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Role of *Morinda citrifolia* on Oxidative Stress Induced Cataract Formation

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ABSTRACT

This review examines the hypothesis that oxidative stress is an initiating factor for the development of cataract and describes the events leading to lens opacification. H2O2 at high concentrations found in cataract stage can cause lens opacification and produces a pattern of oxidation similar to that found in cataract. It is concluded that H2O2 is the major oxidant involved in cataract formation. This viewpoint is further supported by experiments showing that cataract formation in organ culture caused by superoxide radical, H2O2, and hydroxyl radical is completely prevented by the addition of Morinda citrifolia juice because of its phytochemical constituents mainly flavonoids having anti-oxidant activity.

KEYWORDS : Oxidative stress, Morinda citrifolia, lens epithelial cells, reactive oxygen and nitrogen species, cataract formation, and Divine noni.

Oxidative stress:

The term oxidative stress describes a significant imbalance between the formations of free radicals and the body's antioxidant defence and repair systems. It describes that it is an imbalance between oxidants and antioxidants in favour of oxidants (Sies, 1985). Generally the energy needs for complex organisms require higher amounts of ATP. The supply of ATP depends heavily on redox chemistry, as it is driven by changes in free energy associated with electron or hydrogen transfers. Redox signaling is the concept that electron-transfer processes play a key messenger role in biological systems. At the heart of redox signaling are the so-called reactive Oxygen species (ROS), a term that includes oxygen radicals and also nonradical derivatives of O_2 (H_2O_2). The discovery of the reactive nitrogen species expanded this term to reactive oxygen and nitrogen species (RONS) they are:

1. Reactive oxygen species:

(a). Radical form - Superoxide, hydroxyl, peroxyl, alkoxyl, hydroperoxyl

(b). Non radical form - Hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), ozone (O_3), singlet oxygen, peroxynitrite.

2. Reactive nitrogen species:

(a). Radical form - Nitric oxide, nitrogen dioxide

(b). Non radical form - Nitrous acid (HNO_2), dinitrogen trioxide/tetroxide (N_2O_3/N_2O_4), nitronium (nitryl) ion (NO_2^+), peroxynitrite ($ONOO^-$), alkyl peroxynitrite (ROONO), nitroxylanion (NO^-), nitrosyl cation (NO^+), nitryl chloride (NO_2Cl).

Free radicals contain one or more unpaired electrons. Since all molecules seek to be balanced, that is, to have an equal number of protons and electrons, the unpaired electron spins of these radicals make them highly reactive.

Reactive oxygen and nitrogen species are produced continuously by the mitochondria (O_2 K$^-$, H_2O_2) of most cells and also by cytochrome P450 (O_2 K$^-$ and H_2O_2), macrophages (O_2 K$^-$, H_2O_2), and peroxisomes (H_2O_2). Given the high reactivity of RONS, it is not surprising that the cell has invested heavily into an antioxidant defense system to contain RONS. This defense system includes:

a. Classic antioxidant enzymes, such as superoxide dismutase (SOD), catalase, glutathione (GSH) peroxidase, glutaredoxin, and thioredoxin. These enzymes are distributed in mitochondria, peroxisomes, and cytoplasm.

b. Non classic antioxidant enzymes, for example, Haem oxygenase-1.

c. Phase II detoxifying enzymes, recently shown to be protective, such as GSH reductase, and GSH transferase.

d. Non enzymatic antioxidants, such as vitamins E and C, and catechins (Rigas and Sun, 2008). In addition to these well described anti-oxidant enzymes, a novel class of peroxide scavengers, termed peroxiredoxins has been isolated, and is thought to be the chief H_2O_2 removal system within the brain (Rhee et al., 2005). Thus if the production of ROS increases too quickly, the endogenous antioxidant defense system of the brain appears to be easily overwhelmed. In order to maintain tight homeostatic control of ROS and prevent oxidative stress, external supplementation with dietary antioxidants or herbal preparations may prove useful (Singhal et al., 2012).

Cataract:

Cataract derives from the Latin cataracta meaning "waterfall"

The eye is able to see in bright or dim light, but it cannot see objects when light is absent

The eye consists of these parts

- Conjunctiva: external cover of the sclera is to keeps the eye moist.
- Cornea: transparent c overing of the front of the eye. It allows for the passage of light into the eye and functions as a fixed lens.
- Sclera: a tough white layer of connective tissue that covers the entire eyeball except the cornea.
- The iris regulates the size of the pupil.
- Choroid: thin, pigmented layer lining the interior surface of the sclera. Prevents light rays from scattering and distorting the image.

