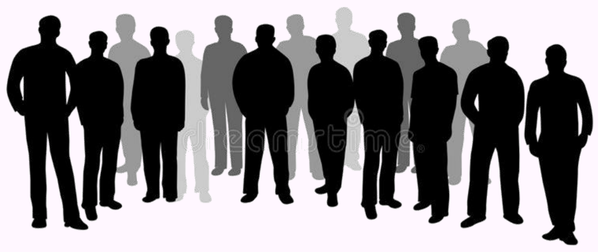
# DIABETIC COMPLICATIONS

# Use of 5-carboxymetyl-1,2,3,4-tetrahydro-1H-pyrido[4,3-b]indoles and their pharmaceutical composition

*Šoltésová Prnová Marta, Balleková Jana, Májeková Magdaléna, Štefek Milan*

## DIABETES IS ON THE RISE



**422 million adults have DIABETES**

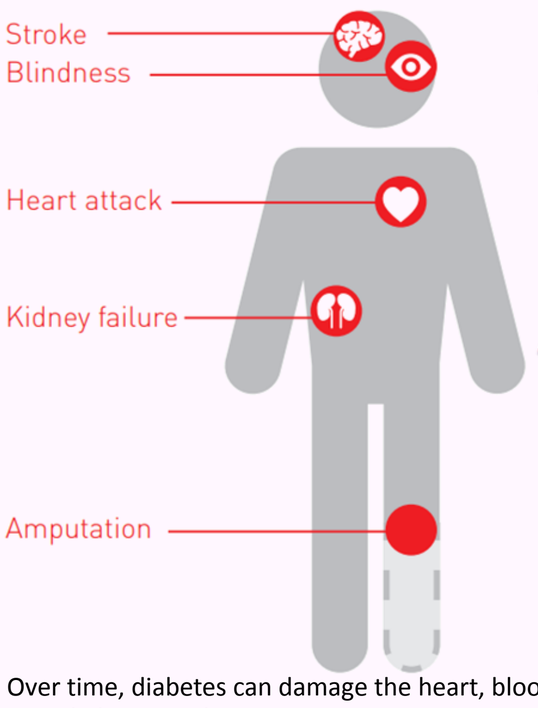
**THAT'S 1 PERSON IN 11**

**Anually, for 3.4 MILLION PEOPLE, death cause is high blood glucose!**

The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014

## Consequences

Diabetes can lead to complications in many parts of the body and increase the risk of dying prematurely.




**Cataract**

**Retinopathy**

**Angiopathy**

**Nefropathy**

**Neuropathy**

- Over time, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves.
- Adults with diabetes have a two- to three-fold increased risk of heart attacks and strokes .
- Combined with reduced blood flow, neuropathy (nerve damage) in the feet increases the chance of foot ulcers, infection and eventual need for limb amputation.
- Diabetic retinopathy is an important cause of blindness, and occurs as a result of long-term accumulated damage to the small blood vessels in the retina. 2.6% of global blindness can be attributed to diabetes .
- Diabetes is among the leading causes of kidney failure

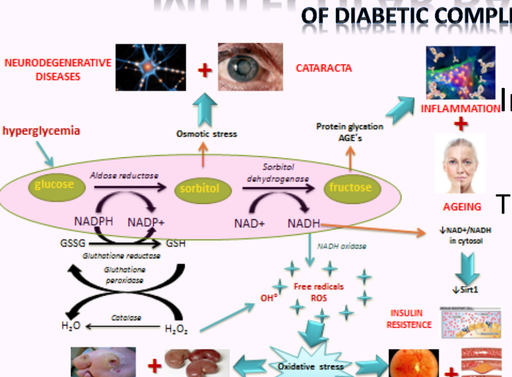
**Jules Verne**
(1828-1905)
Death cause,
diabetic complications
http://www.nndb.com

