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AMALAKI RASAYAN AS ANTIOXIDANT IN DIABETIC RETINOPATHY –REVIEW

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ABSTRACT

Diabetic retinopathy is a disease resulting from diabetic chronic hyperglycemia characterized by microvascular complications in the retina, where neuronal elements responsible for vision are located. It is the main cause of adult blindness in developed countries. Oxidative stress has been widely regarded as the key factor for the emergence of ocular disease and has been involved in increased vascular permeability, disruption of blood-retinal barrier, apoptotic loss of retinal capillary cells, microvascular abnormalities and retinal neovascularization. Dietary supplementation with antioxidants has been related with inhibition of diabetes-induced abnormalities of retinal metabolism, reduction of apoptosis and partial restoration of pericytes. Moreover, the use of antioxidants to treat or delaying oxidative stress-related ocular manifestations is still poorly explored, while current diabetic retinopathy therapy includes invasive methods, like surgery. Ocular antioxidant potential therapy represents a non-invasive, safe and less painful methodology, which slows the natural progress of the disease and improves the effectiveness of treatment without significant systemic toxicity. This review underlines the innovative medicines exploited for ocular conditions, a further insight on ocular delivery and, additionally, offering new potential applications of antioxidants for the prevention, treatment and control of diabetic retinopathy.

KEYWORDS: Diabetic retinopathy; oxidative stress; Antioxidant properties of amalaki rasayan.

INTRODUCTION

Diabetes mellitus (DM) long-term complications are progressive and almost resulting by chronic exposure to high blood levels of glucose resulting from defects in insulin metabolism and dysfunction in carbohydrate, lipid and protein metabolism. The diabetes complications are equally associated with the both types of DM. However, the severity of the disease is related to the longterm exposure to uncontrolled glycemia. The incidence of DM, especially in industrialized countries has dramatically increased over the past two decades and it is expected to increase in future. This disease has become one of the most challenging health problems of the 21st century. It affects more than 230 million people worldwide, and this number is expected to reach 350 million by 2025. Globally the affected people are unaware of the disease and only half receive adequate treatment. It is therefore not surprising that diabetic retinopathy (DR) is the leading cause of blindness in people aged 25-74 years worldwide.

MATERIAL AND METHODS

The vascular commitment is the most serious and common condition in DM. Mediators of vascular damage of DM include poor glycemic control, lipoprotein abnormalities, hypertension, oxidative stress (OS), inflammation and advanced glycation end-products (AGEs), which are modified proteins formed by nonenzymatic glycation. Pathological vascular dysfunction related with DM include DR like all diabetes conditions, is a progressive disease caused by chronic exposure to hyperglycemia, and recognized as a characteristic vascular disease, diabetic nephropathy (kidney) and diabetic neuropathy (peripheral nervous system). There is also evidence that hyperglycemia may induce diabetic angiopathy through the generation of OS, *per se,* or through the accumulation of AGEs, leading to nitrous oxide systems (NOS).

Retinopathy is characterized by increased vascular permeability, by vascular closure mediated by the formation of new blood vessels— neovascularization, on the retina and posterior surface of the vitreous. Generally, neovascularization results from occlusion of fragile capillaries and frequently originate pre-retinal and vitreous hemorrhage in case of vitreous detachment.

Without an effective medical treatment, cells and tissues of the retina become malnourished and progressively degenerate, which leads to damage in cells responsible for vision, leading to the inevitable loss of vision. Approximately 25% of patients with type-1 DM have

been shown to be affected with retinopathy, with the incidence increasing to 60% after 5 years and 80% after 10 to 15 years of affliction. The type-2 DM accounts for a higher proportion of patients with visual impairment. Moreover, in general there are more adult onset cases than juvenile ones.

However, more recently, much attention has been focused on the role of OS(OXIDATIVE STRESS), and has been suggested that this may constitute the cause of different pathogenesis in diabetic complications, such as DR.

