Cancer Chemopreventive action of α-(-)-Bisabolol

CSIR-CIMAP

Suchita Srivastava, Suaib Luqman*

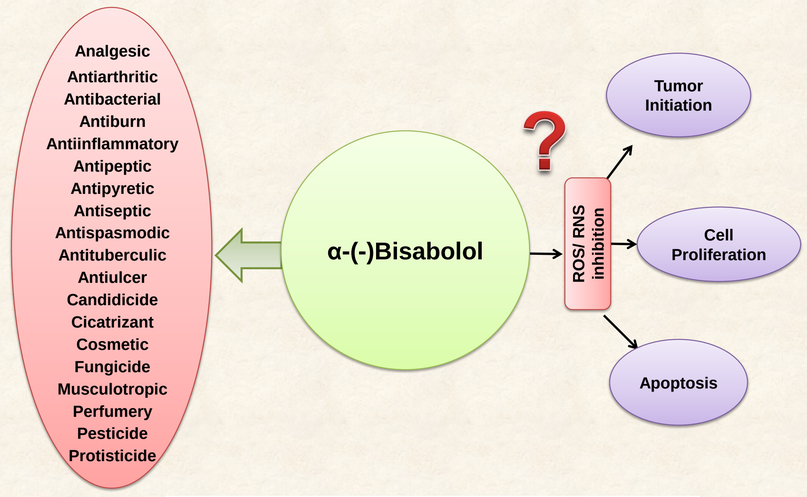
CSIR- Central Institute of Medicinal and Aromatic Plants, Lucknow-226015, India

* Author for Correspondence: s.luqman@cimap.res.in

INTRODUCTION

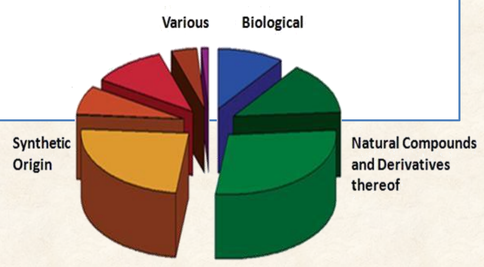
- Phytomolecules play an extremely important role in the development of therapeutics because of their enormous structural diversity, serving as privileged scaffolds in drug discovery.
- Among all the known phytomolecules, terpenes are the most prominent group of plant secondary metabolites which are known for their chemotherapeutic and chemopreventive agents
- α-(-)-Bisabolol, or more formally levomenol, is a natural monocyclic sesquiterpene alcohol which was first isolated in 1951 from *Matricaria chamomilla* belonging to family *Asteraceae.*
- It is one of the primary constituent of the essential oil (16%- 92%) from various plant species such as *Angelica archangelica, Artemisia annua, Cannabis sativa L., Salvia sclarea L., Lavandula latifolia etc.*
- Natural Alpha Bisabolol is 97% as active (-) –alpha-bisabolol isomer whereas synthetic Alpha Bisabolol is 42.5% as active (-) –alpha-bisabolol isomer.

Pharmacological properties of α-(-)-Bisabolol

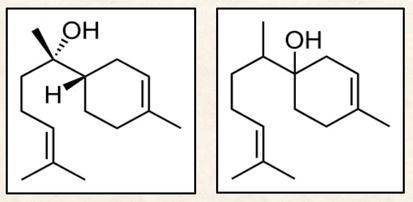


OBJECTIVE

To investigate chemopreventive action of α- (-)- Bisabolol on key targets of Cancer



Natural compounds or derivates: green, synthetic origin: red/yellow, biologicals: blue, various: purple.

