

Anti-Diabetic Retinopathy Potential of Noni: The beneficial effect and possible mechanism

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Abstract

Noni (*Morinda citrifolia* L.) is being evaluated in laboratory research for its benefits as an antioxidant and immunity booster, as well as for its properties to prevent tumors and cure diabetes. The vast spread of Noni in tropical region of the globe, from America reaching to Africa and Southeast Asia, contributed in enhancing its usage and potency due to the diversity in harvest zone. Noni parts comprise fruits, seeds, leaves, and flowers are being used for individual nutritional and therapeutical values. Nevertheless, the fruit is widely characterized to contain the most valuable bioactive substances. On the other hand, diabetic retinopathy (DR) is a microvascular disorder impacting the small blood vessels in the retina, which includes microaneurysms, retinal hemorrhages, and hard exudates results from prolonged exposure to high blood glucose levels. The anti-diabetes effect of Noni extract and juice has been examined but the beneficial role of Noni and its potential mechanisms against the development of diabetic retinopathy phenotype is still ambiguous. This review, therefore, will discuss in details the pharmacological actions of *M. citrifolia* fruit, along with their isolated phytochemical compounds on diabetic retinopathy markers, through describing the conducted *in vitro* and *in vivo* studies as well as clinical data.

Keywords: noni; diabetic retinopathy; potential mechanisms; health benefits; bioactive compounds

Morinda citrifolia (Noni)

Morinda citrifolia L. generally recognized as noni, which is belonging to the Rubiaceae family. It is a small evergreen tree or shrub, native to the tropical zones of South Asia, Hawaii, islands of French Polynesia and Australia (Deng et al., 2008). The designation as *Morinda citrifolia* is referring to the botanical appellation that is initially resulting from the two Latin words “morus” imputing to mulberry, and “indicus” imputing to Indian [157]. In Hawaii *M. citrifolia* is known as Noni, while in India *M. citrifolia* is known as Indian mulberry and nuna, or ach. Malaysians refer to *M. citrifolia* as mengkudu whereas in Southeast Asia *M. citrifolia* is known as nhaut, but in Caribbean, *M. citrifolia* is known as the cheese fruit or painkiller bush (Chan-Blanco et al., 2006). Noni fruit are distinctly recognizable. White tube-shaped flowers are formed in collections on the early fruits. The syncarpous fruit develop to be approximately 5–10 cm in length long and roughly 3–6 cm wide-ranging in an elliptical form, fleshy having stamped form which transform from a green coloration to a glowing yellow to white coloration after complete ripping (Lachenmeier

et al., 2006; 156]. The fruit exterior is enclosed with multilateral segments which surrounded post flowered nectarines that continually function throughout fruit development (Dixon et al., 1999). Over 20 century, the plant has been recognized as a curative plant by Polynesians and Tahitians and is utilized for therapy. *M. citrifolia* fruit is usually utilized and consumed as a juice, even though the flower, leaves, root and bark also can be utilized in preparing traditional medicine (McClatchey, 2002; Wang et al., 2002). In recent times, the health claims associated *M. citrifolia* comprise of wide-ranging health benefits in individual having infections, hypertension, arthritis, cancer, pain, diabetes and asthma. *M. citrifolia* is described to possess wide-ranging therapeutic properties (Figure.1), which comprising of anti-inflammatory, analgesic, immune enhancing, antituberculous, antioxidant, antistress, antihypertensive, antiviral, anticancer, antiprotozoal, antibacterial, antifungal, and similarly tranquillizing characteristics. Nevertheless, the underlying mechanisms of these properties are still unidentified (Kumar et al., 2010; Krishnaiah et al., 2012). The numerous therapeutic profits of Noni are as a result of the phytoconstituents of the plant.

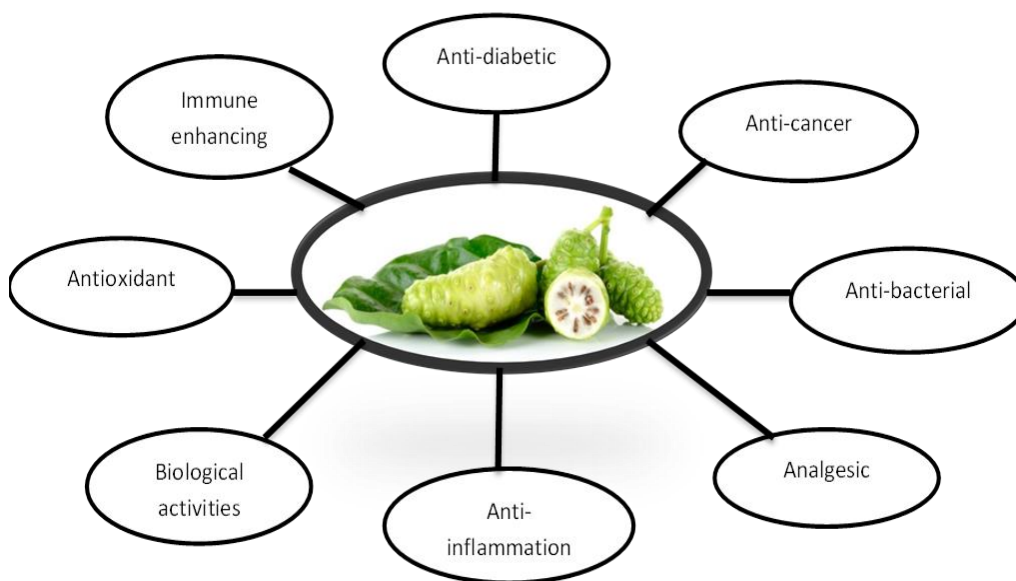


Figure 1. Therapeutic effects of *Morinda citrifolia* (Noni).

Phytochemical constituents of Noni fruit

Amongst the entire fruits evaluated till now, Noni fruit comprises one of the broadest collections of chemical constituents through having a minimum of 200 phytochemicals that includes phenolic compounds, alcohols, carbohydrates, organic acids, precursors, lignans, proteins, anthraquinones, alkaloids, vitamins, minerals, esters, fatty acids, glycosides, carotenoids and plant sterols [203, Motshakeri & Ghazali, 2015].(Table 1)

Malaysian medicinal plants book revealed that *M. citrifolia* chemical components are: 5,7-Acacetin-7-O-β-D(+)-glycopyranoside, chrysophanol (1,8-dihydroxy-3-methylanthraquinone), damnacanthol, ajmalicine isomers, alizarin, asperuloside, asperulosidic acid, digoxin, 5,6-dihydroxylucidin-3-β-primeveroside, 5,6- dihydroxylucidin, 5,7-dimethylapigenin- 4'-O-β-D(+)-galactopyranoside, 2-methyl-3,5,6-trihydroxy anthraquinone, lucidin-3-β-primeveroside, lucidin, 3-hydroxymorindone, α-methoxyalizarin, 3-hydroxymorindone-6-β-primereroside, mono ethoxyrubiadin, morindin, morindadiol, 2-methyl-3,5,6-trihydrox yantraquinone-6-β-primeveroside,morindone (1,5,6-trihydroxy-2- methylanthraquinone), morindone-6-b-primeveroside, nordamnacanthal, alcohols, quinoline, rubiadin, saronjidiol, rubiadin 1-methyl ether, ursolic acid, alkaloids, anthraquinones and their glycosides, caproic acid, caprylic acid, fatty acids (C5-9), flavones glycosides, flavonoids, glucose(β- D -glucopyranose), indoles, purines, and b-sitosterol (Krishnaiah et al., 2012) (Figure.2). The fruit of *M. citrifolia* similarly is revealed to have a unique constituent, proxeronine, alkaloid xeronine precursor in addition to proxeronase, which revealed to possess wide-ranging of biological actions, for example strengthening of cell and revitalizing actions (Pawlus & Kinghorn 2007).

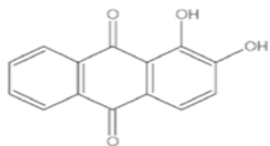
Nearly 100 volatile compounds are revealed to be recognized in Noni fruit, comprising fatty acid esters, short chain fatty acids and monoterpenes (Potterat & Hamburger 2007; Pino et al., 2010). The maximum copious volatile compounds are octanoic acids and hexanoic in addition to their equivalent ethyl and methyl esters (Farine et al., 1996; Wei et al., 2004). The principal secondary metabolites of Noni fruits are anthraquinones, flavonoids and phenolics with all that serve a significant role in its therapeutic characteristics (Baque et al., 2010).

COMPOUND	CONCENTRATION
Protein (g/100g)	0.55
Fat (g/100g)	0.10
Moisture (g/100g)	91.63
Ash (g/100g)	0.54
Carbohydrate (g/100g)	7.21
Fructose (g/100g)	1.07
Glucose (g/100g)	1.30
Sucrose (g/100g)	<0.1
Kilojoules/100g	135.56
Dietary fibers (g/100g)	2.01
Ca (mg/100g)	48.20
K (mg/100g)	214.34
Na (mg/100g)	16.99
Mg (mg/100g)	26.10
P (mg/100g)	20.35
Fe (mg/100g)	0.74
Cu (mg/100g)	0.08
Mn (mg/100g)	0.47
Se (mg/100g)	0.01
Zn (mg/100g)	0.06
B-caroeene (µg/g)	19.09
Niacin (mg/g)	0.03
Vitamin C (mg/g)	1.13
Thiamine (mg/g)	<0.018
Riboflavin (mg/g)	<0.018
Vitamin B6 (mg/g)	<0.018
Vitamin B12 (µg/g)	<0.0012
Vitamin E (µg/g)	10.96
Folic acid (µg/g)	<0.06
Biotin (µg/g)	0.02
Pantothenic acid (mg/g)	<0.018
Vitamin K (µg/g)	<0.10

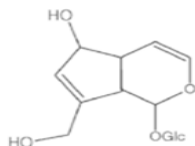
Table 1. Nutrient content of processed noni fruit puree (adapted from West et al., 2011)

Several in-vitro and few in-vivo biological investigations have been achieved on the crude extracts and numerous pure Noni components. These investigations show that Noni plant display countless usage in alternate treatment of numerous diseases for example diabetes, arthritis, high blood pressure, pains, menstrual difficulties, muscle aches, headache, gastric ulcer, sprains, mental depression, heart diseases, AIDS, senility, arteriosclerosis, blood vessel problems, poor digestion, drug addiction, cancers and several other diseases (Yang et al., 2010; Gupta & Patel 2013; Basar et al., 2010; Gilani et al., 2010). Additionally, several

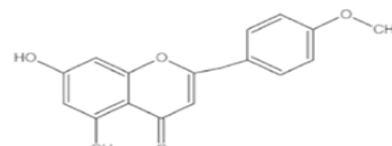
in vitro biological measures is been described, for example antioxidant activity, angiogenesis inhibition, cyclooxygenases-1 inhibition and also inhibition of cyclooxygenases -2, and tyrosine kinase. Nevertheless, majority of these are tested with extract from the crude or noni plant fractions, whereas the compound(s) accountable for the biological activities is yet to be completely determine, apart from the two compounds, americanin A and neolignan that were Identified in an n-butanol- soluble partition of methanol extract of noni fruits (Su et al., 2005; Zin et al., 2002).



