

Herbal Plants: A Boon in the Treatment of Diabetic Retinopathy

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ABSTRACT

Background: Among the various medical complications of diabetes mellitus, the one with the most dreadful and griming outcome is diabetic retinopathy, which grounds serious sight threatening conditions by causing severe damage to the retina (the projection screen of the eye). This damage is owed to the various alterations caused in the blood capillaries, which supply blood to the retina, as a result of hyperglycemia prevalent in the body of the diabetic person. It being one of the most prevalent causes of blindness incurs a compelling need for its prevention and cure. Looking at the severity of this disorder, various researches have been conducted to find as many ways to treat it as possible. **Objective:** This review is aimed at giving an account of the various herbal plants such as *Pinus pinaster*, *Azadirachta indica*, *Ginkgo biloba*, *Anisodus tanguticus*, *Stephania tetrandra*, *Salvia miltiorrhiza* and *Gymnema sylvestre* which have till now shown successful results in their employment as a possible treatment of diabetic retinopathy. **Conclusion:** Some more studies need to be done for their validation so that they can not only actively substitute or be used in conjunction with the present options of treatment in order to summon the best results which can prevent or cure this disorder effectively but also restore the damage done to the sight of the diabetic patient.

Key words: Diabetic retinopathy, pycnogenol, *Azadirachta indica*, *Ginkgo biloba*, anisodamine, tetrandrine

Pharmacologia 6 (1): 1-10, 2015

INTRODUCTION

Diabetic retinopathy refers to a condition in which damage occurs to the blood vessels which carry blood to the retina of the eye because of the prevailing high levels of glucose in the body. It is one of the leading causes of blindness in the world. The prediction of the occurrence of this disorder can be made from the duration of diabetes itself. The epidemiology of retinopathy has been found to increase with increase in the duration of time for which the patient has been enduring with diabetes mellitus. The chances of developing diabetic retinopathy of the patients having diabetes from the past 5 years are around 17 and 97.5% (for having suffered with diabetes for 15 years or more) (Klein *et al.*, 1984). Hyperglycemia causes various alterations in the microvasculature of these blood vessels such as thickening of basement membrane, increase in vascular permeability, tissue ischemia and liberation of angiogenic factors resulting in angiogenesis. Ischemia and the discharge of certain vasoactive chemicals e.g., Vascular Endothelial Growth Factor (VEGF) kindles the formation of new blood vessels. These new vessels arouse from the retinal surface and their growth occurs on the posterior wall of

the vitreous chamber. Since the newly formed blood vessels have not been properly matured and are very fragile in nature, their contents (blood and fluids) get leaked out very easily resulting in vitreous hemorrhages. Further adverse condition arises when the vitreous chamber begins to constrict resulting in retinal detachment. All these dysfunctions lead to vision loss (Cogan *et al.*, 1961; Ishida *et al.*, 2003).

ROLE OF VARIOUS HERBAL PLANTS IN MEDICINES

Plants remain the most valued source of medicines since the advent of earliest civilizations. Plants provide natural biologically active molecules termed as their active chemical constituents. These molecules themselves as well as the modification of these molecules into their derivatives provide a rich pool of agents with enhanced pharmacological activity against any disease. An estimation of 400 traditional plants being useful for the treatment of diabetes mellitus has been made by different studies. Thus, plants provide a spring of alternate medicinal system or a supplement to the conventional therapies of various disorders (Bailey and Day, 1989). Following are some of the medicinal plants which have shown to possess properties of treating diabetic retinopathy.

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***Pinus pinaster*:** *Pinus pinaster* is an evergreen tree belonging to the family Pinaceae. It is commonly known as Maritime Pine Tree. It is native to the Mediterranean regions of Europe. Pycnogenol is an extract prepared from the outer bark of this plant. Pycnogenol describes the name of a group of compounds that contain proanthocyanidins. It contains phenolic compounds such as taxifolin, catechin and epicatechin and acid derivatives of phenol such as p-hydroxybenzoic acid, protocatechuic acid, vanillic acid, gallic acid, cinnamic acid, p-cumaric acid, caffeic acid and ferulic acid. Some inorganic metal ions such as calcium, potassium, iron and traces of manganese, zinc and copper are also found to be present in it. Pycnogenol has been studied vastly for the purpose of its use in the treatment of diabetic retinopathy (Rohdewald, 2002).