The retina is highly susceptible to OS because of intense exposure to light and oxygen and its high polyunsaturated fatty acid (PUFA) content that is prone to lipid peroxidation. These oxidation products are toxic to the microvascular walls and therefore, may have a causal role in diabetic microvascular damage and also in the blood–ocular barrier alteration. Since OS is increased in the diabetic retina, the levels of oxidatively modified DNA and nitrosylated proteins are elevated, and antioxidant defense enzymes are impaired. It has been reported that the level of antioxidant enzymes along with potential antioxidant vitamins are decreased in diabetic experimental animals and humans. Due to this intimate relationship between OS and dysmetabolisms implicated in the pathogenesis of DR, the use of appropriate antioxidants may have potential on the metabolic and functional abnormalities in DR. Antioxidants may act at different levels, including the inhibition of the formation of reactive oxygen species (ROS), scavenging free radicals, or increasing the antioxidants defense enzyme capabilities. This suggests that potential management of diabetes could benefit from use of dietary or local biofactors of medicinal and aromatic plants. There is, therefore, research specificities to focus on the molecular mechanisms of action of the biofactors such as flavonoids, proanthocyanidins and alkaloids and/or extracts derived from plants .

Numerous drugs LIKE AMALAKI RASAYAN have been developed based on the current understanding of the complicated and intricate biochemical and pathophysiological aspects of the DR. However current therapy for DR includes laser photocoagulation, surgery, and metabolic control. Having this in mind this paper suggests the high potential of antioxidants AS AMALAKI RASAYAN to avoid the DR progression and consequent blindness.

Human cells protect themselves from free radical damage by enzymes like superoxide dismutase, catalase and compounds like ascorbic acid, glutathione, etc.

Amalaki Rasayana is one such herbal formulation prepared from *Phyllanthus emblica* Linn. (*Amalaki*) belonging to the family Euphorbiaceae. *Amalaki* is highly nutritious and is an important dietary source of Vitamin C, minerals and amino acids. Fruit also contains

phyllemblin and curcuminoides. The fruit contained 482.14 units of superoxide dismutase/g fresh weight, and exhibited antisenescent activity. The ascorbic acid content of the fruit has been assayed at approximately 1 g per 100 ml of fresh fruit juice and accounts for 45-70% of the antioxidant activity. The Ayurvedic process of preparing the *Amalaki Rasayana* results in a 3‑fold increase of ascorbic acid and an increase in the concentration of polyphenols. This procedure mixes dried fruit powder with fresh emblica juice for a few hours, and then the mix is dried and powdered again.

This process is repeated, making this method of fruit processing nutritionally beneficial.

This is the need of an hour to find out the possible reasons for such improved activity through differences in phamocognostical parameters. Till date, there is no reference regarding impact of *Bhavana* on the pharmocognostical parameters of *Amalaki*. Hence, for the present study an attempt has been made for the SAME.

Chemical Constituents
A good source of vitamin C; carotene, nicotinic acid, riboflavine, D‑glucose, D‑fructose, myoinositol and a pectin with D‑galacturonic acid, D‑arabinosyl, D‑xylosysl, L‑rhamnosyl, D‑glucosyl, D‑mannosyl and D‑galactosyl residues, embicol, mucic, indole acetic acid and four other auxins – a1, a3, a4 and a5, two growth inhibitors – R1 and R2; phyllembic acid and phyllembin (fruits) and fatty acids (seed oil); leucodelphinidin, procyanidin, 3‑0‑gallated prodelphinidin and tannin (bark); ellagic acid, lupeol, oleanolic aldehyde and 0‑acetyl oleanolic acid (root); tannins, polyphenolic compounds; 1,2,3,6‑trigalloyglucose, terchebin, corialgin, ellagic acid, alkaloids, phyllantidine and phyllantine (leaves and fruits). The dominant active constituent of Amalaki is a group of tannins derived from gallic and ellagic acids, which make up a large portion of the extractable non‑nutritive constituents.

Pharmacologically it has cardio‑protective action, hepato‑protective action, cholesterol‑lowering effect, anti‑diabetic effect, anti‑cancer effect and immuno‑modulatory effect.