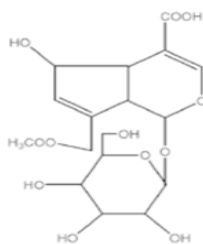
alizarin



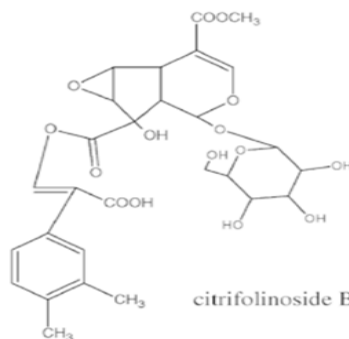
aucubin



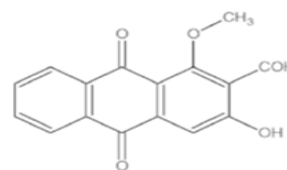
aracetin



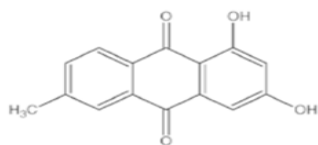
asperulosidic acid



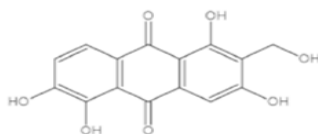
citrifolinoside B



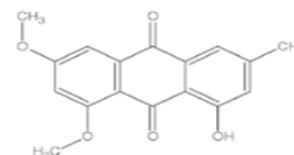
damnacanthal



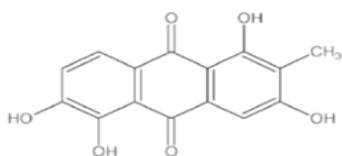
1,3-dihydroxy-6-methyl anthraquinone



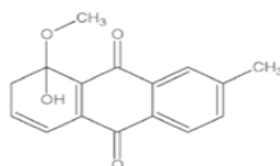
5,6-dihydroxylucidin



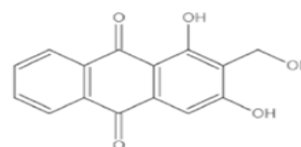
2-methyl-4-hydroxy-5,7-dimethoxyanthraquinone



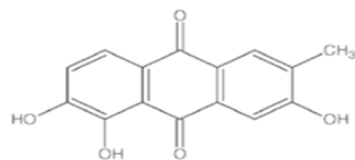
3-hydroxymorindone



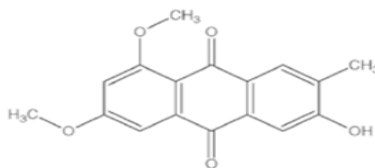
8-hydroxy-8-methoxy-2-methyl-anthraquinone



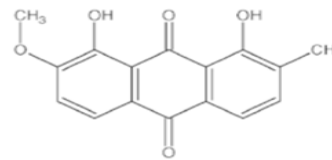
lucidin



2-methyl-3,5,6-trihydroxyanthraquinone



morenone 1



morenone 2

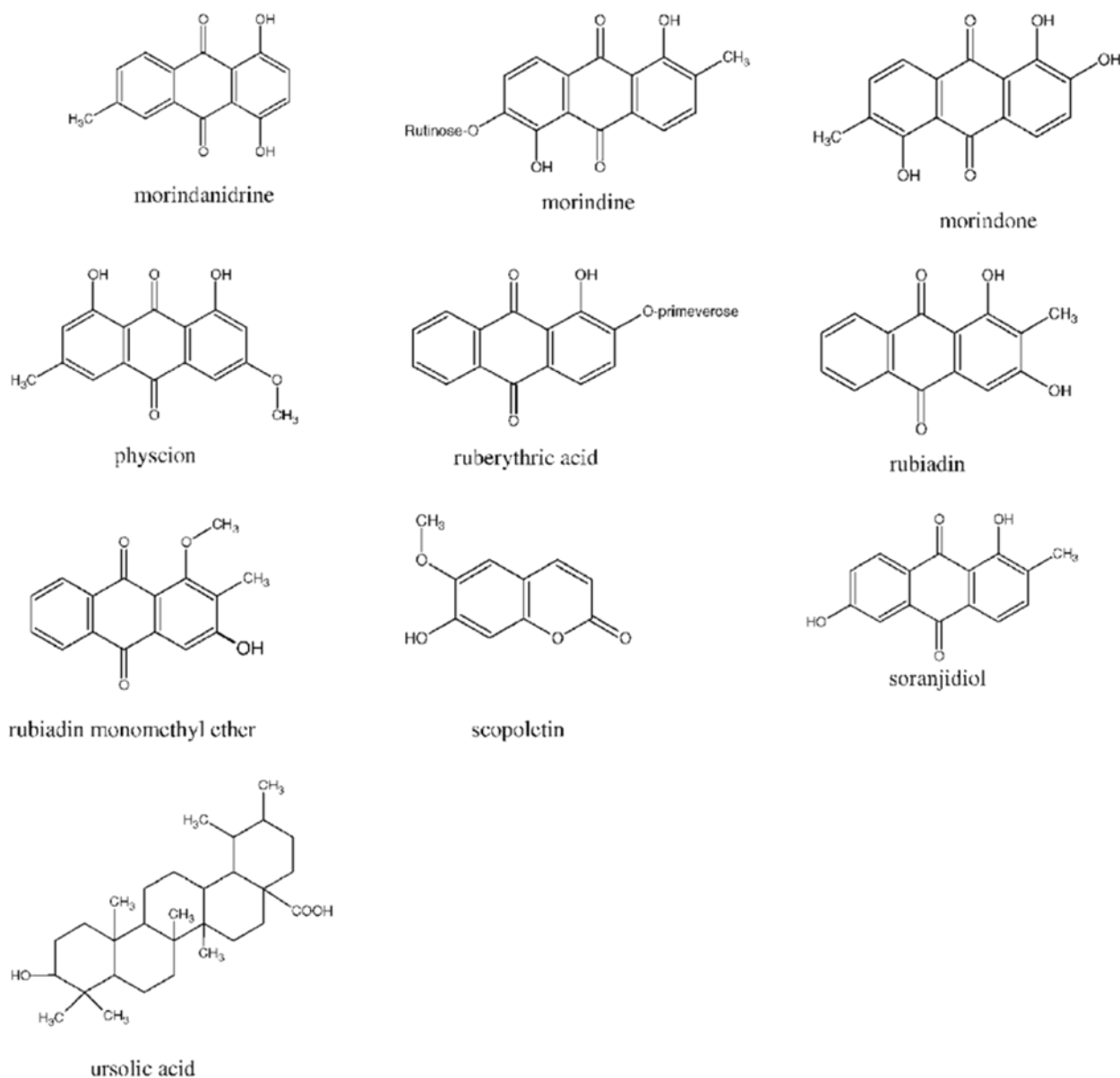


Figure 2 The most common pharmacologically active ingredients chemical structure of morinda citrifolia (Noni) (Chan-Blanco et al., 2006)

Anti-Diabetic Potential of Noni

Amongst the numerous health benefits of noni, fermented Noni juice has been recognized to increase insulin sensitivity, improve glucose metabolism, and inhibit gaining of weight in diabetic animal models (Nayak et al., 2010; Nerurkar et al., 2012; Lee et al., 2012). Indeed, Sabitha et al stated that there is improvement Noni fruit demand as alternate medicine for diabetes mellitus. It is proposed that antidiabetic effect of noni could be as a result of the stimulatory influence on the residue β -cells in secreting additional insulin (Mustaffa et al., 2011).

Rao and Subramaniam, stated that the level of blood glucose, glycosylated hemoglobin is lowered and the insulin level improved in streptozocin-diabetic rats treated with noni ethanolic extract. Additionally Horsfal et al in their study stated that fruit juice from Noni possess blood glucose reducing action. Nayak et al. 2010, stated that there is an encouraging outcome in regulating blood glucose through the consumption of the fermented noni juice, Tahitan Noni Juice was utilized in the management of diabetics and the outcome revealed that the juice

possesses the greatest glycaemic regulatory action compared to normal group, diabetic standard group and diabetic not treated group. Similarly, fermented juice from noni fruits displayed positive outcome in regulating level of blood glucose.

In addition to the anti-diabetic action, Noni juice similarly prevented complications of diabetes in animal models for example enhanced healing of wound in diabetic rats, it also prevent infarction, damage of the neurons and post-ischemic glucose intolerance development. Japan Noni juice enhanced memory in male ddY strain diabetic mice, whereas extracts of noni fruit obtained from India prevent streptozotocin- induced memory impairment in mice (Harada et al., 2010; Nayak et al., 2007; Pachauri et al., 2013). Possibility of preventing development of cataract was shown by inhibition of rat lens aldose reductase (RLAR) activities and improved free radical scavenging actions in vitro by using noni fruits aqueous extracts (Gacche & Dhole, 2011).