- It is said to increase the membrane integrity of the capillaries (due to the presence of procyanidins; a class of non-hydrolysable tannins, as its active constituent, which has a large affinity for binding with the proteins of the cellular membrane). Thus, it stabilizes the walls of the blood capillaries
- It improves the resistance of leakage of blood and fluids from the blood capillaries into the retinal cells (Spadea and Balestrazzi, 2001)
- It improves microcirculation and also reduces the capillary permeability. This accounts for inhibiting the formation of edema (Steigerwalt *et al.*, 2009)
- Its potent antioxidant capability is due to its free radical scavenging activity. This contributes in lowering the amount of Reactive Oxygen Species (ROS) in the body which are responsible for the activation of advanced glycation products due to the accumulation of glycolytic metabolites
- The radical scavenging property of pycnogenol is also responsible for its anti-inflammatory property. Thus, reducing the degeneration of capillaries by various inflammatory mediators (Packer *et al.*, 1999)
- The reducing compounds present in pycnogenol are responsible for decreasing the amount of advanced glycation end-products (AGEs), which are greatly responsible for the progression of diabetic retinopathy in diabetic patients (Schonlau and Rohdewald, 2001)

Thus, pycnogenol is responsible for reducing the progression of diabetic retinopathy in the diabetic patients in many ways. The mechanism of its action for this is explained in brief in the flow chart in Fig. 1.

***Azadirachta indica*:** *Azadirachta indica* is a fast growing tree belonging to the family Meliaceae. It is commonly known as Neem. It is native to India and is also found in some other Asian countries such as Pakistan, Bangladesh, Sri Lanka, Thailand, Malaysia, Mauritius, Myanmar, Nepal and in some parts of Africa. It contains a wide variety of chemical constituents namely diterpenes (sugiol and nimbiol), triterpenes (beta-sitosterol and stigmasterol), tertaterpenoid (azadirachtin-k), sulphur containing compounds (nimbin, nimbidin, nimbinin and nimbidol), limonoids (maliantrioland nimbendiol), flavonol glycosides (nimaton, quercetin, myricetin, kaempferol) along with certain other compounds such as nimbolide, olichinolide B, 6-deacetyl-nimbin, salanin and azadiradione (Kokate *et al.*, 2006a).

The leaf extract of *Azadirachta indica* is known to show anti-hyperglycemic effect, thus can be used in treating diabetes. Besides, after getting successful results in the studies done on the leaf extract for its activity of lowering hyperglycemia in the body, it has also shown useful results in the treatment of diabetic retinopathy. The mechanism behind it is not so clear but is said to be related to its anti-serotonin activity.

Serotonin is found to be present intracellularly in the pancreatic cells of the diabetic patients. It is said to have the following effect in the insulin secretion physiology:



Various studies conducted suggest that some of the constituents found in *Azadirachta indica* are involved in exhibiting certain effects which act as serotonin antagonists and inhibits this activity of serotonin and prevent hyperglycemia (Feldman *et al.*, 1972). This is explained as follows:

- Scientific facts suggest that serotonin has an inhibitory effect on the release of insulin due to a process in which serotonin inhibits the formation of cyclic adenosine monophosphate (cAMP), which is an important secondary mediator in the pathway responsible for insulin release (Feldman and Lebovitz, 1970; Yajima *et al.*, 1999). This has been supported by the evidences that antagonists of alpha-adrenergic receptors (such as phentolamine) have shown a counter-inhibitory effect on the inhibition of insulin release by serotonin in the process of dibutyl cyclic adenosine monophosphate mediated release of insulin