## Flow of money on diabetic market

- In 2011 the size of diabetic market was **50,8 billion USD** (including therapeutic drugs, diagnostics and medical devices).
- Assumption - in 2018 = **98.4 billion USD**

➢ **From this amount - therapeutic devices and drugs = 72.4 billion USD**

## MOLECULAR BACKROUND OF DIABETIC COMPLICATIONS




Incresed flow of glucose through **POLYOL PATHWAY**

The first enzyme = **ALDOSE REDUCTASE**

**Therapeutic target**

## EPALRESTAT: Clinically used INHIBITOR of ALDOSE REDUCTASE

**Epalrestat**

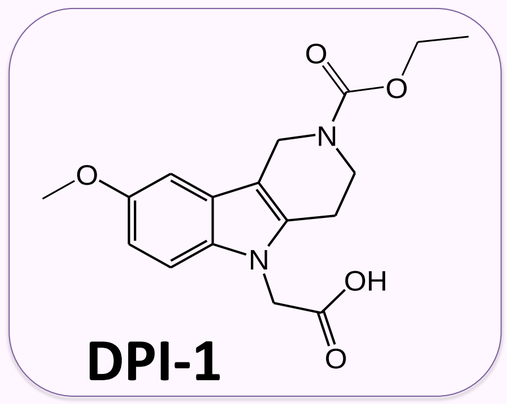
IC$_{50}$ ~ 100-280 nM

**!!!Only Asia market!!!**

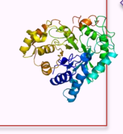
EPAREL 50(MICROLABS LTD)
ALDONIL (ZYDUS MEDICA)
ALRISTA (MACLEODS)
LISTAP-50 (VIVID BIOTEK)
EPALRICA-M (ORDAIN GLOBAL)

The worldwide sales of epalrestat in 2010 was **154 MIL. USD**

## PP 50049-2016




**ALR2 – rat aldose reductase**
IC$_{50}$≈ 0.012 µM
**AKR1B1 – human aldose reductase**
IC$_{50}$ ≈ 0.083 µM

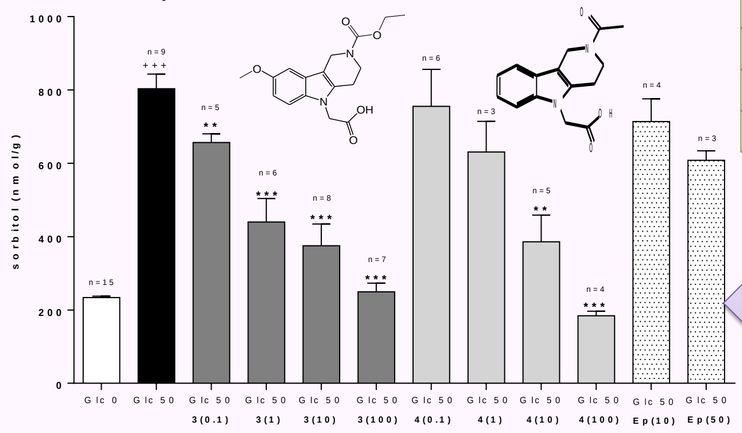


**High inhibition activity**

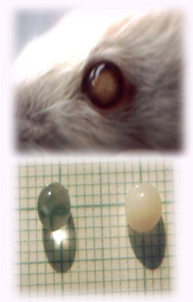
## EYE LENS SORBITOL ASSAY *EX VIVO*

**Effect of DPI-1, Compound 2 and Epalrestat on Sorbitol Accumulation in Isolated Rat Eye Lenses Cultivated with High Glucose**