Factually, blood glucose reduction activities take effects as a result of the presence of antioxidant characteristics which includes triterpenoid,

flavonoids saponin and triterpenes in Noni plant. Saponin which is one of antioxidant properties could stimulates the release of insulin from the pancreas. Alternatively, Flavonoids for example rutin which exist in Noni fruit could act as substance that leads to additional substance to be secreted, which inspires secretion of insulin by a mechanism linked the sucrose (Mustaffa et al., 2011; Shetty et al., 2004)

Anti-oxidant effect of *Morinda citrifolia*:

Previous studies revealed a close link between diabetic retinopathy and oxidative stress (Nita & Grzybowski, 2016). In line with this notion, antioxidant compounds have been studied with regard to their ability to inhibit retinal degeneration and diabetic retinopathy (Williams et al., 2013). In recent times, there is a rising move away from synthetic antioxidants usage heading for the use of antioxidant that is natural. This tendency is as a result of side effect of synthetic antioxidants for example butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) on human being health (Thoo et al., 2013).

Previous studies revealed that high intake of fruits and vegetables having high content of phenolic antioxidants prevent low density lipoprotein (LDL) oxidation, hence slow the procedure of many disease [203]. Fruit of Noni plant contains numerous antioxidants for example ascorbic acid, beta-carotene, carotene, terpenoids, alkaloids, beta sitosterol, polyphenols for example flavonoids, rutin and flavone glycosides (Ramamoorthy & Bono, 2007). It is hopeful seeing that the entire chromatographic fractions achieved from Noni root, leaf and fruit revealed high antioxidative activities as compare to α -tocopherol or butylated hydroxytoluene (BHT) (Zin et al., 2006). Zin et al. 2002 investigated the antioxidant property of ethyl acetate and ethanol extracts of Noni fruit through the use of thiobarbituric acid test (TBA) and ferric thiocyanate method (FTC). Zin et al. 2002 discover that the extract of ethyl acetate strongly inhibit lipid oxidation, as compare to the pure butylated hydroxyl toluene (BHT) and α -tocopherol same weight. Radical scavenging activities were assessed in vitro through the tetrazolium nitroblue (TNB) test in commercially processed juice by evaluating the juice capability in protecting cells and lipids from oxidative changes stimulated by superoxide anion radicals (SARs). SAR scavenging actions of Noni juice was revealed to be 2.8 times greater as compare to the vitamin C, 1.4 times as compare to pycnogenol (PYC) and virtually the same level compare to powder of grape seed (Yang et al., 2007). Additionally, coumarin, flavonoid and phenolic acid groups in Noni fruit juice revealed a variety of free radical scavenging capability as portion of their antioxidant property (Dussosoy et al., 2011). In some investigation, Noni anti-oxidant activities was assessed as a naturally derived anti-pigmentation agent through the effect of 50% ethanol extracts of Tahitian Noni fruit flesh, seeds and leaves on the tyrosinase enzyme accountable in the control of melanin production. This assessment was done in vitro through the use of tyrosinase inhibitory evaluation, displaying that seed extract possess robust tyrosinase inhibition and antioxidant action as compare to the fruit, whereas the extracts from the leaf does not possessed tyrosinase inhibitory activities at all concentration. Tyrosinase inhibitory action was connected to lignans present in Noni, predominantly americanin A and 3, 3'-bis demethylpinoselinol (Masuda et al., 2009). Furthermore it is stated that extract of Noni seed display substantial antioxidant activities in Oxygen Radical Absorbance Capacity (ORAC) and Ferric Reducing Antioxidant Power (FRAP) tests (West et al., 2011).

Noni fruit anti-oxidant property was similarly associated to other health improvements actions. In vitro assessment of chloroform, butanol, ethanol, methanol and Indonesian Noni fruit aqueous extract, the entire extracts were seen to be capable of inhibiting Low-density lipoprotein (LDL) oxidation as a result of Noni lignans, for example americanin A, americanol A, americanoic acid A, isoprincepin and morindolin (Kamiya et al., 2004). Some in vitro investigation advocate that Malaysian ethanol extract of Noni leaf was exceedingly efficient natural supplement against

obesity as compare to the fruits. Methanol extracts of fruit and leaf inhibit the lipoprotein lipase activities. Equally the extracts comprises of high content of phenolic components which includes catechin, rutin and epicatechin that acts synergistically demonstrating this action (Pak-Dek et al., 2008). Also, Tahitian Noni juice is revealed to have the capability in reducing obesity linked to insulin resistance through preventing the reactive oxygen species and mitochondrial impairment in mouse muscle cells C2C12 in vitro culture (Nerurkar and Eck, 2008). Recently, in vitro experiment, Konada et al. (2015) examine the participation (divine NONI) in defense against oxidative stress in the lens of chicks epithelial cells which were exposed to hydrogen peroxide (100 μ M H₂O₂). He stated that Noni juice and extract can preserve functional ability viability of epithelial cells of chick lens in the course of oxidative stress, which advocate that "Divine NONI" can be efficiently used in patients with cataract.

A study of streptozotocin induced diabetic rats which were given extract of Noni fruit daily at a concentration of 300 mg/kg body weight orally revealed that intake of noni fruit is nontoxic and is also hepatoprotective (Rao & Subramanian, 2009). Additionally, the occurrence of biologically active constituents for example flavonoids, alkaloids, minerals, vitamins and triterpenoids is accountable for antioxidative and antihyperglycemic property of Noni fruits (Rao & Subramanian, 2009). Other in vivo investigations suggest that a naturally fermented product of Noni fruits distinctly decrease the oxidative stress through scavenging free radicals in addition to inhibition of lipid peroxidation and also to some extent increase glucose metabolism in streptozotocin diabetic rats (Chaiyasut et al., 2011). Hepato-protective properties of Noni was also due to the anti-oxidant properties in Taiwanese fermented fruit juice at a dosage of 3–9 mL NJ/kg BW in hamsters that are fed with a diet high in fat (Lin et al., 2013). In sprague-Dawley rats induced cataract, Noni showed anti cataract activity by inhibiting lipid peroxide and maintaining the antioxidant enzyme levels within the lens to tolerate the oxidative stress (Saminathan et al., 2014).

Amongst the limited positive clinical investigations, Tahitian Noni Juice revealed to be harmless amongst healthy persons whereas added clinical investigations proved decrease oxidative stress, DNA adducts and dyslipidemia amongst chain-smokers taken TNJ (Wang et al., 2009; West et al., 2006; Wang et al., 2013).

Together, these investigations indicate that Noni possess antioxidant prospective equal or like that of artificial antioxidants, for example BHA and BHT that are presently utilized as a food flavors. The antioxidants that are in Noni possess no any dangerous effect, and consequently may substitute synthetic antioxidants in food manufacturing company and possess prospect for usage in protective treatment.

Effect of Noni on aldose reductase (AR) and sorbitol pathway:

Aldose Reductase (AR) inhibition is known as a vital approach in the prevention and decreasing of long-standing complicated diabetics; additionally, AR inhibitors are being investigated as probable treatment against complicated diabetic condition (Lee et al., 2010). Numerous aldose reductase inhibitors (ARI) is been produced for complicated diabetic conditions; nevertheless, no any of the produced ARI realized global usage as a result of inadequate efficiency or unwanted outcome (Akhleshwari et al., 2012). Therefore many researchers have turned toward generally recognized as safe natural products for ARIs. It has been reported that plants of high flavonoids contents revealed several in vivo AR inhibition and antioxidant effects (Lim et al., 2001). Only one study investigated the anti-cataract effects of Noni which were shown through inhibition of rat lens aldose reductase (RLAR) actions and enhanced free radical scavenging actions in vitro through noni fruits aqueous extracts (Gacche & Dhole 2011).

Effect of Noni on angiogenesis:

Few studies on antiproliferation effect of noni is been revealed and the show certain reasonable, nonetheless incomplete, inhibition on certain tumor cell lines (Brown, A. C. 2012). Hornick et al. (2003) reported the prevention of angiogenic commencement and interruption of newly formed vascular network through Noni juice. This study utilized in vitro angiogenesis assay through the use of human placental vein and human breast cancer explants as the source of development of angiogenic vessels. The fruits juice was found to be very active in preventing the commencement of new vessels grows and decreasing the rate of growth and propagation of newly established vascular sprouts. The in vivo anti-angiogenic activity of Noni extracts was evaluated using the chicken embryo CAM assay demonstrated that the methanolic extracts of both noni fruits and leaves showed a good anti-angiogenic activity (Beh et al., 2012).

Effect of Noni on advanced glycation end products

Reduction of AGEs in vitro and in vivo has been reported biological activities of noni. In vitro testing of two dietary iridoids, deacetylasperulosidic acid and loganic acid from noni fruit reveals that these possess potential antiglycation activity. In addition, 8 weeks open-label trial study uses AGE Reader in measuring variations in skin autofluorescence of 34 obese and overweight adults that consumed every day a beverage containing food bases of iridoids, and a cross-sectional study with 3913 population investigated the link between everyday iridoid consumption and accumulation of AGE. Results of the human trial study and the cross sectional people study show that consumption of dietary source of the iridoids leads to decrease in accumulation of AGE (West et al., 2014; West et al., 2012).

The antioxidant action of 95% ethanolic extract of noni on diabetic oxidative stress was evaluated in vitro in various system of test. The outcomes showed that there is a good relationship between total antioxidant actions and antiradical activities by TBARS in addition to glycation (Kusirisin et al., 2009). Koch & Deo (2016) reported the Antiglycation activity of Commercial nutritional supplements of noni juice which determined by using the formation of fluorescent protein-bound AGEs.

