Structural insight into the interaction of flavonoids with aldose reductase

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The Aldose Reductase (AR) enzyme catalyzes the conversion of glucose to sorbitol, which is a major cause of diabetes related complications. Therefore, AR inhibition has emerged as a key strategy for preventing and reducing long-term diabetic complications. Natural products are the main source of lead molecules in drug discovery and development. In particular, polyphenolic compounds such as flavonoids are extensively studied for their antidiabetic activity.

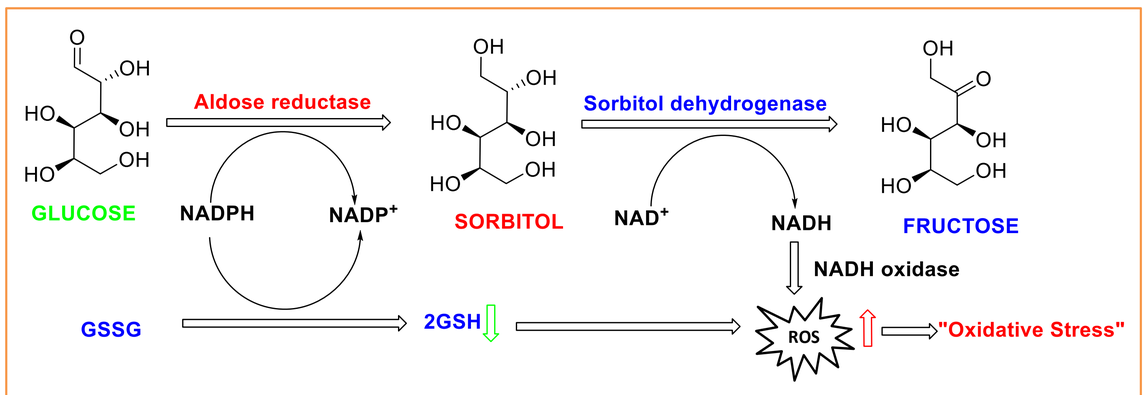

Figure 1: Polyol pathway leads to formation of reactive oxygen species (ROS) and oxidative stress.

A molecular data set of twenty-five naturally occurring AR inhibitors belonging to flavone, isoflavone, flavonol, and dihydroflavone were selected for in-silco analysis. All selected molecules have a common benzopyran-4-one core structure decorated with hydroxyl and methoxy function at various positions. The structure-activity relationship (SAR) was established for AR inhibition with structural or molecular finger prints.

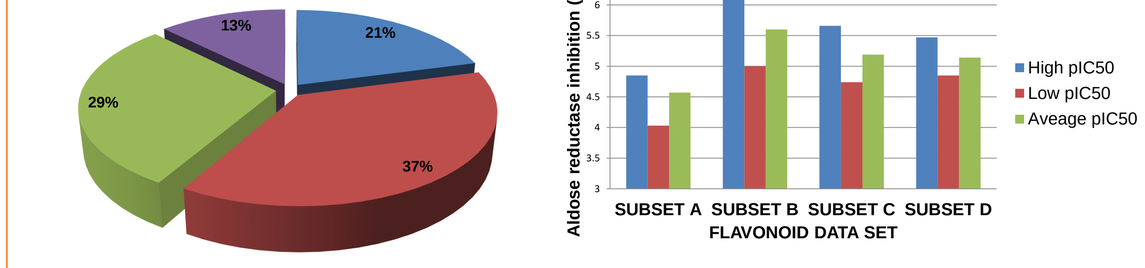

Figure 2. Flavonoid dataset with aldose reductase inhibition used in the SAR study. (A) Chemical diversity within the flavonoid dataset, Isoflavone (21%), Flavone (37%), Flavonol (29%) and Dihydroflavone (13%). (B) Distribution of aldose reductase inhibition activity within the flavonoid dataset (subset A: Isoflavone; subset B: Flavone; subset C: Flavonol; subset D: Dihydroflavone.

