

# Aldose Reductase Inhibitors from Nature: A New Hope for Treatment of Cataract



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## Introduction

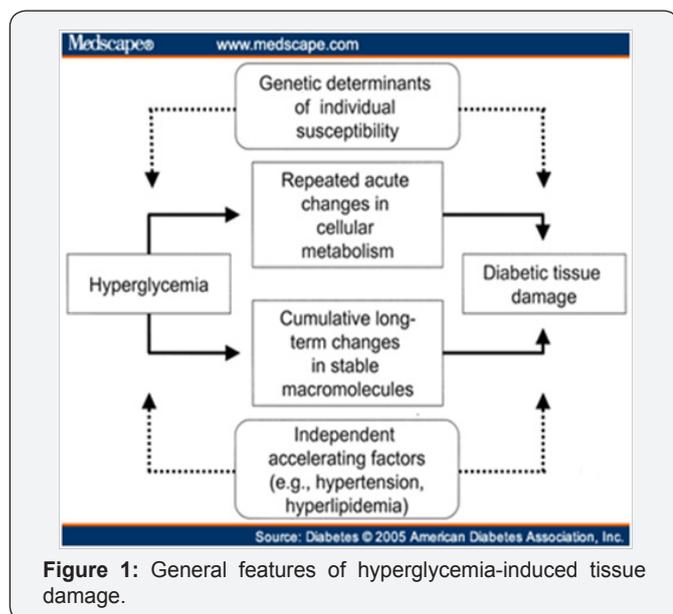
Diabetes mellitus is collection of metabolic disorders characterized by high serum glucose level in the body that is due to low insulin secretion or due to cellular unresponsiveness toward produced insulin. This high level of glucose produces the conventional symptoms of polyphagia, polydipsia and polyuria [1]. Uncontrolled diabetes can cause diverse complications, diabetic ketoacidosis and non ketotic hyperosmolar coma fall under acute complications [2] while chronic complications comprise multiple tissue damage that results in stroke, cardiovascular disease, foot ulcers, renal failure and eye damage [3].

Prospective Diabetes Study) established that hyperglycemia (far left of the figure) causes the clinically manifest diabetic tissue damage (far right). It is affected by genetic determinants of individual susceptibility (top box) and by independent accelerating factors such as hypertension (bottom box), the (inner boxes) is the mechanisms that mediate the tissue-damaging effects of hyperglycemia [4].

Tissue-damaging effects of hyperglycemia mean damage to a specific subset of cell types, mesangial cells (renal glomerulus), capillary endothelial cells (retina) and neurons and Schwann cells (peripheral nerves). These cells are especially vulnerable to high glucose (hyperglycemia bathes all the cells of every tissue) due to that they cannot reduce the transport of glucose inside them under hyperglycemia (other cells are able to do so), so their internal glucose concentration elevate. This is significant, because it indicate involving mechanisms going on inside these cells, rather than outside [5,6]. In the tissue damaging mechanisms polyol pathway was the first discovered mechanism [7]. Then, in the late 1970's, a second mechanism emerged, increased formation of Advanced Glycation End products (AGEs) [8]. In the late 1980's and early 1990's, a third mechanism was elucidated, hyperglycemia-induced activation of protein kinase C (PKC) isoforms [9]. And finally in the late 1990's, latest mechanism was clarified, increased hexosamine pathway flux and consequent over-modification of proteins by N-acetyl glucosamine [10].

## The polyol pathway (Aldose Reductase Enzyme)

**Physiological Significance of aldose reductase:** At present, physiological functions of aldose reductase have not been entirely clarified; its general role in most body tissues is to reduce toxic aldehydes in the cell to inactive alcohols, furthermore, some other specific roles have also been clarified [11].



**Figure 1:** General features of hyperglycemia-induced tissue damage.

The general features of hyperglycemia-induced tissue damage are shown schematically in (Figure 1). The DCCT (Diabetes Control and Complications Trial) and the UKPDS (U.K.

**Seminal energy production:** The polyol pathway was first identified in the seminal vesicle by Hers, who demonstrated the conversion of blood glucose into fructose in seminal vesicle as an energy source for sperm cells [11].

