# Interaction and inhibition of α-glucosidase with selected monoterpenes

Prapti Behera, Arnab Mukerjee, **S. Balaji***

Manipal Institute of Technology, MAHE, Manipal, Karnataka, India

E-mail: s.balaji@manipal.edu

# Introduction

- It has been estimated that 425 million people are suffering from diabetes, of which 90% is type 2 diabetes (Choi et al., 2009)

- WHO claims diabetes will be the 7$^{th}$ cause of death by 2030 (Zhang et al., 2019).

- There are synthetic α-glucosidase inhibitors such as acarbose is used as anti-diabetic agents but they have side effects including diarrhea and flatulence (Choi et al, 2009, Van de Laar et al., 2005).

- Hence, there is a need for alternative, preferably phytochemicals.

- There are many reports on monoterpenes as inhibitors of α-glucosidase.

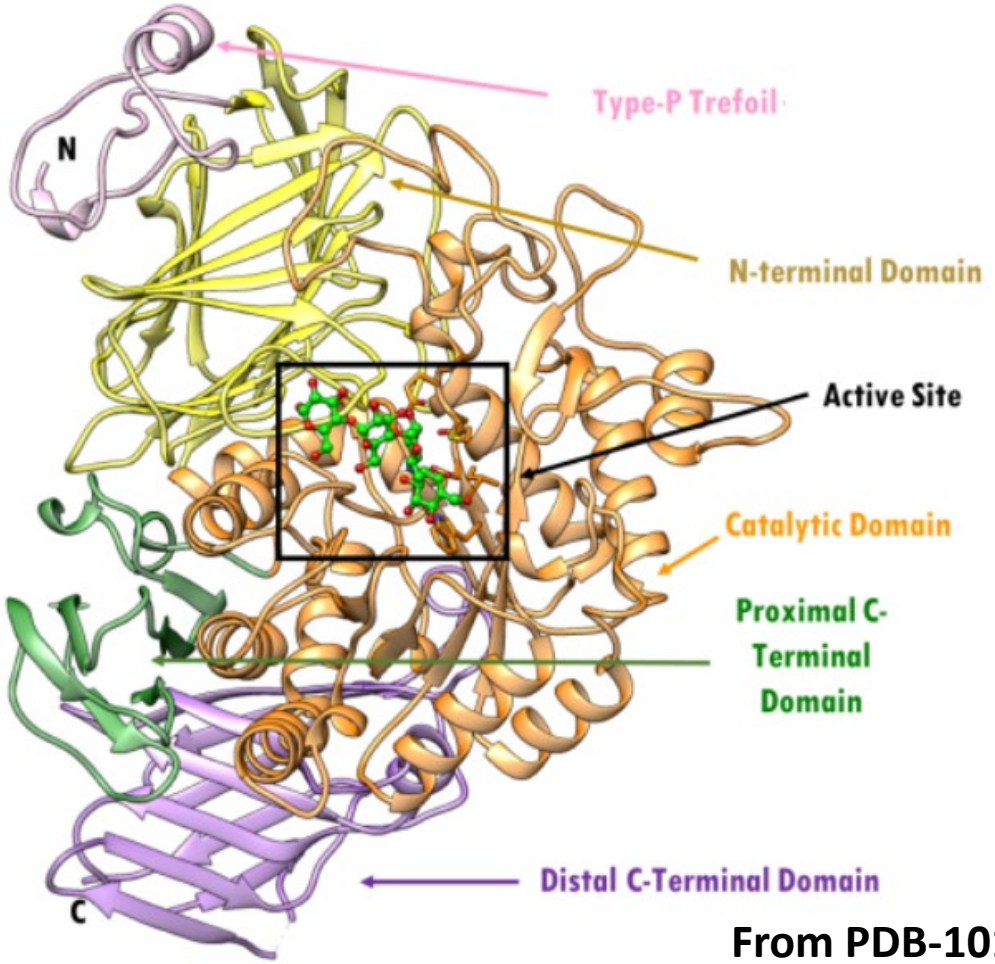
- However, many often the enzyme inhibition studies are conducted for essential oils rather than individual compounds

- Hence, the present study aims to analyze the inhibitory action, interaction potential, and SAR of some selected monoterpenes against α-glucosidase.