· Retina: lines the interior surface of the choroid.

Photoreceptors of the retina.
Rod cells - light sensitive but do not distinguish colours.

Cone cells - not as light sensitive as rods but provide colour vision

Three types of cone cells each with unique photopsin (Red cones, Green cones and Blue cones that is RGB cones). The lens and ciliary body divide the eye into two cavities.

a. The anterior cavity is filled with aqueous humor produced by ciliary body.
b. Behind the lens the cavity is filled with a gel like structure called vitreous humor.Cornea, lens, aqueous humor, and vitreous humor all play a role in focusing light onto the retina. Cataract occurs when there is a build-up of protein in the lens that makes it cloudy. This prevents light from passing clearly through the lens, causing some loss of vision. Cataract, characterized by cloudiness of the eyelens, is one of the earliest secondary complications of diabetic patients(McCarthy and Taylor, 1996; Pollreisz and Schmidt-Erfurth,2010).

Causes of cataract include Various factors such as diabetes, oxidation of lens, dehydration, daylight, diet and lipid-peroxidation which leads to the generation of lens opacification in elderly persons.

Other risk factors such as smoking, environmental factor, lack of consumption of antioxidants, nutritional deficiency and diabetes can also increase the development of cataract. Excessive sorbitol are gradually increased during cataract formation in the lens fibre and consequent osmotic stress. Sorbitol is synthesized from aldose reductase utilising the NADPH and does not cross the cell membranes; it can accumalate in the cells and can cause cell damage due to disturbing osmotic homeostasis. Deficient glutathione is another mechanism behind the formation of cataract. In catract reduced glutathione levels were found to be significantly in low concentration when compared to normal eye (Thiagarajan et al., 2003).The constituents of the young lens differ chemically from the older lens. The differences between young and old lenses are a result of three major processes. First, there are the post translational changes in protein in the inner region of the lens where protein synthesis is insignificant and particular protein macromolecules have been present for many years (Spector, 1995) .All the older cells are compacted into the centre of the lens resulting in the cataract. The lens is made mostly of protein and water sitting right behind the coloured iris and pupil. Protein molecules of the lens are arranged in such a way so as to keep it transparent and allow visible light to pass through it onto the retina. The lens also adjusts the eye's focus, allowing images to be seen clearly from both near and far away. Once this light reaches the retina, it is changed into nerve signals that are sent to the brain and interpreted as sight. For the retina to get a sharp image, the lens must be clear, otherwise vision becomes blurry.

Oxidative stress is one of the major risk factors for senile Cataract (Truscott, 2005). Oxidative stress results in lens opacification both in experimental animal models (Varma et al., 1995; Spector et al., 1995) and in cultured lens (Gupta et al., 2003), (Csukas et al., 1987) systems. H_2O_2 is one of the physiologically relevant oxidants in the lens and in the aqueous humor (Spector, 1981). Levels of H_2O_2 in the aqueous humor of individuals with cataracts are higher than those in the aqueous humor of normal individuals (Bhuyan et al., 1986). Cataracts can be treated if your vision can be corrected to an acceptable level with a change in prescription, eyeglasses, including bifocals or contacts, may be prescribed, eliminating the need for surgery at that time. If the vision loss cannot be corrected with new glasses then there will be a requirement for cataract surgery, which involves removing the clouded lens and replacing it with a clear, artificial one. Cataract surgery usually includes two types of eye surgery. Either extra capsular cataract extraction (ECCE) or intra capsular cataract extraction (ICCE). ECCE surgery consists of removing the lens, but leaving the majority of the lens capsule intact. High frequency sound waves (phacoemulsification) are sometimes used to break up the lens before extraction. ICCE surgery involves removing the lens and lens capsule, but it is rarely performed in modern practice. In either extra capsular surgery or intra capsular surgery, the cataractous lens is removed and replaced with a plastic lens (an intraocular lens implant) which stays in the eye permanently.