**Osmo-regulatory function in the kidney:** Increased aldose reductase expression and accumulation of intracellular sorbitol in the cultured cell line from rabbit renal papilla as result of elevated extracellular sodium chloride was demonstrated [12]. In the renal medulla, mRNA of the enzyme was profusely expressed compared with relatively low cortex expression [13]. Therefore, these findings denote the osmo-regulatory role of aldose reductase in the renal homeostasis. Nevertheless, in non-renal cells, aldose reductase physiological osmo regulatory implications is still unknown.

**Pathological roles of aldose reductase**

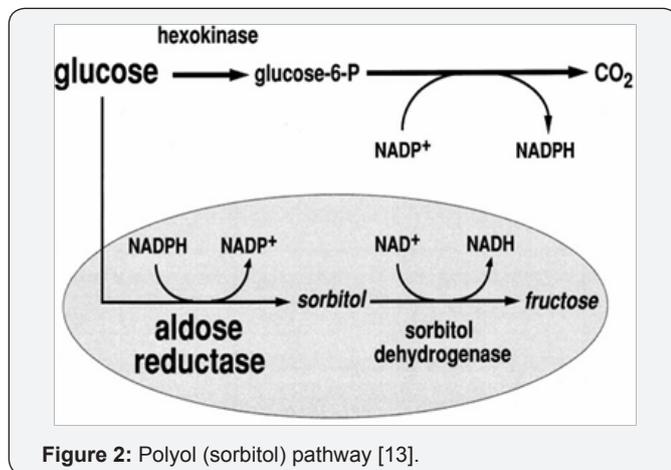


Figure 2: Polyol (sorbitol) pathway [13].

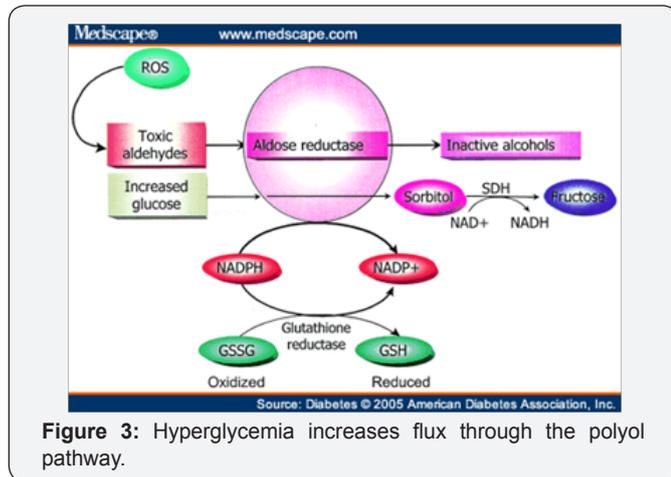


Figure 3: Hyperglycemia increases flux through the polyol pathway.

Under normo-glycemic conditions, through hexokinase pathway, most of the cellular glucose undergoes phosphorylation into glucose 6-phosphate and smaller part of glucose (non-phosphorylated) enters the alternate route of glucose metabolism, the polyol pathway (Figure 2). The rate-limiting step of the polyol pathway is the reduction of glucose to sorbitol by aldose reductase enzyme, sorbitol dehydrogenase enzyme subsequently converts the produced sorbitol to fructose,

thus constituting the polyol (sorbitol) pathway (Figure 3). When hexokinase is saturated by ambient glucose (under hyperglycemia), the flux of glucose through the polyol pathway then increased to account for as much as one-third of the total glucose turnover [14].

This leads to accumulation of the products of the polyol pathway that accompanied with depletion in reduced nicotinamide adenine dinucleotide phosphate (NADPH) as well as the oxidized form of nicotinamide adenine dinucleotide (NAD), the cofactors used in the pathway [15], it is significant to mention that NADPH is essential for regeneration of reduced glutathione (critical intracellular antioxidant) and nitric oxide (NO) synthase (NO is important for micro-vascular arrangement and nerve conduction)so, the polyol pathway induces intracellular hyper-osmolar pressure, increases susceptibility to intracellular oxidative stress , elicits micro-vascular derangement and slows the nerve conduction [16,17].