# Materials and methods

1. **Extraction of maltase** (from Yeast)
2. **α-glucosidase activity** (DNS assay)
3. **Maltase inhibition assay (**the absorbance is recorded at 540nm, from the slope, the IC50 value is calculated)
4. **Ligand preparation** (LigPrep module of the Schrödinger, structurally optimized and protonation states were assigned)
5. **2D-QSAR modelling** (AutoQSAR tool of Schrödinger)
6. **Molecular Docking** (Human maltase-Glucoamylase protein (PDB: 2QMJ) was used as the target, followed Glide protocol

# Maltose glucoamylase in complex with acarbose (PDB ID 2QMJ; Sim et al., 2008).




**From PDB-101**

doi: 10.2210/rcsb_pdb/GH/DM/drugs/gi/glucosidase

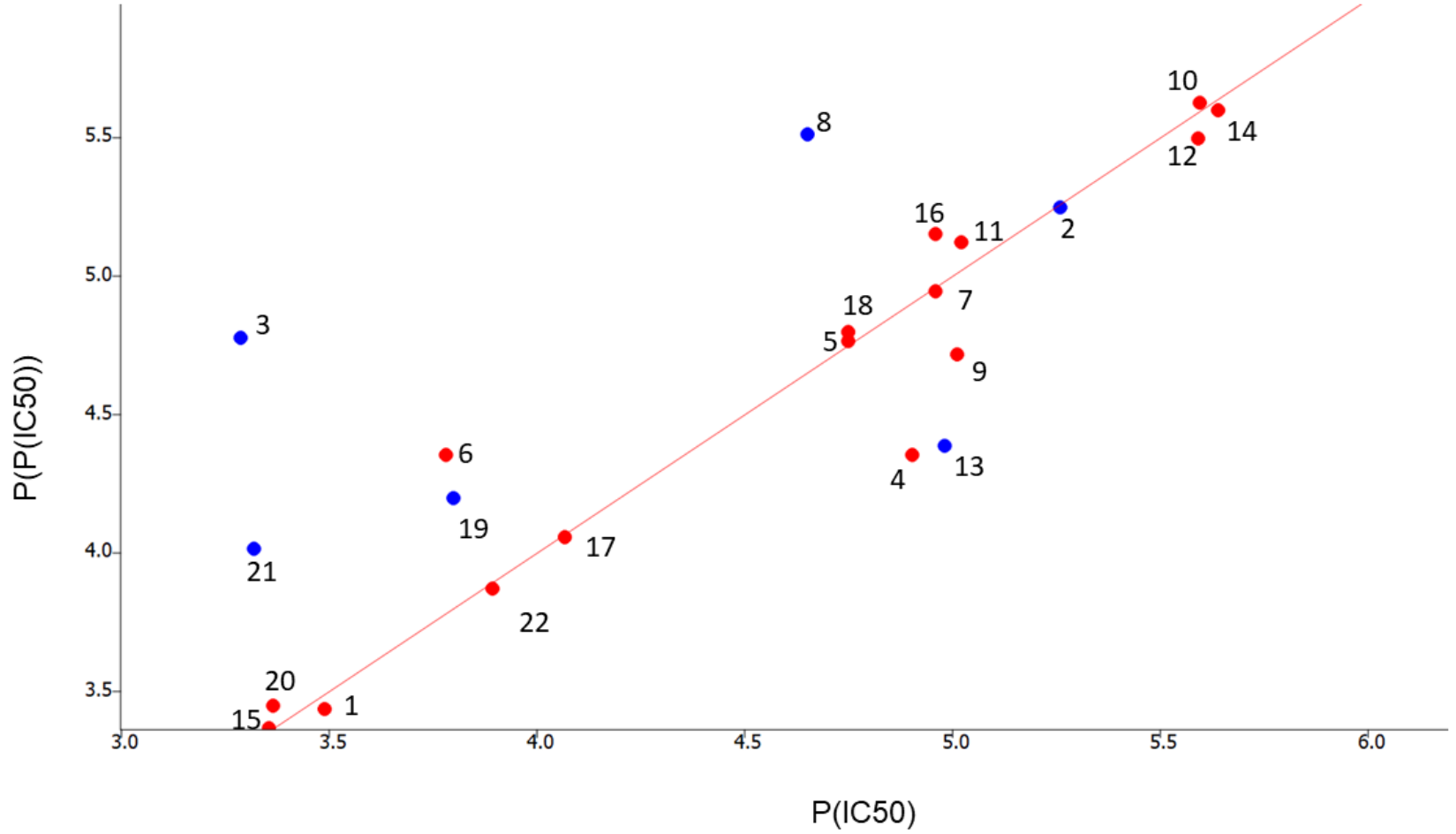
# Results & Discussion

**α-glucosidase activity**

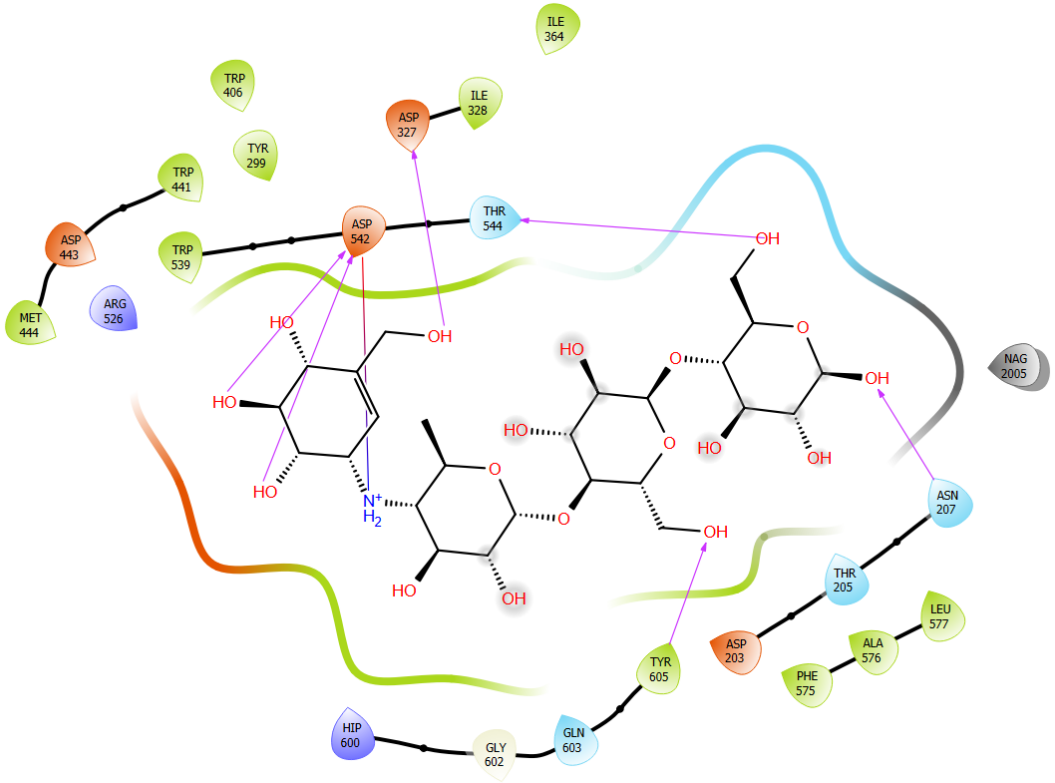
The extracellular enzyme was reacted with α-PNPG substrate, and the reaction mixture turned yellow indicating α-glucosidase (Palleroni and Lindegren, 1953)

| Inhibitor | P(IC50)* |
|---|---|
| Citronellol | 3.363582 |
| Citronellal | 3.318054 |
| 1,8 -Cineole | 3.354187 |
| Camphene | 3.799067 |
| Cinnamic acid | 4.066057 |
| Tris | 3.489683 |
| α-pinene | 4.982132 |
| limonene | 5.020452 |
| p-cymene | 5.011441 |
| Carvacrol | 4.959398 |
| Thymol | 4.749336 |
| Carveol | 3.28735 |

