pentahydrate ($Na_2SeO_3(H_2O)_5$. The pentahydrate is the more common form. [32]

According to the Material Safety Data Sheet (Sigma), the intravenous LD50 of sodium selenite in rats is 3 mg/kg, while the cataractogenic dose is 2.4 mg/kg. At this dose, sucking rats do not show any noticeable side effects other than occasional skin lesions at the injection site. Sodium selenite is excreted in the urine, feces, and expired air. Because selenium is incorporated into tissue proteins, a significant portion of the administered dose remains in the cadavers. Therefore, animal handlers must take precautions when handling sodium selenite injection solutions, animal carcasses, and waste [43].

## Conclusion:

This review summarizes the various etiologies of cataracts. Although cataract has been the leading cause of preventable blindness worldwide for many decades, pharmacological strategies to mitigate, prevent, or cure this blinding disease have remained elusive. Senile cataracts caused by aging are the most common type of cataract. Other risk factors for cataracts include nutritional deficiencies, metabolic and genetic disorders, ultraviolet radiation exposure, and smoking.

Oxidative stress, a major contributor to cataractogenesis, is a key factor in the sodium selenite cataract model. The antioxidant properties of anti-cataract compounds tested using this model have elucidated most of their effects. Therefore, the model is relevant because selenite is a potent oxidant. Selenite-induced lens opacification may partially mimic oxidant exposures that are common in the human environment and/or occur under pathophysiological conditions.

Selenite cataract having many general similarities with human cataract, such as lipid membrane vesicle formation, elevated calcium levels, increased insoluble protein content, enhanced proteolysis, decreased water-soluble protein content, and reduced GSH levels. However, there are also some major dissimilarities, such as the absence of high-molecular-weight covalent aggregates and increased disulfide formation in selenite cataract. Selenite cataract appears to be dominated by rapid calpain-mediated proteolytic precipitation, while human senile cataract is thought to be caused by oxidative stress over a prolonged period.

Overall, the selenite cataract model is a useful biological model for initial drug testing, as it recapitulates many of the key features of human cataract. However, it is important to keep in mind the important differences between the two models when scaling up the results of drug testing.

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