Ethnopharmacology of Noni fruite

Ethnopharmacology is the scientific investigation of traditional medicines, which continue to offer novel drugs and principal molecules for the pharmaceutical industry (Wiar 2007). It is a relatively new science that requires interdisciplinary scientific collaboration between pharmacology, toxicology, chemistry, anthropology, and sociology (Medeiros et al., 2016). Plants are excellent candidates for oral therapy (Shokeen et al., 2008), they are also useful in industrial and medicinal applications (Sastry and Kavatheker, 1990), and several of the presently obtainable drugs are derived indirectly or directly from them (Grover et al., 2002). World Health Organization endorsed the assessment of traditional medicines to advance their usage according to beneficial effects on various disorders as they are active, non-toxic, with a minimal or without side effects and are measured to be outstanding applicants for treatment orally.

Noni is widely used plant in traditional medicine for various health benefits in human. Furthermore, Noni fruit used as valuable dietary adjuvant, medicine or food, different medicinal properties and therapeutic uses of fruit are reported in human (Anugweje 2015; RanvirGD et al., 2017). Noni is deemed to be the second most essential medicinal plant in the Hawaiian Islands (Shalan et al., 2017). Noni juice extract is largely processed and dispersed globally as a nutritional supplement. The first products resulting from Noni fruit is been marketed in the USA as long as the 1990s and are progressively spread to the entire globe (Santhosh

Aruna et al., 2013). In 1996, Tahitian Noni juice emerges as a wellness beverage, as a result of several reports testifying its beneficial effects (Kamiya et al., 2009). Considering the health benefits of Noni juice, Noni fruit juice was accepted as a novel food by European commission in 2003; nonetheless, the endorsement was restricted to the Tahitian fruit juice and not extra products (Potterat and Hamburger, 2007). Till now 119 patents linked to Noni is been enlisted with the US Patent and Trademark Office (Pandy & Khan 2016).

Administration of Noni can be topically or orally. The fruit and juice can be orally consumed for different health purpose. The leaves and fruit are utilized in the preparing of ointment that is topically used in some illnesses for example burns, headaches, arthritis, wounds and sores. Until now, information's accessible for everyday recommendation for oral dosage of Noni is 2 g; nevertheless, no information's on the recommended doses range for preparing topical application (Assi et al., 2015). Traditional folk medicine knowledge in Malaysia, commended that Nani fruit should be taken maximally a fruit per week (Lagarto et al., 2013).

Regarding the safety of Noni, limited evaluation of clinical safety have been done, nonetheless there have been limited side effect recounted after the use of Noni fruits, Nani fruits has been taken as food for several centuries (Nerurkar et al., 2015). In 2002 safety evaluation of one of the product of Noni juice by European Scientific Committee on Food resolved that there were no signs of any contrary effect in animal investigation on the subacute and sub-chronic toxicity, allergenicity and genotoxicity (Potterat and Hamburger, 2007). The phase-I clinical trial examined the toxicity and efficiency of freeze-dried fruit ripe noni extracts amongst cancerous patients to retrogress progressive cancers. Twenty nine patients having progressive tumor were treated with pills comprising Noni fruit extract of ripe noni fruit. Randomly selected patients were group into five groups treated with drugs comprising 2, 4, 6, 8 or 10 grams of noni per day for 28 days. Effects on numerous life quality processes were reported even though it is not statistically significance, but for pain decrease. No opposing effect or tumor reaction attributed to Noni was seen (Issell et al., 2005; Issell et al., 2009). Evaluation which was supported by Tahitian Noni, the leading worldwide noni juice producers, stated that there was no toxicity from taken of Noni juice (West et al., 2009; West et al., 2006). Safety placebo-controlled and double-blinded, trial examination of Noni fruit juice which was done in 96 healthy volunteers revealed no any substantial side effect using up to 750ml of noni juice per day for four weeks. Four to six weeks consumption of noni juice revealed no any adversarial effect on functional test of kidney and liver, hematological analysis, differential white and red blood cell count, blood pressure and heart rate (West et al., 2006; Langford et al., 2004).

Herbal preparations comprising noni products are deemed harmless by publics as a result of their natural backgrounds. Hence, herbal toxicities are challenging to detect, as patients mostly not reporting the utilization of natural enhancers to their healthcare workers or providers. From year 2000 to 2015, eleven noni-associated toxicity cases have been recounted; nine cases were reported of hepatotoxicity in earlier healthy individuals taken Noni products in the year 2005 to 2011. It's not clear if Noni juice was really the reason for the toxicity in the liver. The liver function tests was better when the Noni product was stopped nonetheless other elements or remedy could have be accountable for the toxicity (Brown., 2012; Gupta 2013). Recently, toxicity reported in 2012, in 45 years old female patient, taking Euforia juice that containing Noni juice alongside with other natural products for a month in treating systemic sclerosis, finally resulted in jaundice which gives rise to high serum transaminases level. She was finally established to have hepatocellular necrosis and histopathological variations shows toxic hepatitis. This situation was better after a year and six months when Euforia juice usage was discontinued, however, precise toxicity mechanisms are still undefined

(Jiménez-Encarnación et al., 2012). In a 38-year old woman concurrent taking of low dosage of phenobarbital for 7 months in preventing electroencephalogram-associated seizure, taken Noni juice for a week was linked to severe herbal drug liver toxicities (Mrzljak et al., 2013). Recently a report of poor control of seizure in 49 years old epileptic man was ascribed to simultaneous usage of phenytoin, a drug used for the control of seizure, and noni juice. Decrease of noni juice intake and adding another anti-seizure medicine aid in regaining control of seizure (Kang et al., 2015). Noni comprises of moderately high potassium levels (comparable to those in tomato and orange juice) and hyperkalaemia situation was seen in a patient diagnose with a chronic renal deficiency (Mueller et al., 2000). Current report equated the long-lasting toxicity of Noni fruit and edible water extracts of leaf (two dosages each of them) in feminine mice, the extracts of noni fruit was linked to chronic liver toxicity at a higher dosage of 2 mg/mL intake water, this was supported by histological confirmation of hepatocyte necrosis, an higher liver enzyme level, a lesser albumin level circulation, with 40% rate of mortality within 3 months. By contrast, there was no significant toxicity with either a low or a high dose of noni leaf extracts (Shalan et al., 2017). The authors hypothesized that the toxicity of the Noni fruit extract might be as a result of anthraquinones in the seeds and skin, which possess potent quinone reductase inducer action and could damage the liver. Indeed, the toxicity study applied different methods to extract noni juice from various parts of the plant, and used different doses and animal species from those of the current study performed by Lin et al. Furthermore, Lin et al, 2017 did not find evidence of liver inflammation in Wistar rats with 8-week treatment; by contrast, noni juice even ameliorated thioacetamide-induced liver injuries. Nevertheless, the various results remind us of the necessity of a careful and thorough search of the beneficial and harmful components from the *M. citrifolia* tree, and the need to find a safe dosing schedule for humans (Huang 2017).

In conclusion several *in vitro* and *in vivo* studies, primarily using the extracts fruits, suggest that noni may have potential for a variety of health problems (Torres et al., 2017). Furthermore, Different chemical compounds found in the noni fruit extracts could be valuable in exploring broad range of pure chemical compounds from the noni fruit aqueous and ethanol extracts, warrants for critical isolation, identification and the characterization of biologically active compounds in pure form that could be more potent in improving quality of life and health benefits (RanvirGD et al., 2017). Nevertheless, well-designed and conducted clinical trials in humans are necessary to support the present findings and to guarantee and validate its efficacy and safety. Thus, noni like so many other plants used by traditional medicine may have therapeutic properties in humans, but only more research will tell.

Diabetes Mellitus

Diabetes Mellitus (DM) is one of the common metabolic disturbance characterized by abnormal increase in the blood sugar level and disorders in fat, protein and carbohydrate metabolism as result of deficiencies in secretions and actions of insulin, (Surya et al., 2014). It has grown into the level of epidemic and global disease of this century. The global occurrence of DM in adults has been increasing in the last decades. About Four hundred fifteen million adults globally were existing with diabetes in 2015 (global prevalence 8.8%), and it is estimated that by the year 2040 over 642 million will be diabetic, as a result of higher rate of obesity, longer life spans, urbanization, dietary intake and earlier disease detection (Maiorino et al., 2017). The World Health Organization (WHO) forecasts that diabetes may be the seventh principal reason of death in 2030 (Sturgeon et al., 2016).

The common cases of diabetes are categorized into two etiopathogenetic classes: type I DM, which is accountable for 5–10% of diabetic patients, formerly refer to as insulin-dependent diabetes or juvenile-onset diabetes, triggered by complete insufficiency of secretion of insulin. Type 2 DM,

which is accountable for about 90–95% of diabetic patients, earlier term as non-insulin dependent diabetes, type 2 diabetes, or adult-onset diabetes, includes persons who possess insulin resistance and frequently possess relative (rather than absolute) insulin deficiency (American Diabetes Association. 2010 ; Targher et al., 2011). Additionally, female's that develop diabetes through their gestation period are categorized as having pregnancy diabetes and it is not clearly diabetes (Kaul et al., 2013). DM might also be as a result of infections, drugs, endocrinopathies, pancreatic damage, and genetic deficiencies (Kaul et al., 2013; American Diabetes Association, 2013; TA, 2014).

DM is linked to a high danger of increasing vascular complication which add to morbidity and death of the patient. The inadequate glycemic and blood pressure control result to vascular complication that impact large (macrovascular), small (microvascular) vessels or both. The macrovascular problems, which affect large vessels of the circulatory system which could result to higher occurrence of coronary heart disease (CHD), peripheral vascular disease and stroke (CVA) which may lead to ulceration, gangrene and extremities amputations especially the lower extremities (Boyle, 2007; Ceriello, 2010). Microvascular complications include destruction of the small blood vessels and add to diabetic neuropathy (nerve damage), retinopathy (eye disease) and nephropathy (kidney damage). Diabetic retinopathy (DR) is a major long-term problem of diabetes and the major reason of visual impairment and blindness below 75 years of age in developed countries (Williams, et al., 2004). Additionally, diabetes raises the risk of cataract and glaucoma. The incidence of these problems is depending on the type and period of diabetes and glycemic control. Additional risk factor for these problems is hypertension, management modality and dyslipidaemia. The growing universal populace, increase in age and forecast increase in the percentage of adults having diabetes will unavoidably be complemented through a rise in diabetic complications (Tattersall, 2010).