Diabetic retinopathy
The major risk factors for DR are known to be predominantly the hyperglycemia and the increased duration of diabetes. Other risk factors include hypertension, hyperlipidemia, pregnancy, and microalbuminuria. All of these risk factors contribute and exacerbate retinal metabolic changes and microvascular injury that result in DR condition. Intensive glycemic control, like in other diabetes conditions, substantially reduces the incidence and progression of DR in type I and II diabetes, as well as blood pressure control. Evidences of a causal

relationship between insulin resistance and hypertension is increasing. It is also increasingly clear that antihypertensive medications have disparate effects on insulin sensitivity in patients with essential hypertension, which makes the administration of specific antihypertensive agents relevant in these patients.

Abnormalities in retinal metabolism, including elevated polyol pathway activity, increased nonenzymatic glycation, accumulation of AGEs, uncontrolled OS, protein kinase C activity (PKC) and the expression of vascular endothelial growth factor (VEGF), result from glucose dysmetabolism and evidently also contribute to the development of retinopathy. However the exact mechanism is still elusive.

The initial disease is characterized by increased vascular permeability due to a breakdown in the blood-retinal barrier (BRB), which causes macular edema, with a progressive vascular occlusion and retinal neovascularization.

Medical diagnosis, support, advices and treatment are fundamental, to avoid the malnourished and degenerative retinal cells/tissues, which leads to damage in the cells responsible for vision. The clinical profile of this condition is chronologically subdivided in two stages, nonproliferative (NPDR) and the proliferative diabetic retinopathy (PDR). NPDR is the initial stage of the disease progression.

Loss of retinal capillary pericytes and endothelial cells has been demonstrated early in diabetes and underlies the clinical signs of NPDR, which include intra-retinal dot-blot hemorrhages, microaneurysms, and venous beading. At this stage, blood and fluid leak from the blood vessel into the retinal tissue, resulting in retinal swelling and the formation of lipoprotein exudates deposits. When neuronal cells in the retina begin to be compromised the process of neurodegeneration begins and culminates in more advanced stages of diabetic retinopathy.

The retinal edema is asymptomatic, if it occurs outside of the macula, but will impair vision when the macula is affected.

With progression of the disease to moderate or severe NPDR, blood vessels may be blocked in the retina, which, in turn, causes ischemia, hypoxia and deprival of nutrient nourishment in the affected area.

This blockade subsequently leads to pathologic growth of new blood vessels, which often causes catastrophic loss of vision and featuring the main serious stage of the disease - PDR.

The occlusion of capillaries in retinopathy induces angiogenesis in the afflicted retina, leading to the release of VEGF and insulinlike growth factor (IGF), which induce growth of new vessels on the optic disk, iris, retinal surface and into the vitreous, known as retinal neovascularization. New blood vessels are fragile and may hemorrhage into the vitreous or form fibrous bands, causing tractional retinal detachment. Neovascularization of the iris may occlude aqueous outflow, resulting in neovascular glaucoma. New vessels are sometimes accompanied by a fibrovascular ridge extending into the vitreous cavity or along the surface of retina. As microvascular damage weakens the BRB, plasma leaks from vessels into the retina; when this fluid is reabsorbed, lipid and lipoprotein elements are retained in the retina and are visible as yellow exudates. Thus, retinal detachment may occur and lead to vision loss and blindness. These features are detectable by ophthalmoscopy, because the pigment (hemoglobin) in blood or the lipid exudates stand out in contrast to the otherwise transparent retina. These changes have led to the general assumption that DR is solely a microvascular abnormality.

Most patients with DR are asymptomatic until very late.

Oxidative stress clinical impairment
In diabetes, the retina exhibit increased OS since the eye is constantly subjected to light irradiation, atmospheric oxygen, environmental chemicals, and physical abrasion. The retina has also a natural high content of PUFA and possess the highest oxygen uptake and glucose oxidation relative to any other tissue, which makes it more susceptible to OS than other organs or structures. All these factors, if not controlled induces can ultimately contribute to ocular surface damage and disease. Natural protective components like water-soluble antioxidants (e.g., vitamin C, L-cystine, reduced glutathione - GSH, uric acid, pyruvate, and tyrosine), lipid-soluble antioxidants (e.g., tocopherols and retinols), and highly specialized enzymes (e.g., superoxide dismutase - SOD, catalase, and Gluthathione peroxidase - GPx) have all been identified in human tear fluid collected at normal and stimulated secretion rates. These components are thought to serve as a frontline defense for the ocular surface tear film and underlying tissues. However, mechanisms or glandular sources of these antioxidants have not been identified.