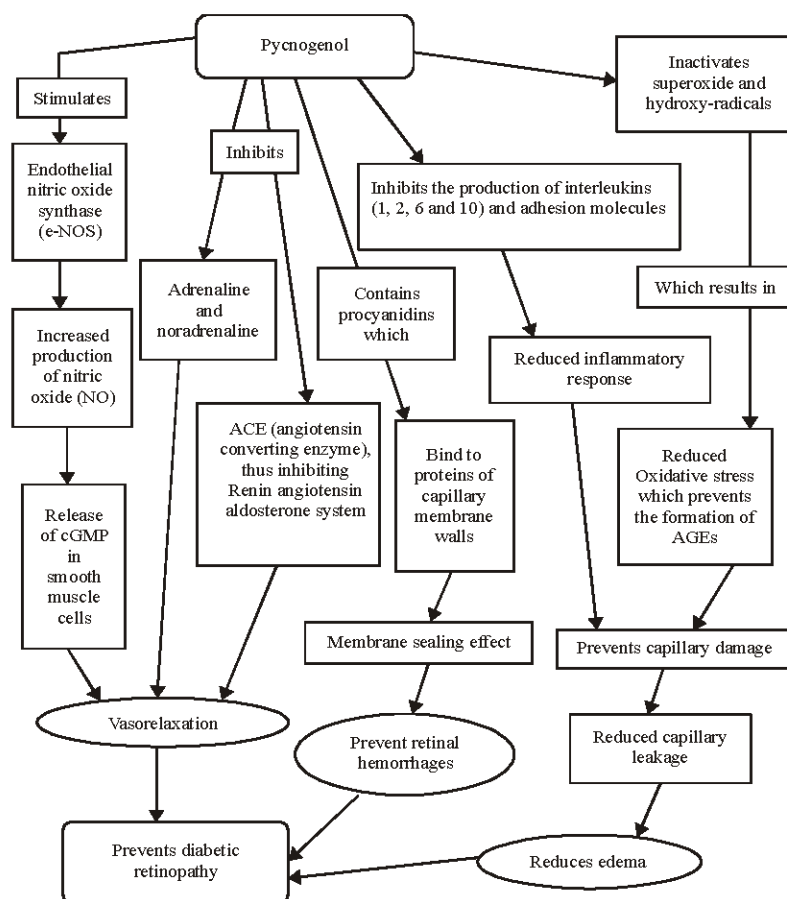


Fig. 1: Mechanism of action of pycnogenol for the prevention of diabetic retinopathy

- Moreover, alpha adrenergic agents also cause the inhibition of insulin release via epinephrine and norepinephrine pathways, which inhibit the secretion of insulin by enhancing glucose or glucagon stimuli. Thus, the alpha adrenergic system is, undoubtedly, responsible for inhibiting the release of insulin. On the other hand, it has been seen that beta adrenergic agents have the opposite effect to that shown by the alpha adrenergic agents, i.e., they stimulate the release of insulin (Feldman and Lebovitz, 1970)

Thus, the constituents suspected to be involved in the anti-hyperglycemic activity of *Azadirachta indica* (viz., Quercetin-3-O-beta-D-glucoside, Myricetin-3-O-rutinoside, Quercetin-3-O-rutinoside, Kaempferol-3-O-rutinoside, Kaempferol-3-O-beta-D-glucoside and Quercetin-3-O-alpha-L-rhamnoside) are said to act as beta adrenergic agents and stimulate the release of insulin in the following manner shown in Fig. 2 (Chattopadhyay, 1999).

Ginkgo biloba: *Ginkgo biloba* is a large tree belonging to the family Ginkgoaceae and it is now the only surviving member of this family. It is commonly known as maidenhair tree. It is native to China. It is believed to be the oldest living species of trees on Earth. The various chemical constituents found in this plant are terpenes which include ginkgolides (which are derivatives of lactone) and bilobalides (which are mostly found in the form of coumaric esters of glucorhamnosides) and flavonoids (particularly flavonol and flavone glycosides). Other compounds present are quercetin, kaempferol, isorhamnetin, bilobetin, ginkgetin, isoginkgetin, scieadopitysin, proanthocyanidins, ginkgolic acid, carotenoids, ascorbic acid, catechin, iron-based superoxide, 6-hydroxykinuretic acid, 3,3'-dimethoxy-4,4'-dihydroxy-stilbene, protocatechuic acid, shikimic acid, sterols, fatty acids, tannins, resins and vanillic acid. Commonly found ginkgolides are ginkgolide A, B, C, J and M, out of which ginkgolide B is the most active. It also possesses a toxic substance known as ginkgotoxin which is chemically 4-O-methoxypyridoxine. It