# 2D-QSAR model



# Acarbose




- Charged (negative)
- Charged (positive)
- Glycine
- Hydrophobic
- Metal
- Polar
- Unspecified residue
- Water
- Hydration site
- Hydration site (displaced)
- Distance
- H-bond
- Metal coordination
- Pi-Pi stacking
- Pi-cation
- Salt bridge
- Solvent exposure

# Conclusion

- Monoterpenes interacted with maltase/glucoamylase and had an inhibitory effect
- Ligands such as Carvacrol, carveol, citronellal, and citronellol had H-bond mediated interactions
- Whereas, p-cymene and thymol had Pi-Pi stacking with Tyr, Trp & Phe and
- 1, 8- cineole, a-pinene, limonene had non-bonded interactions
- The binding energy of ten monoterpenes with target proteins varied from -4.9 to -1.0 kcal/mol and Acarbose possess lowest binding energy of -9.8 Kcal/mol.
- Hence, the search for novel ligands from natural source will always continue…

# References


1. Choi CW, Choi YH, Cha M-R, Park JH, Kim YS, Kim Y-K, Choi SU, Yon Gh, Hong KS, Kim YH, Ryu SY, “α-Glucosidase Inhibitiors from Seed Extract of *Paeonia lactiflora*”, J. Korean Soc. Appl. Biol. Chem. 52(6), 638-642 (2009).

2. Zhang CC, Geng C-A, Huang X-Y, Zhang X-M, Chen J-J, “Antidiabetic Stilbenes from Peony Seeds with PTP1B, α-Glucosidase, and DPPIV Inhibitory Activities”, J. Agric. Food Chem. 67, 6765−6772, (2019).

3. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R, On behalf of the IDF Diabetes Atlas Committee, “Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition”, Diabetes Research and Clinical Practice 157, 107843 (2019). https://doi.org/10.1016/j.diabres.2019.107843

4. Zhang N, Yang X, Zhu X, Zhao B, Huang T and Ji Q, “Type 2 diabetes mellitus unawareness, prevalence, trends and risk factors: National Health and Nutrition Examination Survey (NHANES)1999–2010”, Journal of International Medical Research, Vol. 45(2) 594–609, (2017).

5. Rother KI, “Diabetes Treatment - Bridging the Divide”, N Engl J Med 356, 1499-1501,(2007).

6. Casirola DM and Ferraris RP, “Alpha-glucosidase inhibitors prevent diet-induced increases in intestinal sugar transport in diabetic mice”. Metabolism 55, 832-841, (2006).

7. Van De Laar FA, Lucassen PL, Akkermans RP, van de Lisdonk EH, Rutten GE, and Van Weel C, “α-Glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and metaanalysis”. Diabetes Care 28, 154-163, (2005).

8. Habtemariam S, “Antidiabetic potential of monoterpenes: A case of small molecules punching above their weight”, International Journal of Molecular Sciences, 19,4, (2018).

9. Tholl, D. Biosynthesis and biological functions of terpenoids in plants. Adv. Biochem. Eng. Biotechnol., 148, 63–106, (2015)

10. Dewick, P.M. The biosynthesis of C5–C25 terpenoid compounds. Nat. Prod. Rep., 19, 181–222. (2002)

11. Rehman, R.; Hanif, M.A.; Mushtaq, Z.; Al-Sadi, A.M. Biosynthesis of essential oils in aromatic plants: A review. Food Rev. Int, 32, 117–160, (2016).