So it can be clearly assumed that OS and ROS maybe a causal link between elevated glucose and the important metabolic abnormalities in the development of DR.

Free radicals are defined as an atoms or molecules that contain one or more unpaired electrons, making them unstable and highly reactive. ROS are produced continuously in all cells to support normal cellular functions. Under normal physiological conditions, approximately 0.1%–5% of oxygen that enters the electron transport chain is reduced to superoxide, ROS and the rest is used in metabolic processes. ROS can also be generated from other sources including cytochrome P450, the NAD(P)H oxidase(s) and Nitric Oxid (NO) synthases.

Excess production of ROS originated from endogenous or exogenous sources, and/or inefficient removal by scavenging system of ROS, can result in excessive levels of either molecular oxygen or ROS, thus resulting in increased OS, which often leads to damage of cellular macromolecules and destruction of small antioxidant molecules. These events are central to the pathogenesis of diabetes and its complications. Major ROS include superoxide, peroxynitrite, NO and a combination of superoxide and NO.

These ROS oxidize proteins, lipids (lipoxidation), and carbohydrates (glycoxidation). The resulting oxidized molecules can cause further oxidative damage to cells leading to structural and functional changes of cellular organelles, especially when oxidized molecules accumulate intracellularly.
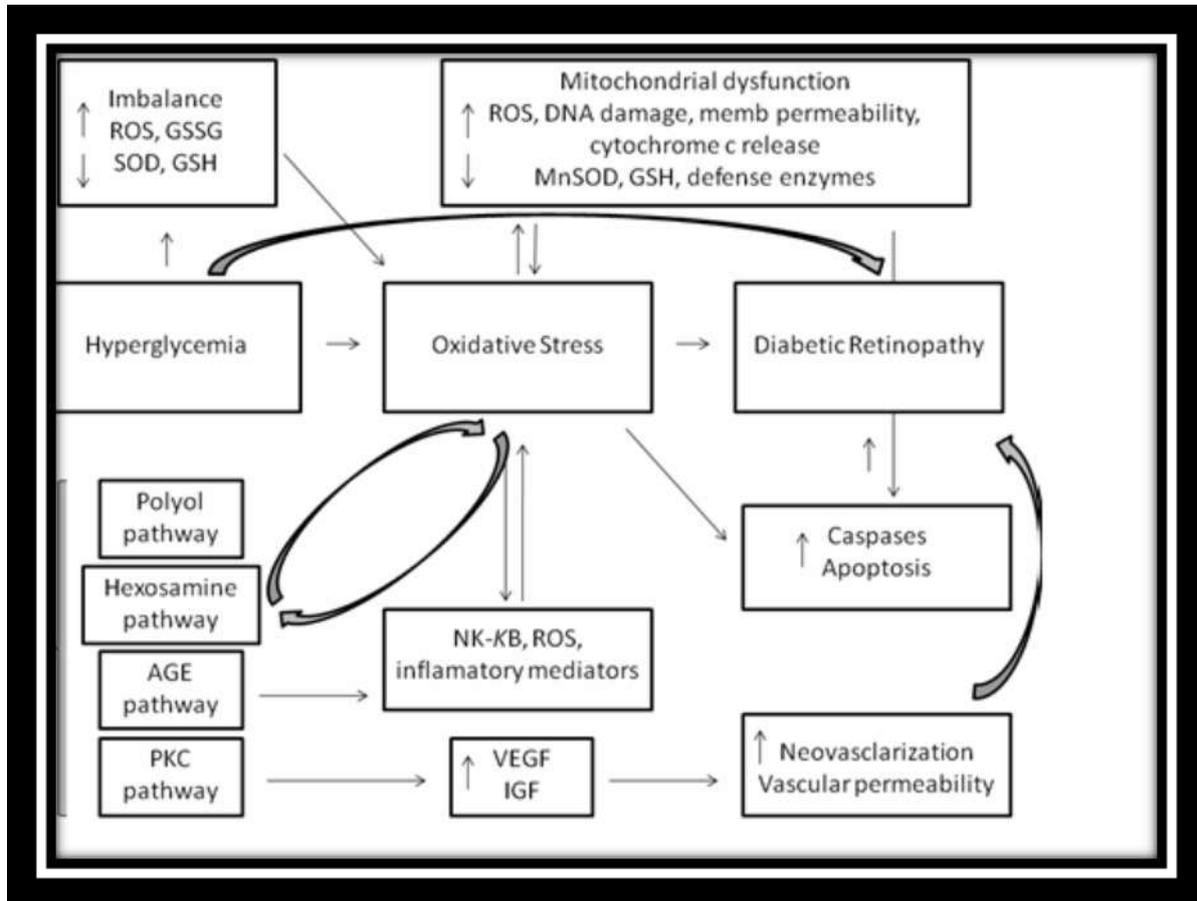
OXIDATIVE STRESS CYCLE
In retinopathy, OS has been widely involved in decreased retinal blood flow, increased vascular permeability, disruption of BRB and the appearance of acellular capillaries from the apoptotic loss of retinal capillary cells. OS has also been linked to microvascular abnormalities in DR, degenerative process of retinal neovascularization, and the suppression of antioxidants systems.