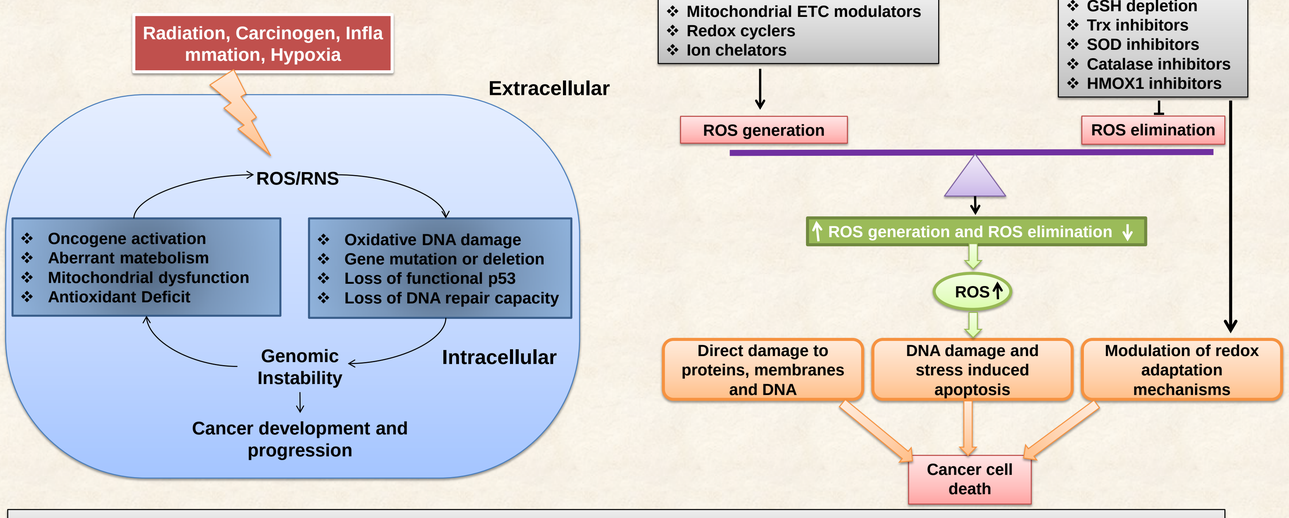


α-(-)-Bisabolol β-(-)-Bisabolol

MOLECULAR TARGETS IN CANCER CHEMOPREVENTION

Class	Primary target
Cyclooxygenase -2 inhibitor	Cyclooxygenase -2
Selective esrrogenase receptor modulators	Estrogen receptor
5-alpha reductase inhibitor	5-alpha reductase (type -1)
Ras inhibitor	Farnysyl transferase
Tyrosine kinase inhibitor	Tyrosine kinase
Matrixmetalloproteinase inhibitor	Matrixmetalloproteinase
Polyamines biosynthesis inhibitors	Ornithine decarboxylase, Aromatase, S-Adenosine decarboxylase
PPAR-γ agonist	PPAR-γ
RXR selective ligand	Panagonist RARs,RAXs
Cellular retinol binding protein ligand	Cellular retinol binding protein
AP-1 inhibitors	AP-1
Jun kinase inhibitor	Junkinase
Cyclin dependent kinase inhibitors	Cyclin dependent kinase
Monoclonal Abs	Her-2,EGFR,VEGF
Gene therapy	p53