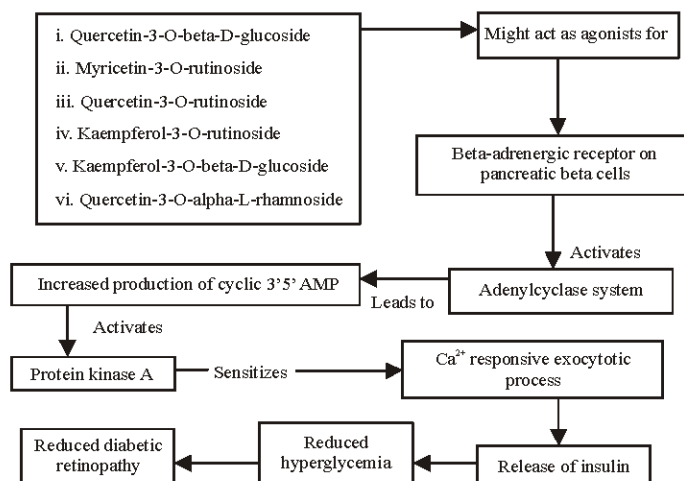


Fig. 2: Mechanism of action of the various constituents of *Azadirachta indica* in the prevention of diabetic retinopathy

substance is known to show anti-vitamin B6 activity and also inhibits the formation of GABA (Gamma amino butyric acid). This property of this plant results in the occurrence of convulsions and loss of consciousness (Chi *et al.*, 1997; Del Tredici, 2000; Kokate *et al.*, 2006b).

Various chemical constituents of this plant which are responsible for its pharmacological action include the terpene lactones, ginkgolides and flavonoids. The possible mechanism of action by which these chemical constituents present in *Ginkgo biloba* are said to treat diabetic retinopathy is proposed as follows:

- *Ginkgo biloba* is regarded as a blood thinner. Due to this property, it is responsible for increasing the blood circulation in the body, thus reducing any chances of the adhesion of leukocytes and preventing other inflammatory actions (Chung *et al.*, 1999)
- It acts as anti-inflammatory due to its property of inhibiting platelet-activation. Due to this property, it is successfully able to prevent the inflammatory response which plays a critical role in the pathogenesis of diabetic retinopathy
- The flavonoids present in this plant are responsible for the anti-oxidant properties. They help in scavenging the reactive oxygen species present in the body and thus relieves the body from oxidative stress (Akiba *et al.*, 1998)
- Among the ginkgolides, Ginkgolide A is responsible for the inhibition of the down regulation of endothelial nitric oxide synthase and prevents any reduction in the levels of nitric oxide in the body.

The result of these actions in vasorelaxation, which reduces the hypertension prevalent in the capillaries, thus preventing diabetic retinopathy (Fig. 3) (Zhou *et al.*, 2006)

***Anisodus tanguticus*:** *Anisodus tanguticus* is a perennial flowering plant belonging to the family Solanaceae. It is also called *Scopolia tanguticus*. It is native to China where it is commonly known as Zang Qie. It is also found widely in Tibet. The chemical constituents found in *Anisodus tanguticus* are tropane alkaloids such as anisodamine, anisodine (which is hydroxyhyoscyne), hyoscyamine, 6-hydroxy-hyoscyamine, scopolamine, tropine, apoatropine, 3- α -(4,4,4-trichloro-2-phenylbutyryloxy)tropane and a non-tropane alkaloid-cusgohygrine. Out of all these, anisodamine (which is 6- β -hydroxy-1- α -H, 5- α -H-tropane-3- α -ol tropane) is the most active compound of this plant. Anisodamine and its derivative anisodamine hydrobromide are responsible for the various pharmacological activities of this drug as anti-cholinergic agents (Tang and Eisenbrand, 1992a; Trease and Evans, 2002).