In rat as model, aldose reductase mRNA was highly expressed in the prime target organs of diabetic complications, the lens, the retina, and the sciatic nerve [13]. In the lens, the sorbitol accumulation induces cataract formation due to leakage of amino acids, glutathione, and myo-inositol because of hyperosmotic swelling and derangement of the cell membrane. In the retina of experimental models, the early lesion emerged in vascular component with localization of aldose reductase in retinal micro vessels [18-20]. In the nerves, perturbation in the vasculature and metabolic disturbance in the neural cells contributes to the development of diabetic neuropathy [21-23]. In fact, aldose reductase immuno reactivity was found in the paranodal cytoplasm of Schwann cells as well as in pericytes and endothelial cells of endoneurial capillaries [24]. Although insulin treatment effectively delay the onset of long term diabetic complications and slows their progression in patients with insulin-dependent diabetes mellitus (IDDM), it is practically impossible, even with best clinical management available, to maintain normo-glycemic state at all times throughout the life of diabetic individuals [25]. Accordingly, chemical agents that effectively halt the hyperglycemic injury in diabetic patients would be of great clinical importance.

**Inhibitors of Aldose Reductase Enzyme**

Depending on the previous observations, development of many aldose reductase inhibitors as possible therapeutic agents (with diverse chemical structures) for diabetic complications (to prevent retinal damage, cataracts, and nerve damage) became critical. The clinical efficacy of Sorbinil, ponalrestat, and tolrestat (the most studied inhibitors) in diabetic patients has not been fully proved to meet the standards of the Food and Drug Administration [26].

**Synthetic aldose reductase inhibitors**

Although many synthetic Aldose Reductase Inhibitors such as sorbinil and tolrestat exhibit potent inhibition, their use is

now limited (or they have been withdrawn from clinical trials) because of decreased penetration, low efficacy, and safety problems) [27-29].

**Sorbinil:** When diabetic patients without any symptomatic neuropathy were treated with it, significant improvement in the velocity of conduction was observed in all nerves tested (the peroneal motor nerve, the median motor nerve, and the median sensory nerve) [30], because of the difference in the study design, subjects with various degrees of symptomatic neuropathy, and neuro physiological parameters examined as study endpoints, the overall effect turned out to be disappointingly modest [21].

**Ponalrestat:** Another aldose reductase inhibitor of a different chemical structure, with no clinically important adverse reaction observed (c.f. sorbinil), its beneficial effect failed to be proved in randomized controlled study [31], later, it was shown

that it didn't penetrate the human nerve at doses sufficient to decrease the nerve sorbitol levels [32].

**Tolrestat:** The efficacy of this class of inhibitor was the modest in diabetic patients already symptomatic of neuropathy, the only adverse reaction reported on it was an increase in serum levels of liver enzymes (alanine aminotransferase ALT, aspartate aminotransferase AST), clinical development of tolrestat was withdrawn, due to the inability to demonstrate efficacy on the nerve conduction velocity in the multicenter double-blind studies on diabetic neuropathy [33].

**Ranirestat:** Is in Phase III trials in Europe and the US. Its clinical trial began in June 2009. The only available synthetic inhibitor is Epalrestat that is in Japanese market since 1992. So, there is still an urgent need for development of improved Aldose reductase inhibitors [34].