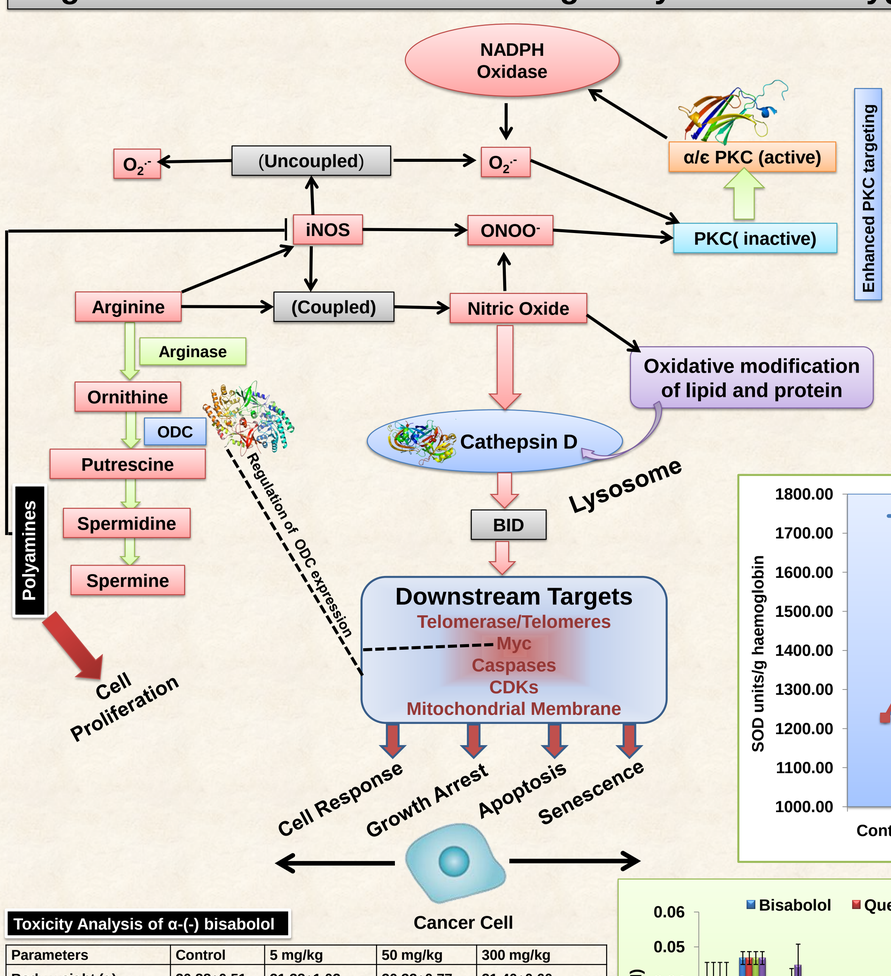
HYPOTHESIS



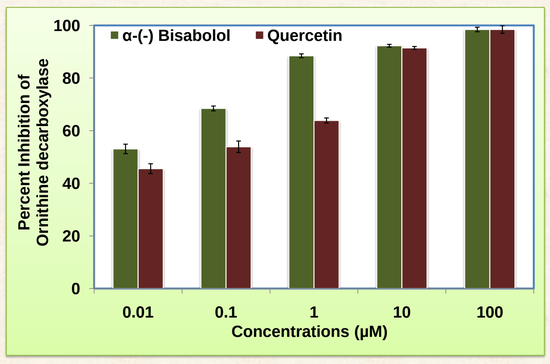
EXPERIMENTAL REFERENCES

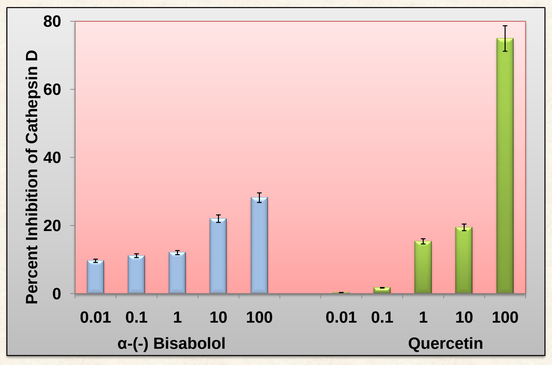
Ornithine Decarboxylase Activity: *Analytical Biochemistry* (1987);160, 290-293
Cathepsin D Assay: *Biochemical Journal* (1970); 117, 601-607
Glutathione Estimation: *Pharmaceutical Biology* (2009); 47(6), 483-490.
Lipid Peroxidation Estimation: *Phytotherapy Research* (2006); 20(4), 303-306.
Superoxide Dismutase Activity : *Journal of Biological Chemistry* (1969); 244, 6049-6055.
Catalase Activity Determination: *Journal of Biochemistry* (1983); 94: 403-408.
Nitric oxide scavenging Assay: *Biochemical Biophysical Research Communications* (1994;) 201, 748-755

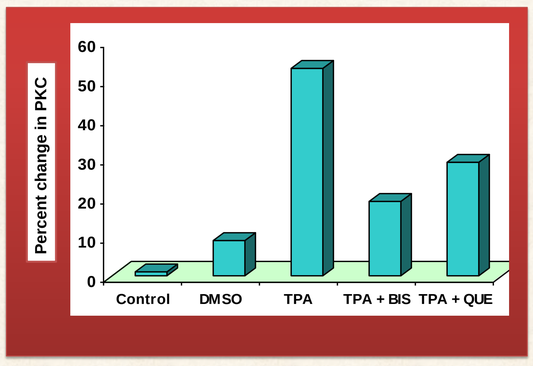
Regulation of Cancer MolecularTargets by Reactive Oxygen/Nitrogen Species