Anisodamine (6-hydroxyhyoscyamine) is said to be effective in the treatment of diabetic retinopathy. The mechanism of action by which it exhibits this property is still unknown and is an area of active research. Some studies have been conducted till now to find out its mechanism of action but they could not give a definite conclusion. But some predictions made from the results of all these studies are as follows:

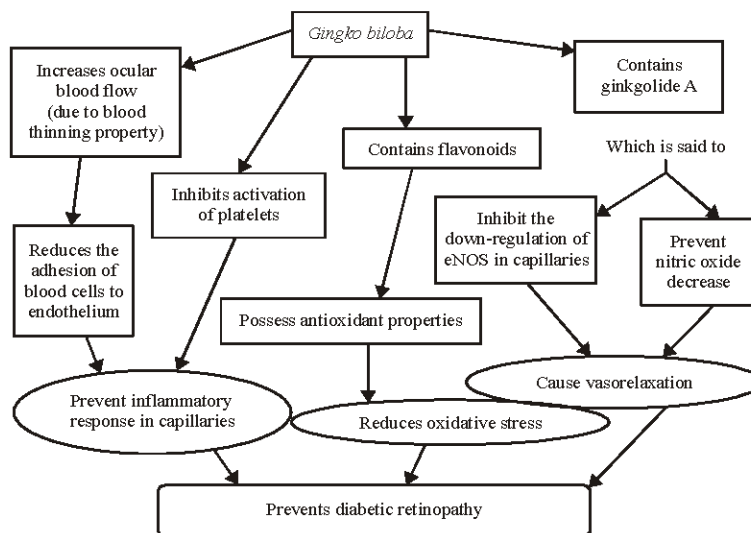


Fig. 3: Mechanism of action of *Ginkgo biloba* in the prevention of diabetic retinopathy

- Earlier it was believed that the anti-shock and anti-hemorrhagic activities of *Anisodus tanguticus* are due to its vasodilating property. But only a slight vasodilation was observed in animal models after the administration of an appropriate dose of anisodamine. Thus, this possibility for the mechanism of its action had to be ruled out (Su, 1992)

Then, another possibility which was suspected regarding the mechanism of action of anisodamine was its anti-hemorrhagic property (Su *et al.*, 1984). Further studies were performed to find another possible reason for its properties and the following conclusions were made from them:

- **Improvement in the microcirculatory blood flow:** Due to various effects of anisodamine shown in the body namely fibrinolytic activity, reversal of endotoxin induced vascular leakage, stabilization of lysosomes and inhibition of cathepsin, it is known to have improvised effects on the blood circulation in the microvasculature supplying blood to retina, thus inhibiting inflammatory responses in the capillaries. This anti-inflammatory action of anisodamine is thus accountable for preventing diabetic retinopathy
- **Involvement of cholinergic anti-inflammatory pathway:** Anisodamine acts as a muscarinic receptor antagonist, thus blocking the muscarinic receptor. This action leads to the rerouting of

acetylcholine to alpha-7 nicotinic acetylcholine receptor, which results in the activation of cholinergic anti-inflammatory pathway. This pathway is responsible to stimulate the vagus nerve and thus activating the vagal-immune reflex which has an anti-inflammatory response. This response is responsible for the anti-hemorrhagic property of anisodamine (Zhao *et al.*, 2011)

- **Protective action:** Anisodamine is known to show cell-protective action on the cells, thus causing stabilization of the membrane, which inhibits the inflammatory action (which is responsible for the development of retinal hemorrhages), thus preventing the hemorrhages which occur in diabetic retinopathy (Su, 1992)

The flow chart showing cell protective action of anisodamine in the prevention of diabetic retinopathy is shown in Fig. 4.

Thus, the above mechanisms have been proposed as the possible reasons for the anti-hemorrhagic property of anisodamine but they are yet to be conceptually finalized. More studies and researches are going on regarding this perspective.