S.No	Chemical Class	Compound	Aldose reductase inhibition IC_{50}	pIC_{50}
1	ISOFLAVONE	Daidzein	24	4.62
2		Genistein	20	4.70
3		Tectorigenin	14	4.85
4		Glycitein	93	4.03
5		Biochanin A	22	4.66
6	FLAVONE	7-Hydroxy flavone	10	5.00
7		Chrysin	8.5	5.07
8		4',7-Hydroxy flavone	3.8	5.42
9		3',7-Hydroxy flavone	0.37	6.43
10		3',4',7-Hydroxy flavone	0.3	6.52
11		Apigenin	2.2	5.66
12		Luteolin	0.45	6.35
13		Diosmetin	8.5	5.07
14		Pilloin	12	4.92
15	FLAVONOL	Kaempferol	10	5.00
16		Quercetin	2.2	5.66
17		Rhamnetin	2.7	5.57
18		Tamarixetin	11	4.96
19		Ombuine	6	5.22
20		Ayanin	34	4.47
21		Fisetin	3.7	5.43
22	DIHYDROFLAVONE	Liquiritigenin	3.4	5.47
23		Eriodictyol	7.7	5.11
24		Fustin	14	4.85

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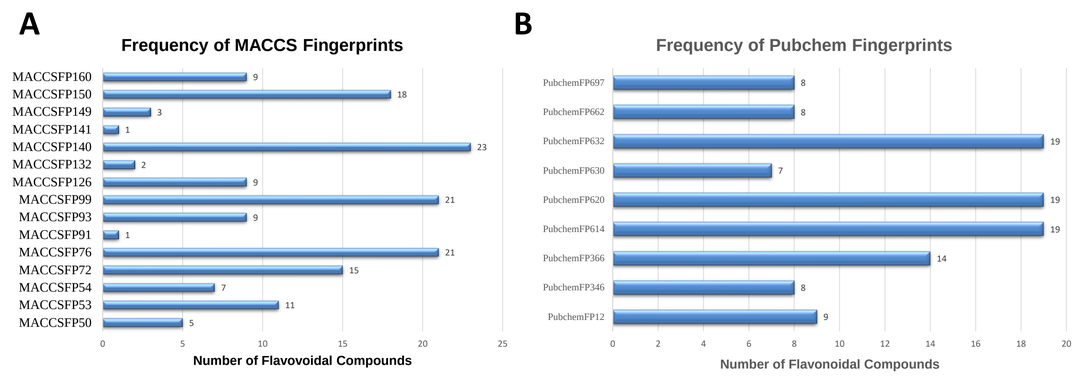

Figure 3. Fingerprint based structure-activity relationship. (A) frequency distribution of MACCS fingerprint (B) frequency distribution of Pubchem fingerprints

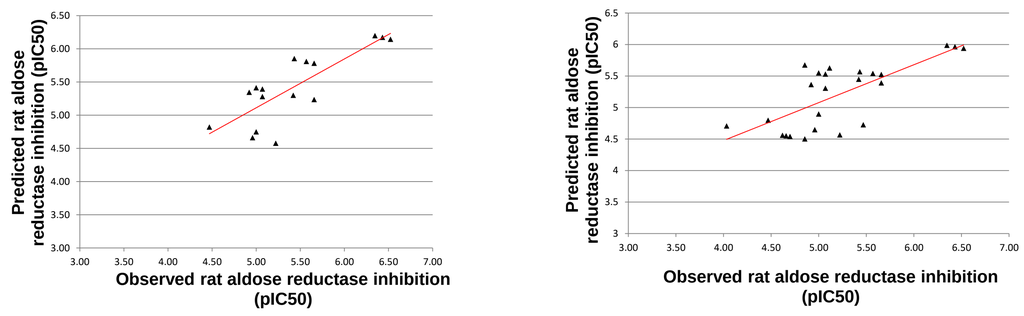

Figure 4. (A) flavonoids subset B and C aldose reductase inhibition (B) flavonoids subset A, B, C and D aldose reductase inhibition