Morinda citrifolia*:*
Morinda citrifolia L. is commonly known as Great *Morinda*, Indian mulberry, Beach mulberry and noni. The noni fruit has been used in tropical regions as both Food and folk medicine. The recent use of *M.citrifolia* as a dietary supplement has increased greatly and is reported to have a broad range of therapeutic effects, including antibacterial, antiviral, antifungal, antitumor, anthelminthetic, analgesic, hypotensive, anti-inflammatory, and immune enhancing effects. Chemical constituents of *M.citrifolia* are glycosides, alkaloids, flavonoids and many more bioactive compounds (Peter, 2007; Morton, 1992; Farine et al., 1996; Peerzada et al., 1990; Moorthy and Reddy, 1970; Singh and Tiwari, 1976; Simonsen, 1920; Wang et al., 1999; Solomon, 1999). Scopoletin – has antibiotic activity. Beta-sitosterol – has potential for anti-cholesterol activity. Damnacanthal – an anthraquinone having potential as an inhibitor of HIV viral proteins. Other components being octoanoic acid, potassium, vitamin C, terpenoids, Alkaloids, anthraquinones (such as nordamnacanthal, morindone, rubiadin, and rubiadin,methyl ether, anthraquinone glycoside), carotene, vitamin A, flavone glycosides, linoleic acid, Alizarin, amino acids, acubin, L-asperuloside, caproicacid, caprylic acid, ursolic acid, rutin, and a putative proxeronine. *M.citrifolia* is the rich source of antioxidants. The high anti-oxidant property of *M.citrifolia* helps to prevent the formation of cataract. And it was hypothesized that the antioxidants in *M.citrifolia* may have cataract preventive effects by scavenging reactive oxygen free radicals. And many Fruits and vegetables constitute the major sources of carotenoids in human diet (Mangels et al., 1993; Jhonson, 2002). Three new glycosides as listed below were isolated from *M.citrifolia* (Rangadhar Satapathy, 2007).1. 6-O- (beta-D-glucopyranosy) -1-O-octanoyl-beta-D-glucopyranose,2. 2. 6-O- (beta-D-glucopyranosy) -1-O-hexanoyl-beta-D-glucopyranose,3. 3-methylbut-3-eny16-O-beta-D-glucopyranosyl-beta-D-glucopyranoside.Chemical constituents of *M. citrifolia* have led to the isolation of about160 compounds(Cimanga et al., 2006; Siddiqui et al., 2003; Sang et al., 2001; Deng et al., 2007; Dalsgaard et al., 2006; Samoylenko et al., 2006; Bui et al., 2006; Pawlus et al., 2005; Liu et al., 2001; Wang and Su, 2001; Dittmar, 1993; Heinicke, 1985). Americanin, Loganic acid, Rhodolatouside and 4-Ethyl-2-hydroxysuccinate (Yang Xiao et al., 2009) are some of the chemical constituents of *M. citrifolia* seeds.

1,3-dimethoxyanthraquinone,1,2-dihydroxyanthraquinone,morinaphthalenone, hydroquinone, scopoletin, 1,8-dihydroxy-6-methoxy-3-methyl-9-anthrone, 2,4-dimethoxy-9-anthrone, morindafurone, morinaphthalene, 3,3′-bisdemethylpinoresinol, americanol A, morindolin and isoprincepin are the major constituents of the *M.citrifolia* fruit.

Xeronine:
It is very important alkaloid present in *M.citrifolia*. It is a relatively small alkaloid which is physiologically active in the picogram range. Pro-xeronine is the precursor of xeronine, it is an inactive compound and requires catalytic activity to convert a biologically inactive compound into an active form called xeronine (Heinicke and Levand, 1968; Heinicke, 1957). Xeronine belongs to the alkaloids, small but physiologically active. Proxeronine works by wrapping itself around the enzyme present in our intestine known as proxeronase. Thus xeronine, by converting the body's procollagenase system into a specific protease, quickly and safely removes the dead tissue from burns. Because of this reason noni is effective in the treatment for burns. Proxeronase joins the two club-like ends of the proxeronine together and then cuts off the useless chain. The remaining conjoined club-like parts combine with serotonin to make xeronine (Heinicke and Levand, 1968; Heinicke, 1957).Xeronine has the capability to modify the molecular structure of proteins and this is indeed an essential mechanism for many biological activities. The binding of protein compounds in our body require specificity in order to work efficiently. The role of xeronine is to order the protein in our body to fold into proper conformation to work correctly. It is encouraged to increase intake of fruits such as *M.citrifolia* that is packed with pro-xeronine because of its many health benefits to monitor and help to correct problematic proteins due to incorrect Folding or conformation.

Conclusion:

Based on literature review oxidative stress is the cause of many diseases particularly in cataract. Not only proxeronine *M.citrifolia* also contains many other bioactive compounds like Vitamin C, Vitamin E, Scopoletin, Damnacanthal, Quercetin and many more compounds. To conclude, it can be said that the highest scavenging activity of noni fruit juice makes it unique as a wellness drink. Hence it can be used as a food supplement for prevention of cataract and other oxidative stress related diseases.

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