***Stephania tetrandra*:** *Stephania tetrandra* is a perennial vine belonging to the family Menispermaceae. It is native to China where it is commonly known as Han Fang Ji. The main chemical constituents found in this plant are two alkaloids of bisbenzylisoquinoline type Han Fang Ji. The main chemical constituents found in this plant are two

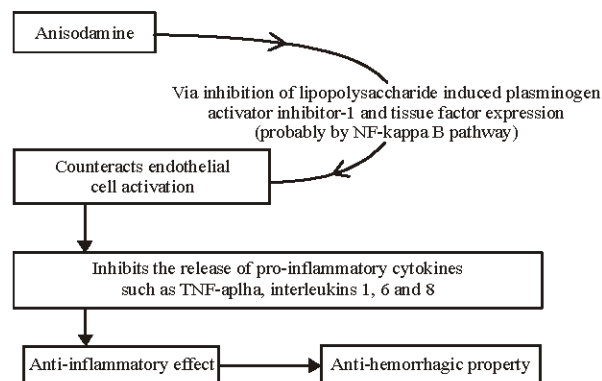


Fig. 4: Cell protective action of anisodamine in the prevention of diabetic retinopathy

alkaloids of bisbenzylisoquinoline type namely Tetrandrine and Fangchinoline, in which two ether linkages connect the two benzylisoquinoline moieties. Another such alkaloid found later was berbamine. In addition to these, a protoberberine type quaternary alkaloid was also found which is now named as cyclanoline. Two more alkaloids, namely oxofangchirine and stephananthrine, were discovered recently, out of which the former is a bisbenzylisoquinoline type and the latter consists of a skeletal structure of phenanthrene with a tertiary amino side chain. Other compounds include dimethyltetrandrine iodide, menisine, menisidine, stepholidine and some flavonoids (Tang and Eisenbrand, 1992b).

The studies conducted on *Stephania tetrandra* show that it is effective in preventing diabetic retinopathy due to the presence of an active constituent tetrandrine which works as follows:

- Tetrandrine is said to be responsible for a decrease in the production of nitric oxide due to its blocking action on the voltage gated calcium channels. This results in a reduction in the release of vascular endothelial growth factor (which is a necessary growth factor in diabetic retinopathy for the process of formation of new blood vessels). This accounts for prevention in the process of angiogenesis (Wang and Lemos, 1995; Kwan *et al.*, 1999)
- Tetrandrine is also responsible for the inhibition of many inflammatory mediators which have a vital role in the progression of diabetic retinopathy (e.g., various cytokines such as IL-1, IL-6 and TNF-alpha). This action of tetrandrine further leads to the inhibition of the mechanism by which I-kappa-B-alpha (which is an important factor for controlling the uveoscleral outflow pathway) is

phosphorylated. This inhibits the activation of a nuclear factor (NF-kappa B) which is responsible for angiogenesis, thus preventing the progression of diabetic retinopathy (Kikuchi *et al.*, 2010). The overall mechanism is shown in Fig. 5

- Also tetrandrine is now also being studied for its properties as an anti-inflammatory agent due to the action by which it inhibits the production of prostaglandins and leukotrienes (Teh *et al.*, 1990). Thus, this could be one of another reason due to which it prevents diabetic retinopathy

Salvia miltiorrhiza: *Salvia miltiorrhiza* is a perennial plant belonging to the family Lamiaceae. It is commonly known as Chinese sage or Danshen. It is native to China and Japan and was an extensively used drug in Chinese medicine. Many chemical constituents have been identified in this plant which include diterpenes (called tanshinones), which are lipophilic in nature and polar phenolic compounds. The various compounds which come under tanshinones are tanshinone I, tanshinone IIA and cryptotanshinone. The polar phenolic compounds include phenolic acids like caffeic acid and its derivatives such as danshensu, salvianolic acid A, salvianolic acid B, rosmarinic acid and prolithospermic acid. Other compounds include baicalin, beta-sitosterol, daucosterol, flavanones, vitamin E and tannins. The lipophilic compounds are responsible for its antibacterial, antioxidant and anti-neoplastic properties whereas, the polar (hydrophilic) compounds are responsible for its antioxidant and anticoagulant properties (Zhou *et al.*, 2005; Wang *et al.*, 2007; Jiang *et al.*, 2005).