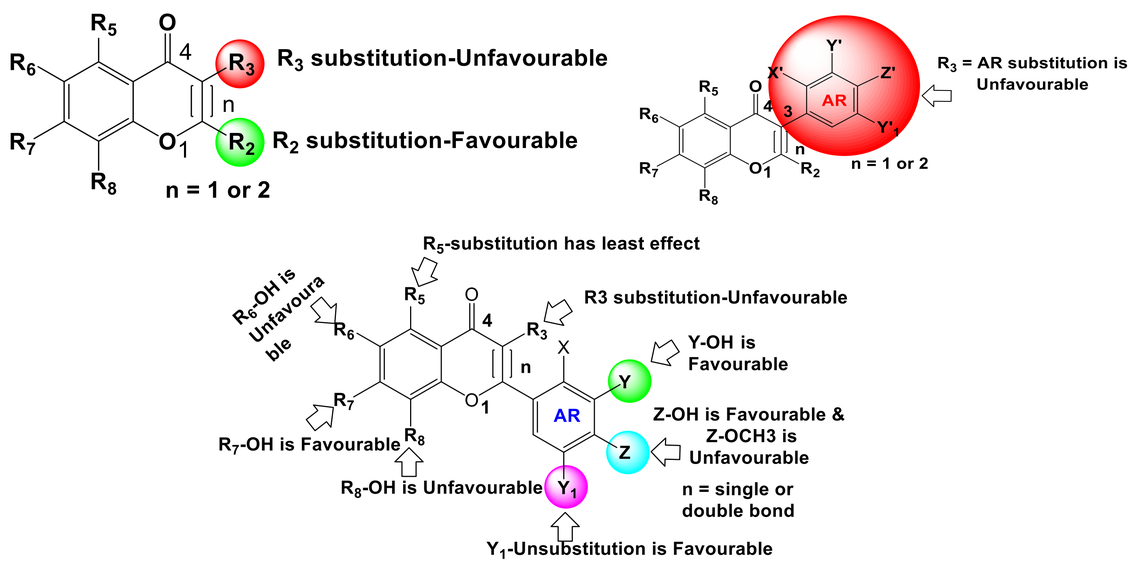

Figure 5. structure-activity relationship showing the substitution pattern of flavonoids that contributes to t

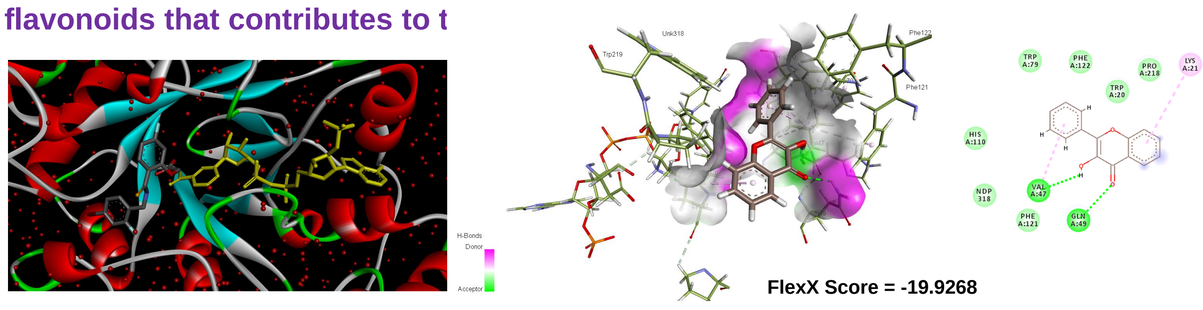

Figure 6. Docking of flavonoid molecules to Aldose reductase enzyme (PDB: 1US0)

- **Conclusion:** The structure-activity relationship (SAR) suggests that 3-phenyl substitution in benzopyran-4-one is detrimental to AR inhibition while 2-phenyl substitution is more effective.
- The presence of 3-OH did not decrease the AR inhibition to a greater extent, which suggests that flavonols are potential leads.
- The molecular docking studies suggests the AR inhibitory potential of these flavonoids at a biomolecular level (propose a binding mode) that explains the aforementioned SARs.
- Docking experiments revealed that the aromatic ring contributed to π−π interaction with the amino residues of AR. In addition, the flavonoid molecules forms hydrogen bonds, which could result in strong AR inhibition.
- Overall, our computational analysis suggested that the 2-phenyl benzopyran-4-one core could be a potential AR inhibition lead for further drug development.

References:

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2. Niinivehmas SP, Manivannan E, Rauhamäki S, Huuskonen J, Pentikäinen OT. Identification of estrogen receptor α ligands with virtual screening techniques. J Mol Graph Model. 2016, 64, 30-39. doi: 10.1016/j.jmgm.2015.12.006.