Diabetic retinopathy

Retinopathy is a universal name for all retina ailments, the light delicate membrane at the back of the eye. Diabetic Retinopathy (DR) is a microvascular disorder impacting the small blood vessels in the retina, which includes microaneurysms, retinal hemorrhages, and hard exudates results from prolonged exposure to high glucose levels (Lai & Lo, 2013). DR is considered the common microvascular impediment of diabetes which was until recent considered as the most predominant reason for visual damage in the working age populace in industrialized countries (Olafsdottir et al., 2016). DR is characterized by gradual and progressive alterations in the retinal microvasculature. Damages to neurons and glia also occur during the course of DR (Sun et al., 2015). Individuals with diabetes, regardless of whether they are afflicted with type 1 or type 2, are all at risk of developing retinopathy. The longer a patient has diabetes, the higher the risk of developing DR is. About 25% of patients with type 1 diabetes revealed to have retinal damage, and the incidence increased to 60% after 5 years and 80% after 10 years to 15 years of affliction (Wu et al., 2014). Type 2 diabetes accounts for the higher prevalence of DR (Thomas et al., 2015).

Clinical, epidemiological and laboratory investigations have improved our understanding of the pathophysiological variations of DR, concluding in recent times in new management alternatives for diabetic DR (Heng et al., 2013). Additionally, selection programmes have allowed initial analysis and rapid management of sight threatening retinopathy. In spite of these improvements in the field, the occurrence of diabetic retinopathy is still high at 40%. Worldwide, there exist about 93 million persons having diabetic retinopathy, 17 million with proliferative retinopathy, 21 million with diabetic macular edema and 28 million with sight threatening retinopathy, making diabetic retinopathy an important worldwide economic and public health problem (Yau et al., 2012; Kumari et al., 2008).

Pathological Classification of diabetic retinopathy

DR is generally classified into two phases: proliferative DR (PDR) and non-proliferative DR (NPDR). (Fig. 3) NPDR arises when there is injury in the blood vessels within the retina leaking fluid to the retina, triggering the retina to be wet and distended. In NPDR, diverse symptom of retinopathy could occur, for example the haemorrhages, exudates (hard and soft), inter-retinal microvascular anomalies and microaneurysms. PDR is a progressive phase of DR where new unusual fragile blood

vessels begin to grow in diverse parts of the retina and could result to full blindness (Crick & Khaw 2003; Akram et al., 2014). Maculopathy can occur in both non-proliferative and proliferative retinopathy and is the commonest basis of visual damage within the diabetic population. Diabetic Maculopathy can be defined as diabetic retinopathy affecting the central macula. The condition can be divided into several subgroups each with a different pattern of disease; focal, diffuse, ischaemic and mixed (Nentwich & Ulbig 2015).

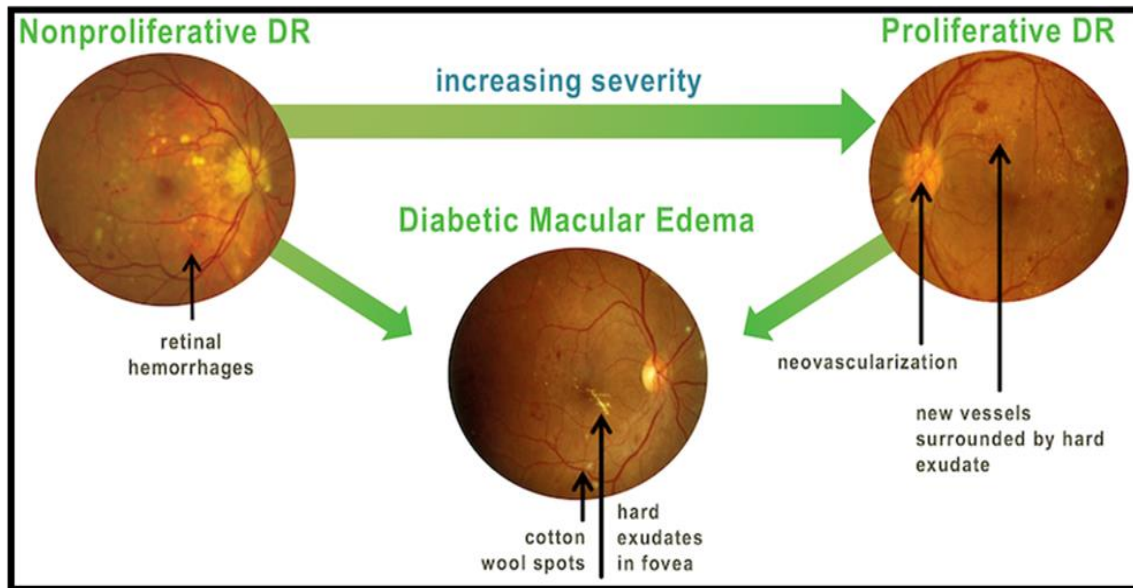


Figure 3. Clinical features of DR.

Pathophysiology of Diabetic Retinopathy

DR is one of the multifactorial diseases and its pathogenesis is exceedingly multifaceted. Several retinal cells are involved in the course, comprising ganglion, Muller, pigment and endothelial epithelium cells (Bhagat et al., 2009). Unsatisfactory glycaemic balance is a fundamental contributor to the pathophysiology of DR (Keel et al., 2014). It is worth to mention hyperglycaemia causes the retinal vasculature to suffer a progressive dysfunction. However, the exact details to explain the Pathogenesis of DR is not completely understood. Several interconnecting biochemical paths are suspected to influence the progress and development of DR (Semeraro et al., 2015). These include, improved actions of the sorbitol pathway, oxidative stress, stimulation of protein kinase C, increased manifestation of growth factors (e.g. vascular endothelial growth factors (VEGF) and insulin growth factors), enhanced formation of advanced glycation end-products (AGEs) formation, hemodynamic variations, activation of the renin-angiotensin-aldosterone system, and inflammation (Tarr et al., 2013; Rask-Madsen & King, 2013; Ahsan, 2015).

The metabolic pathways activated by hyperglycaemia enhance the pro-inflammatory cytokines profile in the retinal tissues, followed by recruiting leukocytes as part of the inflammatory response, and in turn mediate damage to endothelial cells and pericytes, which leads to the visible clinical lesions of microvascular disease. Stiffening of the basement membrane of capillaries in the inner and outer retina leads to a loss of their barrier function and seepage of plasma into the retina. Hence, diabetes induced metabolic mechanisms understanding help in endothelial cell proliferation, pericyte loss, neovascularization, variations in basement membrane structure is essential to deciphering the disease pathogenesis, and development of new pharmacological therapeutic

strategies to treat or prevent early diabetic related microvascular alterations (Abcouwer, 2013; Pipis et al., 2011; Cunha-Vaz et al., 2014).

Oxidative stress and its role in the development of diabetic retinopathy

Oxidative stress

In the past decades, oxidative stress associated mechanisms have been link to the pathology of several ailments (Schieber & Chandel, 2014). Oxidative stress is defined as a disorder in the steadiness between high reactive molecules production (free radicals) and the capability of the biological system in removing dangerous effects by neutralization through antioxidants (Wu et al., 2014).

Typical cellular metabolism constantly produces free radical; the body utilizes about 95% of the free radicals for metabolism and about 5% of the oxygen is transformed into reactive oxygen species (ROS). The reactive oxygen species acts as two fold bordered blade; ROS can be as a messenger in redox signalling, nevertheless it can similarly destroy usual cellular signalling. A very effective endogenous antioxidant protection system with none enzymatic and enzymatic antioxidants efficiently purifies the harmful reactive oxygen species (Kowluru & Mishra, 2015). Nevertheless, in a pathological condition, production and purification of free radicals is decreased, as a result of improved reactive oxygen species production or reduced elimination, and it can be both, leading to an inequity between production and elimination of reactive oxygen species creating an too much bioavailability of reactive oxygen species. Apart from reactive oxygen species, reactive nitrogen species (RNS) are also portion of usual physiological function, and possess high prospective in contributing to oxidative stress (Al-Shabrawey & Smith, 2010). Nitric oxide forms peroxynitrite spontaneously in the occurrence of superoxide. Peroxynitrite is considerably greater reactive as compare to nitric oxide

and superoxide and can exercise straight oxidative changes by one or two electron oxidation progressions. If the destructive free radicals are not freely deactivated, they impair to the macromolecules lipids, DNA and proteins, and also modify the appearance of numerous stress response genes which in addition stimulate extra generation of reactive oxygen species from endogenous bases (Cutler, 2005). Superoxide formation is interceded through the mechanism of non-enzymatic and enzymatic. NADPH oxidase is the principal enzyme accountable for enzymatic reduction of O₂ to superoxide, while production of non-enzymatic superoxide is a result of mitochondrial respiration (Dröge, 2002).

Antioxidants Defenses

Body possesses a number of operational antioxidant protection systems in lowering free radicals concentration in the body system. The name antioxidant denotes to “any element which when exist in little quantity as equated with oxidizable substrate, meaningfully delays or prevents substrate oxidation”. The nature of the antioxidant systems varies depends on the type of cell, tissues and extracellular or intracellular medium localization. There exist diverse varieties of molecules, synthetic and natural, with scavenging or enzymatic actions. (Bonfont-Rousselot et al., 2003; Dal & Sigrist, 2016).