Danshen dripping pills are the commercial preparations prepared from the roots of the plant *Salvia miltiorrhiza*. Several studies have been performed to find out its use for the treatment of diabetic retinopathy. A study performed on a group of 42 patients suffering from diabetic retinopathy of phase, out of which a fraction of them were treated with Danshen dripping tablets, gave the following results:

- Danshen dripping pills were effective in the recovery of the visual physiology of the eyes to some extent. This showed that these pills could be used to reverse the effects of diabetic retinopathy
- These pills were also able to control the leakage of blood and fluids which occur from the small blood capillaries supplying the retina into the retinal cells. These types of further micro-hemorrhages have been seen to be prevented in some patients, after the incorporation of dose of these pills in them

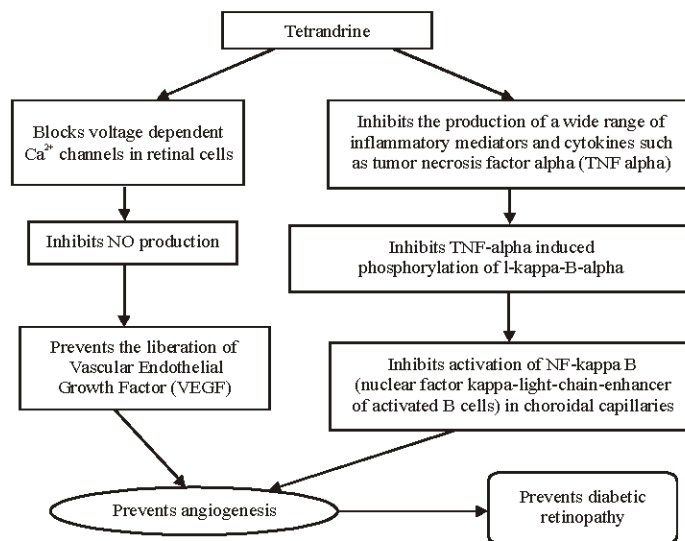


Fig. 5: Mechanism of action of tetrandrine for the prevention of diabetic retinopathy

- Microaneurysms (small structures which appear due to swelling in the blood capillaries due to pericyte loss) which appear like tiny red dots on the surface of the retinal wall were seen to get reduced by the use of these pills (Qi *et al.*, 2007)

Another study conducted separately regarding the usage of Danshen dripping pills in the treatment of diabetic retinopathy showed that:

- Ischemia prevalent in the blood capillaries carrying blood to the retina was seen to improve after administering these pills
- Sight improvement was seen in the visual field after the dose incorporation of these pills which was earlier affected badly due to diabetic retinopathy
- The magnitude of micro-aneurysms was also seen to be decreased in comparison to the earlier conditions. This gave a positive result in the further usage of these pills for the treatment of diabetic retinopathy (Deng *et al.*, 2005)

Although, these results were obtained from such researches, the mechanism of action by which they act to reduce the progression and cure diabetic retinopathy is still unknown but several mechanisms for it have been proposed which might be one of the reasons for its properties. These various possible mechanisms are given in Fig. 6 (Lin and Hsieh, 2010).

***Gymnema sylvestre*:** *Gymnema sylvestre* is a woody, climbing plant belonging to the family Asclepiadaceae. It

is commonly known as meshasringa or gurmar/gudmar. It is native to India and Sri Lanka. The chemical constituents found in this plant are pentriacotane, hentriacontane, phytin, alpha and beta chlorophylls, resin, tartaric acid, formic acid, butyric acid, inositol, d-quercitol, anthraquinone, flavones, lupeol, beta-amyrin, stigmasterol, triterpenoid saponins of class oleanane (such as gymnemic acids I-VII and gymnemasaponins) and dammarene (such as gymnemasides A-F) (Dateo and Long, 1973; Kanetkar *et al.*, 2007).

The leaf extracts of this plant is known to show anti-diabetic effect by lowering the glucose levels in the blood (Khare *et al.*, 1983). Since, many studies have proven this fact that the gymnemic acids present in the plant are effective in reducing hyperglycemia, it was speculated that this effect could be utilized for the treatment of diabetic retinopathy. Therefore, many researches were done regarding the role of gymnemic acids in treating diabetes which led to findings that the gymnemic acids act in the following manner to reduce the blood sugar levels.