### Natural Products as Potential inhibitors

**Table 1:** Plant Extracts with aldose reductase inhibitory activity.

|     | Extract                             | Part used     | Reference                         |
|-----|-------------------------------------|---------------|-----------------------------------|
| 1.  | Azadirachta indica Meliaceae        | leaves        | Halder et al. [38]                |
| 2.  | Aralia elata Araliaceae             | Cortex        | Halder et al. [39]                |
| 3.  | Arctium lappa. Asteraceae           | Ripe fruit    | Xu et al. [40]                    |
| 4.  | Agaricus bisporus Agaricaceae       | Fruiting body | Fatmawati et al. [41]             |
| 5.  | Agaricus blazei Agaricaceae         | Fruiting body | Fatmawati et al. [41]             |
| 6.  | Agrocybe cylindracea Bolbitiaceae   | Fruiting body | Fatmawati et al. [41]             |
| 7.  | Artemisia apiacea Asteraceae        | Whole plant   | Jung et al. [42]                  |
| 8.  | Artemisia. argyi Asteraceae         | leaves        | Jung et al. [42]                  |
| 9.  | Artemisia. capillaris. Asteraceae   | Whole plant   | Jung et al. [42]                  |
| 10. | Artemisia. iwayomogi Asteraceae     | Whole plant   | Jung et al. [42]                  |
| 11. | Artemisia. japonica Asteraceae      | Whole plant   | Jung et al. [42]                  |
| 12. | Artemisia. keiskeana Asteraceae     | Whole plant   | Jung et al. [42]                  |
| 13. | Artemisia. montana Asteraceae       | Whole plant   | Jung et al. [42]                  |
| 14. | Artemisia. princeps Asteraceae      | Whole plant   | Jung et al. [42]                  |
| 15. | Artemisia. rubripes Asteraceae      | Whole plant   | Jung et al. [42]                  |
| 16. | Artemisia selengensis Asteraceae    | Whole plant   | Jung et al. [42]                  |
| 17. | Artemisia stolonifera Asteraceae    | Whole plant   | Jung et al. [42]                  |
| 18. | Artemisia sylvatica. Asteraceae     | Whole plant   | Jung et al. [42]                  |
| 19. | Adhatodavasic Acanthaceae           | Not Specified | Gacche et al. [43]                |
| 20. | Aegle marmelos Rutaceae             | Fruiting body | Gacche et al. [43]                |
| 21. | Biophytum sensitivum Oxalidaceae    | Not Specified | Gacche et al. [43]                |
| 22. | Curcuma longa Zingiberaceae         | rhizome       | Halder et al. [38]                |
| 23. | Cinamomum zeylencium Lauraceae      | Bark          | Saraswat Suryanarayana Reddy [44] |
| 24. | Citrus lemon Rutaceae               | Fruit         | Saraswat et al. [44]              |
| 25. | Citrus sinensis aurantium Rutaceae  | Fruit         | Saraswat et al. [44]              |
| 26. | Cuminum cyminum Apiaceae            | seeds         | Saraswat et al. [44]              |
| 27. | Caesalpinia bonduc Caesalpinaceae   | Not Specified | Gacche et al. [43]                |
| 28. | Cassia fistula Caesalpinaceae       | Not Specified | Gacche et al. [43]                |
| 29. | Catharanthus roseus Apocyanaceae    | leaves        | Gacche et al. [43]                |
| 30. | Embelica officinalis Phyllanthaceae | Fruit         | Suryanarayana et al. [45]         |
| 31. | Eucalyptus deglupta Myrtaceae       | Not Specified | Guzman et al. [46]                |

|     |  |               |                       |
|-----|--|---------------|-----------------------|
| 32. | <i>Eugenia borinquensis</i> Myrtaceae          | Not Specified | Guzman et al. [46]    |
| 33. | <i>Flammulina velutipes</i> . Tricholomataceae | Fruiting body | Fatmawati et al. [41] |
| 34. | <i>Foeniculum vulgare</i> Apiaceae             | Seeds         | Saraswat et al. [44]  |
| 35. | <i>Flemingia lineata</i> Fabaceae              | Roots         | Hsieh et al. [47]     |
| 36. | <i>Flemingia macrophylla</i> Fabaceae          | Roots         | Hsieh et al. [47]     |
| 37. | <i>Flemingia prostrata</i> Fabaceae            | Roots         | Hsieh et al. [47]     |
| 38. | <i>Flemingia strobilifera</i> Fabaceae         | Roots         | Hsieh et al. [47]     |
| 39. | <i>Ficus golmerata</i> Moraceae                | Fruit         | Gacche et al. [43]    |
| 40. | <i>Gymnema sylvestre</i> Asclepidaceae         | Whole plant   | Moghaddam et al. [48] |
| 41. | <i>Ganoderma lucidum</i> Ganodermataceae       | Fruiting body | Fatmawati et al. [41] |
| 42. | <i>Grifora fondosa</i> Polyporaceae            | Fruiting body | Fatmawati et al. [41] |
| 43. | <i>Hericium erinaceum</i> Hericiaceae          | Fruiting body | Fatmawati et al. [41] |
| 44. | <i>Hypoloma sublateritium</i> Strophariaceae   | Fruiting body | Fatmawati et al. [41] |
| 45. | <i>Hypsizygus marmoreus</i> Tricholomataceae   | Fruiting body | Fatmawati et al. [41] |
| 46. | <i>Lentinula edodes</i> Tricholomataceae       | Fruiting body | Fatmawati et al. [41] |
| 47. | <i>Lyophyllum decastes</i> Tricholomataceae    | Fruiting body | Fatmawati et al. [41] |
| 48. | <i>Mangifera indica</i> Anacardiaceae          | Not Specified | Guzman et al. [46]    |
| 49. | <i>Momordica charantia</i> Cucurbitaceae       | Fruit         | Saraswat et al. [44]  |
| 50. | <i>Murrayakoenigii</i> Rutaceae                | Leaves        | Saraswat et al. [44]  |
| 51. | <i>Morinda cerifolia</i> Rubiaceae             | Fruit         | Gacche et al. [43]    |
| 52. | <i>Ocimum sanctum</i> Lamiaceae                | Leaves        | Gacche et al. [43]    |
| 53. | <i>Psoralea corylifolia</i> Fabaceae           | Seeds         | Gacche et al. [43]    |
| 54. | <i>Psidium guajava</i> Myrtaceae               | Fruit         | Saraswat et al. [44]  |
| 55. | <i>Piper nigrum</i> Piperaceae                 | Seeds         | Saraswat et al. [44]  |
| 56. | <i>Pleurotus ostreatus</i> Pleurotaceae        | Fruiting body | Fatmawati et al. [41] |
| 57. | <i>Pleurotus eringii</i> Pleurotaceae.         | Fruiting body | Fatmawati et al. [41] |
| 58. | <i>Pleurotus comucopiae</i> Pleurotaceae       | Fruiting body | Fatmawati et al. [41] |
| 59. | <i>Pholiotina meko</i> Strophariaceae          | Fruiting body | Fatmawati et al. [41] |
| 60. | <i>Panellus serotinus</i> Tricholomataceae     | Fruiting body | Fatmawati et al. [41] |
| 61. | <i>Spinacia oleracea</i> Amaranthaceae         | Seeds         | Fatmawati et al. [41] |
| 62. | <i>Syzygium malaccense</i> Myrtaceae           | Not Specified | Guzman et al. [46]    |
| 63. | <i>Tribulus terrestris</i> Zygophyllaceae      | Fruit         | Gacche et al. [43]    |
| 64. | <i>Tinospora cordifolia</i> Menispermaceae     | Stem          | Gacche et al. [43]    |
| 65. | <i>Trigonella foenum-graecum</i> Trigonalaceae | Seeds         | Saraswat et al. [44]  |
| 66. | <i>Trachyspermum ammi</i> Apiaceae             | Seeds         | Saraswat et al. [44]  |
| 67. | <i>Vaccinium myrtillus</i> Ericaceae           | Not Specified | Guzman et al. [46]    |
| 68. | <i>Withania somnifera</i> Solanaceae           | Root          | Halder et al. [38]    |