Considering the natural antioxidants, the human antioxidant system is separated into two main groups, non-enzymatic oxidants and enzymatic antioxidants. In case of enzymatic antioxidants, they are divided into primary and secondary enzymatic defenses, which are assisted by micronutrients (copper, zinc, selenium) as cofactors (Evans & Halliwell, 2001). Primary defense is comprises of three vital enzymes which stop formation or neutralization of free radicals: catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD) (Rahman, 2007). Secondary enzymatic defense comprises of glutathione reductase and glucose-6-phosphate dehydrogenase NADPH (nicotinamide adenine dinucleotide phosphate – coenzyme used in anabolic reactions) (Gamble & Burke, 1984; Ratnam et al., 2006). The two enzymes don't directly neutralize free radicals, but possess supporting roles to other endogenous antioxidants. The non-enzymatic endogenous antioxidants are in reasonable number, namely Vitamin A or retinol, Coenzyme Q10, Uric acid, Glutathione, ascorbic acid and tocopherols (Vitamins C and E), Vitamin K, Flavonoids, Phenolic acids (including P-coumaric acid, Ferulic acid, Gallic acid and Ellagic acid), Carotenoids and Minerals including selenium and zinc (Carocho & Ferreira, 2013).

To have a standard antioxidant activity assessment system in comparing with natural antioxidants and also to be integrated to food, development of synthetic antioxidants have been achieved. The unadulterated compounds are added to food for it to survive several handlings and circumstances in addition to extended shelf life. The most significant and extensively obtainable synthetic antioxidants are BHA (butylated hydroxyanisole) BHT (butylated hydroxytoluene), TBHQ (tert-Butylhydroquinone) and Octyl gallate (Aguilar et al., 2012).

Oxidative stress and diabetic retinopathy

Diabetes causes oxidative stress in the retina and could play a vital part in DR development through retinal cells destruction (Caldwell et al., 2005). In diabetic retinopathy, the retina experience high production and reduced elimination of free radicals (Kowluru et al., 2001). Nevertheless, current investigation revealed that high polyunsaturated fatty acids content, together with the peak oxygen uptake and glucose oxidation compare to any other tissue, turn the retina to be greatly vulnerable to oxidative stress. This occurrence makes the retina more vulnerable to oxidative stress (Dong et al., 2013), and growing sign, advocates that the connection between hyperglycemia, variations in the redox homeostasis, and oxidative stress are the main process in diabetic retinopathy pathogenesis. The prospective ROS sources in diabetic retinopathy yet to be clear, even

though a number of investigations have revealed that increase glucose and the diabetic condition motivate influx by glycolytic pathway, high cytosolic NADH, rise in tissue lactate to pyruvate proportions, and rise in tricarboxylic acid cycle influx which could flood mitochondria with electrons, thus creating additional stages of ROS (Ido et al., 1997; Madsen-Bouterse & Kowluru, 2008). Additional sources of the production of ROS comprises of triggering Advanced Glycated End products (AGE), Aldose Reductase (AR), hexosamine, and PKC pathways trigger by the means of hyperglycemia (Ola et al., 2012). Nevertheless, Ola's investigation revealed that hyperglycemia as such may not prompt ROS through mitochondria since it could not discover increased fluidity by the tricarboxylic acid cycle or glycolytic (Ola et al., 2006). Additional oxidative stress sources are instigation of NADPH oxidase which could rise superoxide, decreased level of glutathione, xanthine oxidase induction, reduced actions of antioxidant protection of enzymes for example superoxide dismutase and catalase (Al-Shabrawey et al., 2008; Kowluru & Chan, 2007; Madsen-Bouterse & Kowluru, 2008).

Recent clinical investigation has revealed that oxidative stress assists not merely to the increase of diabetic retinopathy but also to the resistance of retinopathy to reverse after excellent glycemic regulator is reinstate the phenomenon of metabolic memory. Diabetic retinopathy resistance to reverse is possibly ascribed to growth of destroyed molecules and ROS which hard to be detached even after excellent glycemic regulator is reinstated (Kowluru et al., 2014; Dong et al., 2013). The level of superoxide are increase in diabetic rats retina and in retinal cells kept in media containing high glucose and content of hydrogen peroxide that is increased in diabetic rats retina (Kowluru & Abbas 2003; Cui et al., 2006) and membrane lipid peroxidation and oxidative injury to DNA (as a result to ROS-induced damage) are high in diabetes patient retina. Membrane lipid peroxidation and oxidative damage to DNA, the significances of ROS induced injury, are high in the retina in diabetes (Kowluru & Koppolu, 2002; Kowluru & Abbas, 2003). In diabetic patients, the actions of antioxidant defence enzymes accountable for scavenging free radicals and sustaining redox homeostasis for example SOD, glutathione reductase, glutathione peroxidase, and catalase are reduced in retina (HASKINS et al., 2003; Kowluru et al., 2001).

It is well-known now that retinal oxidative stress is a pathogenic factor in diabetic retinopathy, due to a certain extent, on earlier investigation via different non targeted and or nonspecific antioxidants, all of which prohibited pathology development. Though; Questions continue, as to how antioxidants are best introduced into the retina with negligible reaction of usual cellular functions (Giordano et al., 2015).

Variations related with oxidative stress suggest several possibilities of treatment objectives creating the area of high attention to production of harmless and effectual managements of diabetic retinopathy. Animal models of diabetic retinopathy have revealed useful properties of antioxidants on the retinopathy development; nonetheless inadequate clinical investigation is yet to be encourage (Kowluru & Mishra 2015).

Several pathways and mechanisms are tempered with through hyperglycemia-induced oxidative stress. Many molecular mechanisms, suggested to clarified the oxidative stress-induced variations in retinal cells that the prospective affects numerous pathways linked with the pathogenesis of diabetic retinopathy are defined below: -

Sorbitol pathway (Polyol Pathway)

A small proportion of glucose is usually metabolized in cellular glucose metabolism through the sorbitol pathway, whereas in diabetes, excess of glucose enters the sorbitol pathway. The sorbitol pathway is consisting of two reactions that controlled by tow enzymes. The first enzyme, Aldose Reductase (AR) (alditol:NADP⁺ oxidoreductase, EC 1.1.1.21), decreases

glucose to sorbitol, which is later transformed to fructose by the second enzyme, sorbitol dehydrogenase (SDH) (1-iditol dehydrogenase, EC 1.1.1.14) (Chung & Chung, 2003; Forbes & Cooper 2013).

Aldose reductase, a cytosolic protein is in to the superfamily of aldo-keto reductases (AKR) which comprise of numerous enzymes that catalyze oxidation and reduction reactions involved in numerous cellular procedures for example detoxification, biosynthesis and metabolism (Barski et al., 2008). Hers 1956, was the first who described the Aldose reductase and the sorbitol pathway in the seminal vesicles where fructose is produces for spermatozoa. Four years after (1959), van Heyningen revealed the buildup of high concentrations of galactitol and sorbitol in the lens of rat which show that this pathway wasn't only limited to reproductive tissue (Kador et al., 1985). AR has been restricted to numerous retinal cell forms. Human, bovine rat and dog retinal pericytes have been revealed to containing AR and to accrue sugar alcohols in reaction to diabetes and galactose feeding (Akagi et al., 1983; Hohman et al., 1989; Li et al., 1986; Chakrabarti et al., 1987; Dagher et al., 2004).

In a high intracellular glucose concentration presence in the retina, aldose reductase, which normally functions to reduce toxic aldehydes in cells to inactive alcohols, reduces glucose to sorbitol. The later process consumes nicotinamide adenine dinucleotide phosphate (NADPH) a vital intracellular antioxidants which play a role in the reduction of glutathione (Fig.4). Decrease in glutathione reduction leads to increased cellular

susceptibility to oxidative stress and damage (Chung et al., 2003). In addition, the strongly hydrophilic sorbitol does not diffuse freely through cell membranes, thereby accumulating intracellularly and leading to likely osmotic outcome, such as damage to retinal cells. Sorbitol is slowly metabolized to fructose, using NAD⁺ as its cofactor, which in turn is phosphorylated to fructose-3-phosphate and degraded to 3-deoxyglucosone. Both of these molecules are strong glycating agents that can lead to the production of Advanced Glycation Endproducts (AGEs), causing further damage (Karen et al., 1995; lee & chung, 1999; Szwergold et al., 1990).

Biochemical significances of polyol pathway initiation as investigated in experimentally diabetic rats retina increased lipid peroxidation products, nitrotyrosine and reduction of antioxidant enzymes (Obrosova et al., 2005). Hence, initiation of the sorbitol pathway starts and many numerous mechanisms of cellular impairment through initiation and AR interaction and new pathogenetic factors for example AGE formation, initiation of oxidative nitrosative stress, and poly ADP-ribose polymerase (PARP) and PKC pathway which could result to inflammation commencement and imbalance of growth factor (Obrosova & Kador, 2011). Usage of fidarestat, which is AR inhibitor, counters diabetes related retinal oxidative nitrosative stress, activation of PARP (Obrosova et al., 2005) and interactions of leukocyte endothelial (Hattori et al., 2010); backings a vital role of AR in diabetes; and offers basis for AR inhibitors development of polyol pathway counteraction (Drel et al., 2008).