- Due to the structural similarities between the gymnemic acid and glucose molecule, the presence of gymnemic acid molecules could be easily be disguised as those of the glucose, thus enabling former molecules to block the receptors of glucose in the taste buds. This filling of the receptor locations present on taste buds disables their activation by the glucose molecules being taken up in the meal

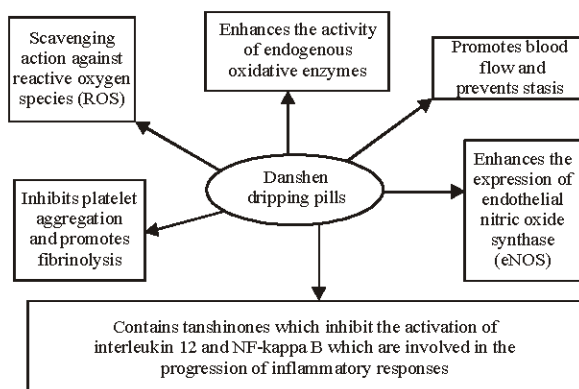


Fig. 6: Possible mechanisms which could be response for the preventing action of Danshen dripping pills against diabetic retinopathy

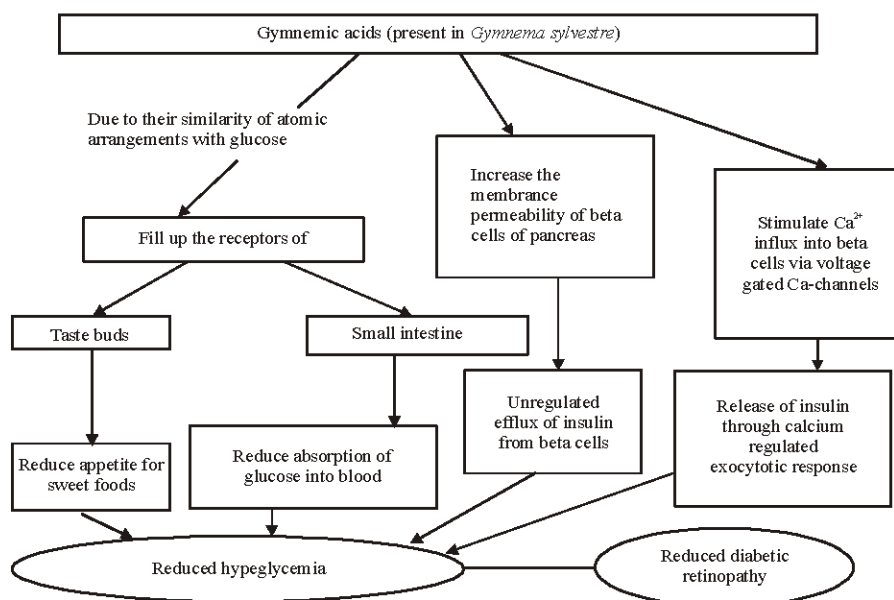


Fig. 7: Mechanism of action of gymnemic acids, the main active constituents of *Gymnema sylvestre*, for the prevention of diabetic retinopathy

- Moreover, the same property of the gymnemic acid molecules help them fill up the position on receptors where otherwise is occupied by glucose molecules in the external layer of small intestine from where absorption of nutrients take place from intestine into the bloodstream. This decreases the glucose absorption from the small intestine, thus helping in reducing its levels in the blood (Kanetkar *et al.*, 2007; Liu *et al.*, 1992)
- Gymnemic acids are also thought to activate Ca^{2+} regulated exocytosis mechanisms by which insulin secretion is increased. But it is not yet

confirmed and further studies are still going on full swing to validate this fact (Persaud *et al.*, 1999). The whole mechanism is shown in Fig. 7

CONCLUSION

Since diabetic retinopathy is an immensely serious complication associated with diabetes mellitus, there is an urgent need to find effective treatments which could eradicate it completely. The various herbal drugs given in this review study aimed at giving an overview of the alternative options available which could be effectively used as a substitute to any modern medications or can be

used along with them as a complementary system in lieu of getting the best possible results in the management of this disorder. There is further call to discover more such recourses which could help improvise the conditions prevalent in the present scenario.

ACKNOWLEDGMENT

We would like to extend our gratitude towards Dr. Anita Kotwani, Associate Professor, Vallabhbhai Patel Chest Institute, University of Delhi, for sharing her valuable ideas and giving various suggestions without which this article would have been incomplete.

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