**Table 2:** Marin sources of aldose reductase inhibitors.

|    |                                   |                      |
|----|-----------------------------------|----------------------|
| 1. | <i>Dysidea</i>                    | Endo et al. [49]     |
| 2. | <i>Irciniaramosa</i>              | Endo et al. [49]     |
| 3. | <i>Dactylospongia metachromia</i> | Endo et al. [49]     |
| 4. | <i>Hippospongia</i>               | Nakagawa et al. [50] |
| 5. | <i>Asparagopsis taxiformis</i>    | Sugano et al. [51]   |
| 6. | <i>Dictyodendrillasp</i>          | Sugano et al. [51]   |
| 7. | <i>Ecklonia cave</i>              | Nakamura et al. [52] |

The benefits of dietary supplements such as naturaceuticals and herbal medicines as pharmaceuticals have gain growing interest due to lack of toxicity and harmful side effects (they are daily consumed). Many structurally diverse phyto chemicals and extracts have been reported as potent aldose reductase inhibitors. Naturally occurring compounds with diverse chemical structures (flavonoids, coumarins tannins, alkaloids, terpenoids and phenolics) have significant aldose reductase inhibitory activity. Most of the natural sources either terrestrial or marine that contain these compounds are presented in Table 1 & 2.

From natural sources that have been reported, Flavonoids and related compounds is the most widely studied natural product family with inhibitory activity. Vitamin C is one of the natural products that entered clinical trials, which showed 81% of in-vitro inhibition [35]. Vitamin C as dietary supplement seems to be effective in decreasing accumulation of erythrocyte's sorbitol and improves endothelium-dependent vasodilatation in diabetic patients [34-56].

### Conclusion

Worldwide, researcher and scientists are widely interested in prevention of diabetic complications. Use of naturally occurring compounds in the treatment of variety of chronic disorders and illnesses is growing, and many extracts and isolated compounds are becoming better alternatives to synthetic drugs, diabetes and its complications can be prevented and/or decreased using these natural molecules. Quercetin, Kaempferol and Ellagic acid is promising naturally occurring compounds that have evidences since a period for their aldose reductase inhibitory activity.

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