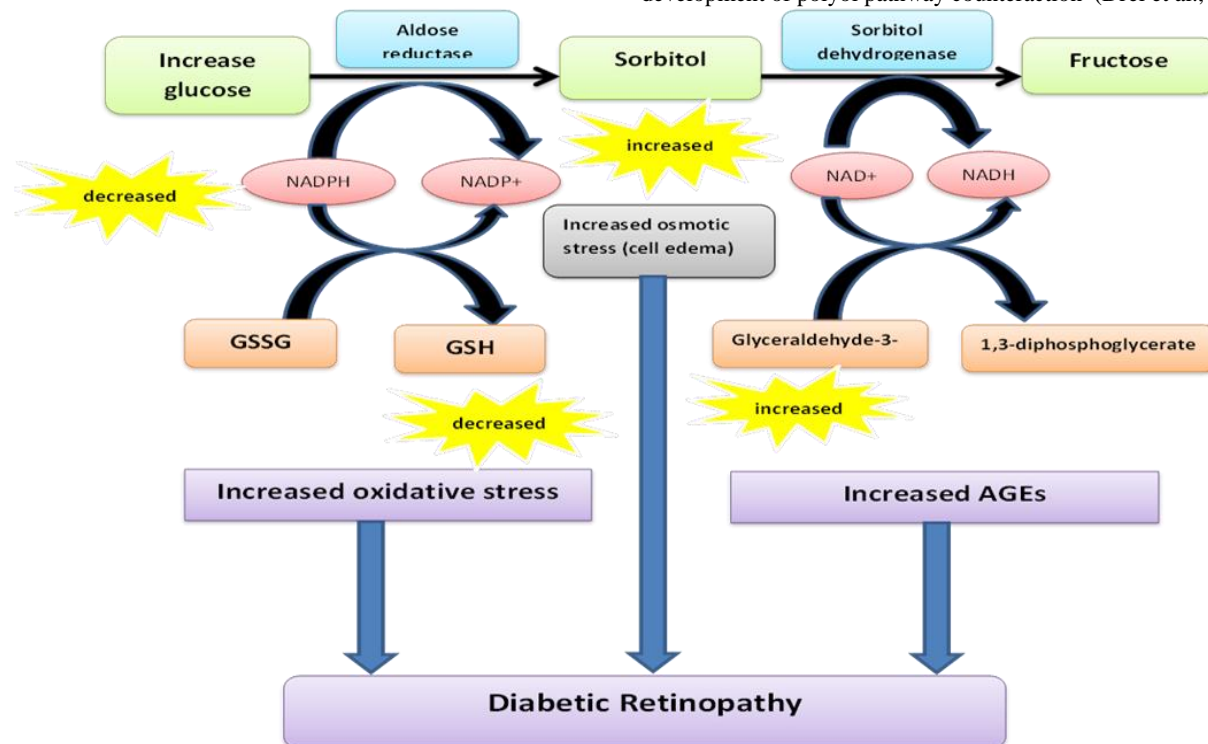


Figure 4. Pathogenesis of diabetic retinopathy.

Advanced glycation end products (AGEs)

Advanced glycation end products (AGEs) denotes to the products of non-enzymatic reaction existing between extra sugars and lipids, amino acid of Proteins and nucleic acid, which is a vital pathogenic factor in DR (Wang et al., 2015). The primary products of this reaction are refers to as Schiff base, which naturally reorganizes self to an Amadori products. Gentle and multifaceted reactions cascades, finally leads to the Amadori products conversion to AGEs formation (Chistiakov, 2011). AGEs are enormous heterogenous group and total AGEs that exist yet to be understood. Till now, only an insignificant AGEs number exist in vivo

have been characterized and defined structurally. Major AGEs appear in vivo to be produced from exceedingly reactive midway carbonyl group which is acknowledged as oxoaldehydes or dicarbonyls, including 3-deoxyglucosone, methylglyoxal and glyoxal (Milne & Brownstein, 2013). In diabetes, high AGEs level are seen inside retinal capillary cells which causes loss of pericyte in diabetic retinopathy. Speeded AGEs buildup in diabetic patients could lead to long lived proteins crosslinking resulting to toughness and vascular dysfunctions. Additionally, AGEs binding to precise cell surface AGE receptors for example the receptor of advanced glycation end product (RAGE) could encourage intracellular signaling, oxidative stress with key pro-inflammatory production and pro-

sclerotic cytokines (Yamagishi, 2011). Additionally, AGEs, through the sequences of molecular and biochemical pathways, stimulate nuclear translocation factor-kB (NF-kB) and caspase-3, leading to capillary cell apoptosis. Nitration of proteins could also interrupt assembly and functions of protein, and may result to endothelial and neuronal cell apoptosis, resulting eventually to pathological outcome and injury of cellular components (Cowell & Russell, 2004). Hence, there seems to be a neighboring loop between oxidative stress and AGEs.

Development and buildup of AGEs plays an essential part in vascular injury in diabetic patients. Nevertheless; many inhibitors of post-Amadori glycation intermediates (glyoxal, methylglyoxal, 3-deoxyglucosone) are defined with aminoguanidine (Soulis et al., 1996; Panagiotopoulos et al., 1998; KELLY et al., 2001) (pyridoxamine, benfotiamine and ORB-9195 (Voziyan & Hudson, 2005; Williams et al., 2007). Several of these, for example ORB-9195 can control of glycation and lipoxidation derivatives generation (Nakamura et al., 1997; Wada et al., 2001) and some could be obtainable for clinical usage in the future (Vlassara & Uribarri, 2014).

Growth factors

Diabetic retinal disease pathogenesis and progression involves proangiogenic, angiogenic and antiangiogenic factors. For example, Vascular Endothelial Growth Factor (VEGF) is a hormone usually secreted by cells in the body in laceration or injury situation or infection forming new blood vessels and restoring oxygen stages in the impaired tissue (Diab et al., 2016). VEGF is mainly secreted from retinal pigmented epithelial cells, astrocytes, pericytes, glial cells, endothelial cells and müller cells (Moran et al., 2016). The VEGF family comprises of five physically connected ligands: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta growth factor (PlGF). The ligands binds in an overlying design to three tyrosine kinase receptors (VEGFR-1, VEGFR-2, and VEGFR-3) (Ferrara, 2004; Simó et al., 2014). The extensively investigated growth factor is VEGF-A (usually denoted to as VEGF), VEGF-A is the first member of the VEGF family to be recognized (Ferrara & Henzel 1989; Plouet et al., 1989; Nagy et al., 2007). Earlier investigation has confirmed that VEGF help angiogenesis, activating quiescent endothelial cells and stimulating vascular penetrability by VEGFR-1 (also recognized as Flt1) binding, and encouraging proliferation of cell by VEGFR-2 (also identified as Flk1) binding (Carmeliet et al., 2001; Autiero et al., 2003; Adams & Alitalo 2007). Additionally VEGF is essential in organizing and enrolling endothelial progenitor cells to the location of neovascularization and regeneration of tissue (Beaudry et al., 2007).

In diabetic retinopathy, hyperglycemia leads to retinal hypoxia as a result the retina not receiving all of the blood and nutrients it needs and pericyte-cell dropout have compromised vascular integrity. Consequently, the retina secretes VEGF, because VEGF leads to angiogenesis, theoretically allowing the retina to receive the oxygen and nutrients it needs to properly function. Angiogenesis promoted by VEGF; lead to collapse of the blood retinal barrier, endothelial cell growth and neovascularisation stimulation; and rise in vascular penetrability in the ischemic retina (Comer & Ciulla 2004; Ishida et al., 2003; Zhang et al., 2009; Tremolada et al., 2012). VEGF-A motivates endothelial cells to discharge matrix metalloproteinases (MMPs) and urokinase-type plasminogen activator, leading to the breakdown of basement membranes and creating movement of cell possible. The stimulated endothelial cells express integrins for example $\alpha v \beta 5$ and $\alpha v \beta 3$ that help in the movement through the breakdown matrix. Increase and movement of endothelial cells is preceded by basement membranes synthesis for the capillaries that are freshly formed. The capillaries steadiness is realized through enrollment of pericytes and smooth muscle cells which are controlled by platelet derived growth factor (PDGF) (Gupta et al., 2013)

It is now well established from a variety of studies, that VEGF is pathogenic factor for the distraction of the blood-retinal barrier (BRB) and neovascularization, which are the main pathogenic measures of DME and PDR, respectively (Gupta et al., 2013; Nguyen et al., 2016).

Insulin-like growth factor-1 (IGF-1) is a polypeptide which controls the multiplying and distinction of numerous cell types (Tonkin et al., 2015). In the eyes of human being, formation of IGF-1 is by the retinal pigment epithelium cells, pericytes, and endothelial cells, and investigational studies show that IGF-1 inspires the production of VEGF. Intensities of intra vitreal IGF-1 were revealed to be considerably high in patient's eye having PDR equated to those patients in a control group (Semeraro et al., 2015).

Besides the VEGF, there are numerous other factors of growth which is a factor in the course of PDR also, for example changing growth factor (TGF)-b, hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), and the pro-fibrotic connective tissue growth factor (CTGF, CCN2) (Klaassen et al., 2015; Van Geest et al., 2012).

The detection of VEGF role in diabetic retinopathy has resulted to the growth of anti-VEGF agents as remedy for the management of diabetic problems.

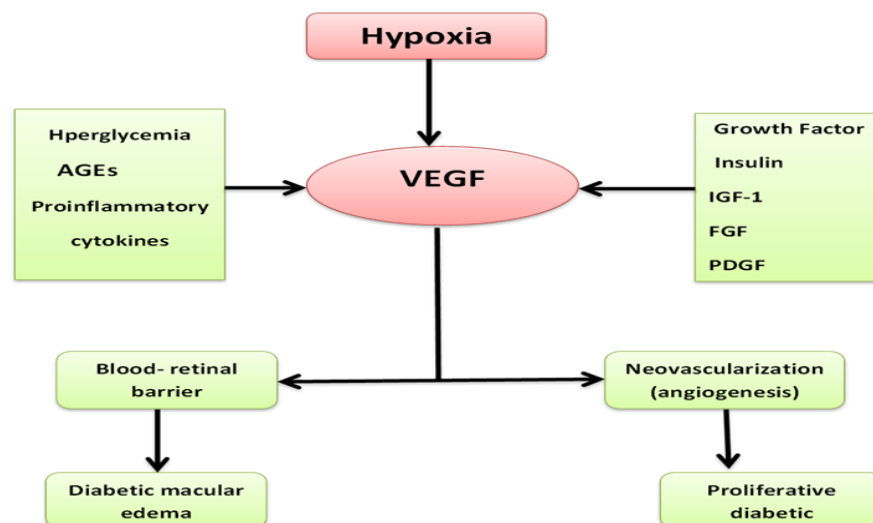


Figure 5 Vascular endothelial growth factor (VEGF) pathways

Treatment of diabetic retinopathy

Depending on the severity of DR, treatment should aim at preventing progression, promote regression and minimize loss of vision.