RESULT AND DISCUSSION
Antioxidants may act at different levels, inhibiting the formation of ROS or scavenge free radicals, or increase the antioxidants defense enzyme capabilities. However, in the case of macrovascular/microvascular complications the antioxidant therapy is beneficial together with blood pressure control, management of dyslipidemia and optimal glucose control. Administration of AMALAKI RASAYAN AS antioxidants to diabetic is able to prevent the

development of retinopathy and also retinal metabolic abnormalities postulated to be involved in the development of retinopathy. Following positive results of the prevention of diabetes-associated vascular dysfunction in a diabetic rat model, high doses of vitamin E, the major antioxidant in lipid phase were studied in the clinic and found to restore retinal blood flow in diabetic type I patients to control levels. The potential benefit of vitamin C, has been shown in DR by its free radical scavenger activity outside the cell through nonenzymatic mechanisms. Studies in humans suggested that antioxidant therapy with vitamin C might normalize diabetic retinal hemodynamics. Trolox is a water soluble analog of vitamin E with potent antioxidant properties. Trolox is shown to partially prevent the loss of pericytes in diabetic via reducing membrane lipid peroxidation.

CONCLUSION
The use of AMALAKI RASAYAN AS antioxidants to treat or delaying oxidative stress-related ocular

manifestations is still unexplored, while current DR therapy includes invasive method like laser photocoagulation or surgery, which may also increase risk of endophthalmitis, cataract formation and retinal detachment. Besides the development of laser for DR, there have been no major advances in treatment for the disease, despite numerous clinical trials. MEDICINE directly ORAL represent a non-invasive and safe methodology, increasing the effectiveness of treatment and reducing toxicity associated with systemic administration.

An ideal anti-angiogenic agent should be developed for neovascularization control and regression. It may inhibit and stabilize the disease, to improve the vision loss and prevent retinal scarring and detachment with no toxicity as well as the formulation should be for long term drug delivery. Agents should also be classified into early and late acting, specific and non-specific, and reversible and irreversible. The understanding of where a drug falls into these classes may help in the comprehension of the potential and/or limitation of the drug when used in the clinic, as well as how to predict potential serious adverse events. Considering this, there are a number of challenges associated to the treatment of ocular diseases. In general, the major problem in ocular therapeutics is to maintain an effective drug concentration at the site of action for an appropriate period of time, in order to achieve the expected pharmacological response.

Polymeric adhesive nanoparticles have been utilized to enhance the performance of common drugs, increasing drug time retention, slow drug delivery, with a specific target while reducing systemic side effects compared with commercial aqueous eye drops. The smart symbiosis of these adhesive particles with a high potent antioxidant could be a hope for future therapies, considering the important effect of OS in the pathogenesis of DR. This therapeutic improvement is expected to offer real benefits in the stability, bioavailability, drug delivery and therapy of the diabetic patients. Thus, successful alternatives for ocular therapies are needed and they should provide non-invasive and a cost effective treatment reaching every economic STATUS.

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