- **1 µmol/l DPI-1 -** almost **50 % decrease** of **sorbitol level**

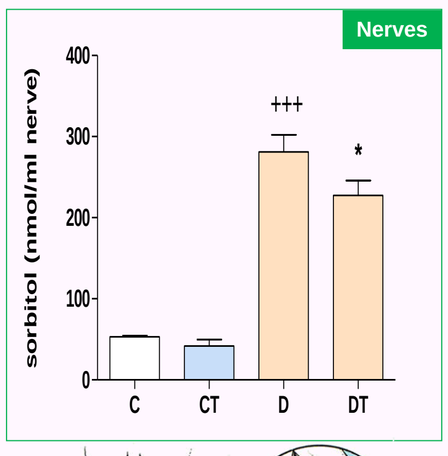


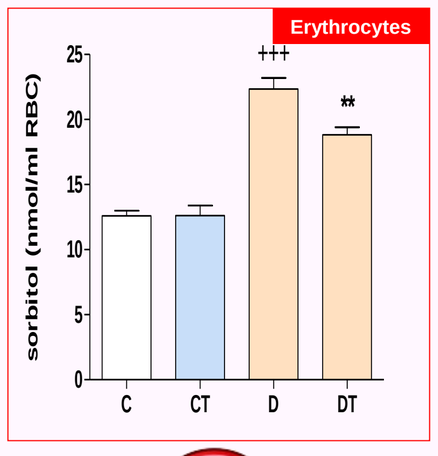

| DPI-1 (µM) | Sorbitol (nmol/g lens) | I (%) | n |
|---|---|---|---|
| 0 | 576.09 +/- 76.21 | - | 3 |
| 0.1 | 469.06 +/- 38.33$^b$ | 18.58 | 3 |
| 1 | 314.44 +/- 87.62$^b$ | 45.42 | 6 |
| 10 | 240.63 +/- 33.96$^b$ | 58.23 | 9 |
| 100 | 174.09 +/- 30.77$^b$ | 69.78 | 8 |

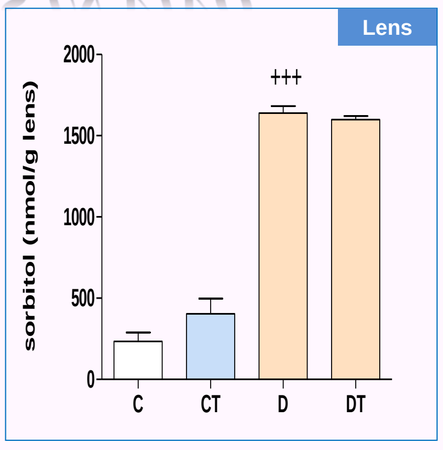


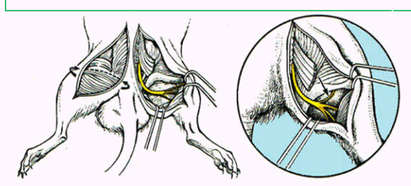
**Good bioavailability**

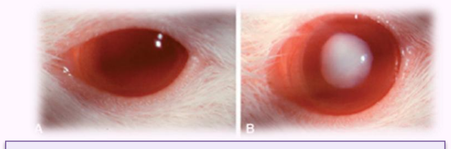
## SORBITOL IN STZ DIABETIC RATS *IN VIVO*





- Diabetes induced by streptozotocin
- Treatment: 5 days
- Dosage of DPI-1: 50 mg/kg/day

***In vivo* effect**
uptake of DPI-1 into the central compartment

## Comparison of the novel aldose reductase Ihibitor DPI-1 with clinically used Epalrestat

| | DPI-1 | Epalrestat |
|---|---|---|
| **MW** | 332 | 319 |
| **Water solubility** | ~1.3 mg/ml | ~ 0.05 mg/ml |
| **ARI (IC$_{50}$)** | 12 nM | 250 nM |
| **Sorbitol in eye lenses ex vivo, I(%)** | 58 % (10 µM) | 11 % (10 µM) |

## Patent application PP 50049-2016

**Title:** Použitie 5-karboxymetyl-1,2,3,4-tetrahydro-1H-pyrido[4,3-b]indolov a farmaceutický prostriedok s ich obsahom
**Owner:** Institute of Experimental Pharmacology and Toxicology, Slovak Academy of Sciences