Glycemic control

Intensive glycemic control (with HbA1c controlled to <6.4% vs. 7.5% in the standard therapy group at 1-year follow-up) revealed to reduce advancement of DR by 33% after 4 years of follow-up. The benefit of intensive blood pressure control is less well-defined. Despite the early positive results from the United Kingdom Prospective Diabetes Study (UKPDS) trial, later investigation including the Appropriate Blood Pressure Control in Diabetes trial and Action to Correct Cardiovascular Risk in Diabetes (ACCORD) Eye Study Group unsuccessful to find any substantial difference in DR advancement between intensive treatment (mean blood pressure, 132/78 mmHg; median systolic blood pressure, 117 mmHg) and standard treatment (mean blood pressure, 138/86 mmHg; median systolic blood pressure, 133 mmHg). (Estacio et al., 2000; ACCORD Study Group & ACCORD Eye Study Group 2010; Yuen et al., 2016).

Laser treatment

Lasers of multiple wavelengths can be used to treat different ophthalmic conditions. The high prevalence of diabetes and DR has made the laser an especially important tool in managing DR and in preventing visual impairment (Romero-Aroca et al., 2014). Laser treatment to retina is administered with short laser pulses of the selected beam size, creating a focal retinal burn in a controlled manner. The radiation energy of the laser pulse is mostly absorbed by the pigment epithelium and underlying choroid. However, it increases also focally the temperature of the retina and the heat effect alters retinal morphology, creating a permanent scar. Laser treatment is essential in preventing tractional retinal detachment, neovascular glaucoma and ultimately severe impairment of visual function (Kaiser et al., 2000). Laser therapy has also been the standard treatment in clinically significant macular oedema and it still remains widely used (Stütt et al., 2015). panretinal laser photocoagulation is usually successful in arresting and regressing neovascular growth when delivered without delay (Chappelou et al., 2012). Focal laser treatment is estimated to reduce the risk of moderate visual loss by 50–70% in treating macular oedema (Mohamed et al., 2007). However, there are limitations to the use and efficacy of laser treatment in the macular area (Romero-Aroca et al., 2014). Due to the tissue destructive nature of retinal lasers, a corresponding scotoma may be detected in the central visual field after extensive macular laser treatment or inadvertent foveal burn. Laser scars may also expand over time. These characteristics mean that therapeutic laser treatment is applicable only in selective cases of diabetic maculopathy. In addition, the complications lead to the need for new way for the treatment of PDR.

Emerging treatments

Prevention of certain biochemical mechanisms connecting hyperglycemia and diabetic retinopathy give rise to inspiring outcomes in animal and clinical patients.

Antiangiogenic therapies

Several anti-VEGF pharmacologic agents are currently available commercially. Bevacizumab (Avastin; Genentech, San Francisco, CA, USA) is a full length recombinant improved anti-VEGF monoclonal antibody, approved by the US Food and Drug Administration for the colorectal cancer treatment (Marshall, 2005). This is a large sized molecule (molecular weight: 148 kDa) and has double half-life as compare to ranibizumab (Abdallah & Fawzi, 2009). Ranibizumab (Lucentis; Genentech USA, Inc., San Francisco, CA, USA/Novartis Ophthalmics, Basel, Switzerland) is an engineered, improved, recombinant antibody portion which is active against entire VEGF- A isoforms. Fc domain is lacking and it possesses half-life as compare to

anti-VEGF agents (Hussain et al., 2007). Lucentis is presently FDA accepted as an intravitreal agent for age related macular deterioration and wet treatment (AMD). Pegaptanib (Macugen, Eyetech Inc., Cedar Knolls, NJ, USA) is a 28-nucleotide RNA aptamer which binds precisely to the VEGF-A165 isomer, the main pathological eye VEGF protein. Aflibercept (Regeneron, Tarrytown, NY, USA) having a commercial name Eylea (which is also refer to as VEGF Trap-Eye), this is a recombinant fusion protein containing the main VEGF binding domains of human VEGF receptors one and two. Aflibercept was established to bind VEGF with a higher attraction as compare to bevacizumab or ranibizumab (Nguyen et al., 2013). The FDA accepted aflibercept for treatment of neovascular AMD in the year 2011.

The outcomes of current clinical investigations recommend for useful consequence of anti-VEGF agents in DMO and PDR (Nguyen et al., 2009; Diabetic Retinopathy Clinical Research Network, 2007; Mirshahi et al., 2008; Osaadon et al., 2014). Useful results were realized with the usage of intravitreal bevacizumab adjunctive therapy for vitrectomy patient as a pre-operative treatment. Pre-treatment with bevacizumab increases cleaning up of vitreous fluid, decreases postoperative hemorrhages, active neovascularization and intraoperative bleeding (Yang et al., 2008; Yeh et al., 2009). Additionally it has been revealed that ranibizumab decreases the danger of NPDR development in eyes treated for DME by about 67% (2/3) within a period of 2 years of injections every month (Ip et al., 2012).

Presently, an anti-VEGF agent is revealed to be efficient and harmless managements of DME, and continuing and upcoming investigation will show their possible significance in the treatment of PDR (Simó et al., 2014). Nevertheless, repetitive intravitreal doses of anti- VEGF agents were revealed to result to adverse effects for example cataract, uveitis, endophthalmitis and retinal detachment (Agrahari et al., 2016).

Aside the VEGF, other angiogenic factors for example angiopoietins, hepatocyte growth factor, platelet derived growth factor, connective tissue growth factor (CTGF), stromal cell-derived factor-1 participate in retinal neovascularization and basic fibroblast growth factor (Simo et al., 2006) and, consequently, are also aims for the growth of new antiangiogenic treatments in DR. (Simo et al., 2015).

Alldose reductase inhibitors

Alldose reductase inhibitors (ARIs) revealed the capacity in reducing oxidative stress and lessen the growth of nephropathies, retinopathies and neuropathies in patient with diabetes (Edwards et al., 2008; Wang et al., 2013). Inhibition investigation in diabetic rats and dogs fed with galactose show that AR inhibition through a number of mechanically varied inhibitors averts loss of pericyte, acellular capillaries formation, and succeeding areas of nonperfusion (G Obrosova et al., 2011). Ohmura (2009) found that gaving epalrestat, an ARI, to type 2 diabetic patients for 3 months significantly reduces lipid hydroperoxide levels by 15%.

The development of a large quantity of synthetic ALR2 inhibitors (ARIs) has been achieved in the past years, and some distinctive ARIs for example Epalrestat, Zenarestat, Lidorestat, Acetic acid derivative of oxadiazol, Sorbinil, Fidarestat, AS-3201, Benzenes sulfonamide, ARI-809 and 2- phenylpyrido [1,2-a]pyrimidin-4-one (PPP) (Kikkawa et al., 1983; Ao et al., 1991; Van Zandt et al., 2005; La Motta et al., 2008; Robison et al., 1995; Asano et al., 2002; Negoro et al., 1998; Mylari et al., 2005; La Motta et al., 2007; Alexiou, & Demopoulos, 2010). Nevertheless, only epalrestat has gotten to the market, in Japan in 1992 and lately in India and China, for the management of diabetic neuropathy. Numerous ARIs that appeared to be capable have however to be clinically effective because of unwanted effects (Ramirez et al., 2008; Zhang et al., 2013). Consequently, pharmaceutical industries and numerous investigators have been doing investigation to find new, effective and safe ARIs from natural sources. Du et al. (2006) found that curcuminoids, phenolic compounds from *Curcuma longa* (turmeric), had potent

inhibitory activity against aldose reductase; curcumin had the strongest action with an IC50 value of 6.8 μ M (2.5 μ g/mL). Fruits, already recognized for their anti-diabetic benefits, are rich in flavonoids, known to be potent ARIs, and are thus an under-explored potential source of natural ARIs (de la Fuente & Manzanaro 2003; Veeresham et al., 2014; Xiao et al., 2015).

Antioxidant and Anti-Inflammatory Agents

Many papers suggest that oxidative stress plays a major part in DR pathogenesis. Therefore, the use of antioxidants may be viewed as potential therapeutics in the treatment of DR. Many phytochemicals have been extensively examined, although much more work is needed to definitely assess their effectiveness as alternative therapies in DR (Hernández et al., 2016). Antioxidants are plentiful in vegetables and fruits, as well as in other foods comprising nuts, grains and certain meats, poultry and fish (Hamid et al., 2010). Investigational data revealed that regulation of oxidative stress through antioxidants and maintenance of mitochondrial homeostasis averts/delays diabetic retinopathy development.

In numerous of animal investigations, dietary supplementation with antioxidants (e.g. vitamin E, vitamin C, β -carotene, and thiols such as DL- α -lipoic acid and N-acetyl cysteine) was revealed to reinstate glutathione levels and hinder oxidative injury of the retina. The investigation cover times of diabetes that normally precedes quantifiable retinal pathology so that the therapeutic consequence is restricted (van Reyk et al., 2013). Additionally Green tea polyphenol have great capacity to reduce lipid peroxidation, SO radicals, scavenging of hydroxyl ion apart from antioxidant potential (Sabu et al., 2002). It has been observed that level of SOD, GSH and serum glucose level in diabetic rats on green tea supplementation (Mustata et al., 2005).

Flavonoids possess antioxidant, antiangiogenic, and anti-inflammatory properties; thus selected flavonoids could be operative in the preventing or treating ocular diseases, including DR (Majumdar & Srirangam, 2010). In this respect, quercetin reduces oxidative stress, neuroinflammation, and apoptosis in streptozotocin- treated rats. Indeed, six-month treatment with quercetin restores glutathione levels and the activities of antioxidant enzymes, reduces the levels of inflammatory cytokines, and protects ganglion cells from apoptotic cell death (Kumar et al., 2014). Carotenoids are also powerful antioxidants. In particular, lutein and zeaxanthin, which in diabetes are decreased in serum and retina, have been reported to inhibit diabetes induced retinal oxidative damage (Kowluru et al., 2008; Kowluru et al., 2014).

Overall, data from literature indicate that phytochemicals can act as effective molecules in the management of retinal complications in diabetes, although additional studies using human clinical studies are required in confirming the valuable effects of phytochemicals in treating DR.

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Conflict of Interest

The authors declare that they do not have any competing interests.

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