

In Search of a “Natural” Treatment of Cataract

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In cataract, opacification of the lens reduces visual acuity, finally leading to blindness if untreated. Cataract is the leading cause of blindness worldwide – there are about 50 million blind people in the world and cataract formation is the cause in half of these cases [1].

Today, cataract is treated by surgery. The cost of the surgery places it beyond the reach of individuals in many parts of the world and there is an urgent need for less expensive, non surgical approaches to cataract treatment [2]. It was estimated that extra-capsular surgery used with 95% coverage of the population would avert more than 3.5 millions disability-adjusted life years (DAILY) per year globally [3]. In 2008, a study showed that the mean total cost of the operation per patient was €714 (SD = €57) and ranged from €437 in Denmark to €1087 in Italy [4]. The financial encumbrance is enormous considering that 28,000 new cases are reported daily [5]. Thus, pharmaceutical interventions that will maintain the transparency of the lens are intensively sought after.

Clearly, to develop such treatments, a precise understanding of the underlying pathophysiological mechanism of cataract formation is required. There are three discrete categories of cataract: the “age-related”, that is associated with aging, “congenital cataract” that is present at birth indicating pathological changes during embryonic development of the lens, and “sugar cataract” which is associated either with diabetes mellitus [6-8] or galactosemia [9].

Sun light and oxygen, that the lens is exposed to, are associated with extensive damage to proteins and other constituents of the tissue. Other risk factors include environmental stress factors such as smoking, excessive UV-light exposure and electromagnetic radiation, life threatening diseases like coronary heart diseases [8], renal failure and many drugs [7]. These factors contribute to the depletion of antioxidants [e.g. vitamins C and E, carotenoids and glutathione (GSH)] and reduction of antioxidant enzymes [e.g. superoxide dismutase (SOD), catalase (CAT) and glutathione reductase/peroxidase (GSR/GPx)]. Furthermore, they may diminish protease (i.e. caspase, nuclease) activity, whose role is the second level of defense (e.g. removal of obsolete proteins).

Diabetes mellitus is another important risk factor. Hyperglycemia induces oxidative stress through a complicated pathway. Evidently, during hyperglycemia the accelerated flux of sorbitol through the polyol pathway and enhanced oxidative stress are implicated in the pathogenesis of secondary diabetic complications, such as cataractogenesis [10]. Aldose reductase (AKR1B1) catalyzes the first and rate-limiting step of the polyol pathway of glucose metabolism.

Several biochemical mechanisms are involved in the opacification of the lens and they have been thoroughly described: i) non enzymatic glycation, ii) oxidative stress, iii) polyol pathway and iv) activation of calpain proteases. The established feature of cataract is the major structural modifications of the water soluble crystallins [11]. Ageing process, diabetes and oxidants lead to impaired membrane function, which results to pathologically elevated levels of intracellular Ca²⁺ [12,13]. Under these conditions, calpains (calpain 1 or μ -calpain, Lp85, calpain 2 or m-calpain, calpain 10 and Lp82) are over activated and the resulting deregulated proteolysis of soluble crystallins leads to

their insolubilization and aggregation. Over activated calpains also degrade the cytoskeleton proteins, which can further elevate Ca²⁺ [14]. The above mechanisms compromise lens transparency and induce cataractogenesis. There are numerous models for *in vitro* and *in vivo* study of cataractogenesis. At *in vitro* experiments, cataractogenic agents such as galactose, glucose, naphthalene, selenite, transforming growth factor- β , methylglyoxal are added to the lens culture. The *in vivo* models include induction of cataractogenesis especially in rodents through streptozotocin-induced diabetes, galactose feeding, ionizing radiation, inhibition of cholesterol synthesis, steroid treatment, and administration of selenite overdose inducing oxidative stress [5].

Over the last decade, an increasing number of studies indicates the possible role of some plant extracts or isolated agents against cataract formation. Plant extracts, like extract of *Ocimum sanctum* [15], aqueous garlic extract [16], onion juice [17], as well as fraction of flavonoids extracted from *Emilia sonchifolia* [18], polyphenolic compounds of *Camelia sinensis* [19] and natural products such as curcumin [20], ellagic acid [21], luteolin [22], acetyl-L-carnitine [23,24], lycopene [25], resveratrol [26] have been proved to ameliorate selenite-induced cataract formation by enhancing antioxidant enzyme activity and inhibiting radical formation and lipid peroxidation. Additionally to their antioxidant potential, some plants or their compounds exhibit anticataract action via maintaining Ca²⁺-ATPase, prevention of Ca²⁺ accumulation, thus inhibiting calpain activation. Such compounds are drevogenin D, an aglycone triterpene [27] and the flavonoid fraction extracted from *Vitex negundo* [28]. Furthermore, it has been found that the carotenoid, astaxanthin, delays lens crystallin precipitation [29], whereas ellagic acid prevents the alteration of lenticular, non-crystallin proteins [30].

Diabetic cataract and the possible preventing properties of some plants extracts or compounds have, also, been studied, but not as thoroughly as the selenite model. *Zingiber officinalis* (ginger) extract [31], *Allium sativum* methanolic extract [32], turmeric and curcumin [33] inhibited the polyol pathway and the advanced glycation of proteins, and protected lens antioxidant enzymes in streptozotocin-induced cataract model. Hydroxytyrosol and oleuropein from olive leaves, as well as caffeine protected lenses from oxidative stress in an alloxan- and a galactose-induced cataractogenesis model, respectively [34].

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An increasing number of herbal extracts is documented to have anticataractogenic potential; whether the tested doses and dosage schemes can be translated in effective agents that will prevent cataract formation in humans is widely discussed. Most studies focus on the antioxidant properties of the natural products. Thus, members of the polyphenol family, i.e. flavonoids, galloyl glycosides, caffeoylquinic acids, known for their antioxidant properties are privileged candidates for development of efficacious preventive agents. Beyond this approach, Babizhayef et al. [35-37] have shown that a natural histidine dipeptide can prevent and reverse cataract. N-acetylcarnosine has been used in several clinical studies as eye drops, in order to assess its ability to treat senile cataract. First results were encouraging, so Innovative Vision Products Inc. (INV) scientists developed the lubricant eye drops Can-C, designed as 1% N-acetylcarnosine (NAC) prodrug of L-carnosine and tested in 75 symptomatic patients 54-78 years old for 9 months. That small-scale study showed that NAC is safe and efficacious for prevention and treatment of senile cataract for long-term use.

The use of "omics" technologies might reveal new molecular targets and, thus, specificity in pharmacological targeting might reveal more effective therapeutics. Inhibition of aldose reductase is the commonest target in order to combat diabetic cataract. Previous studies using normal rats, dogs and mice have identified that AKR1B1 inhibitors are potential drugs to prevent high glucose- and galactose-induced cataracts. Nonetheless, the clinical utility of AKR1B1 inhibitors remains uncertain [38]. Another emerging molecular target is the lens calpains because calpain over activation is the convergence point of all implicated factors, i.e. ageing, diabetes, and oxidation. Among natural products, chalcones were indicated as calpain inhibitors in a recent *in vitro* study [39]. Besides that, the topical application as eye drops of those agents remains an attractive drug delivery means [35,40].

The screening of natural compounds for the identification of potent anticataract agents is a difficult and long-term goal. However, as far as cataract remains a significant public health problem and the only way of treatment is, the unprofitable for the society and for individuals, surgery operation, researchers have to keep seeking an agent that could prevent cataract formation. Nature has certainly arranged it for us.

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