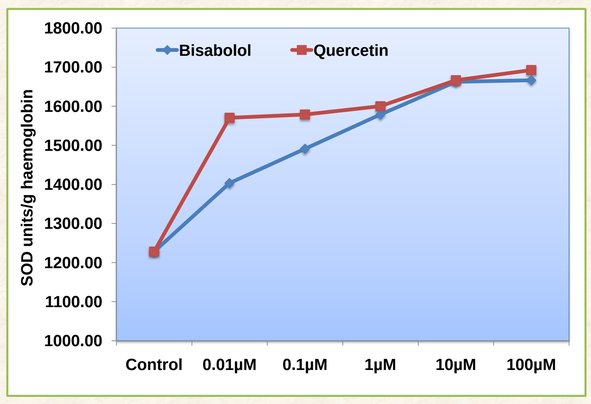


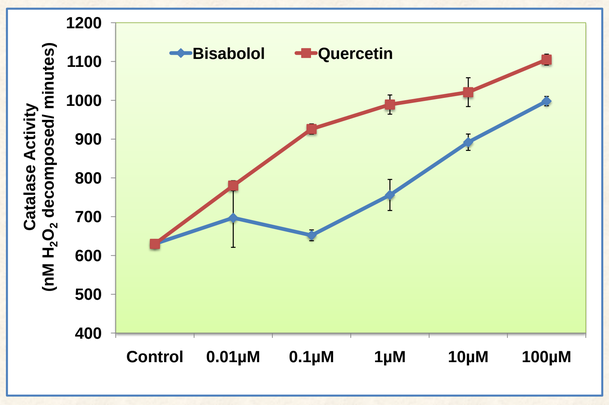
RESULTS

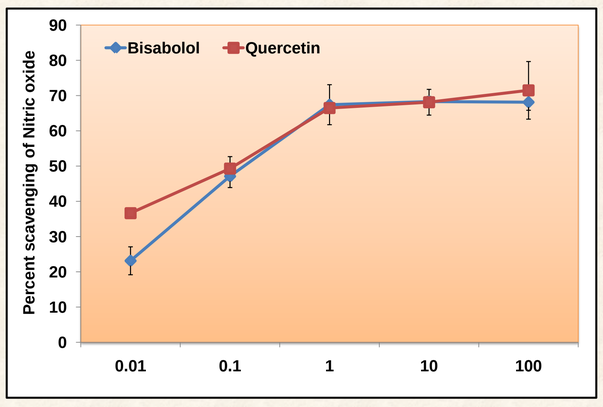






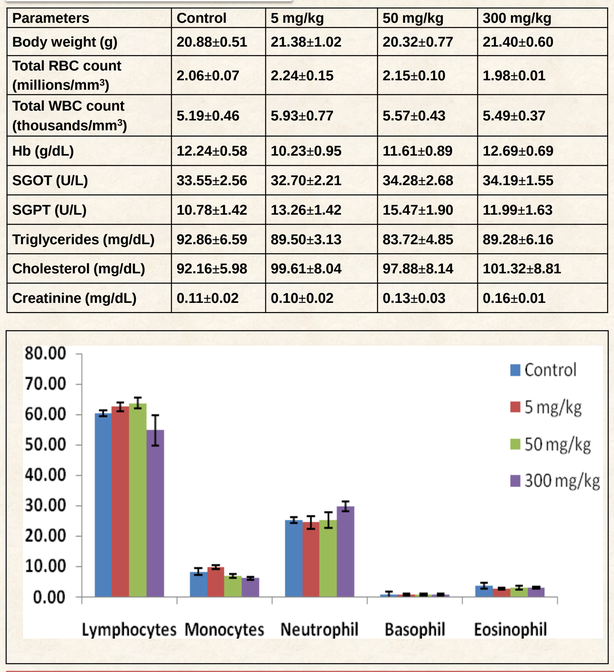


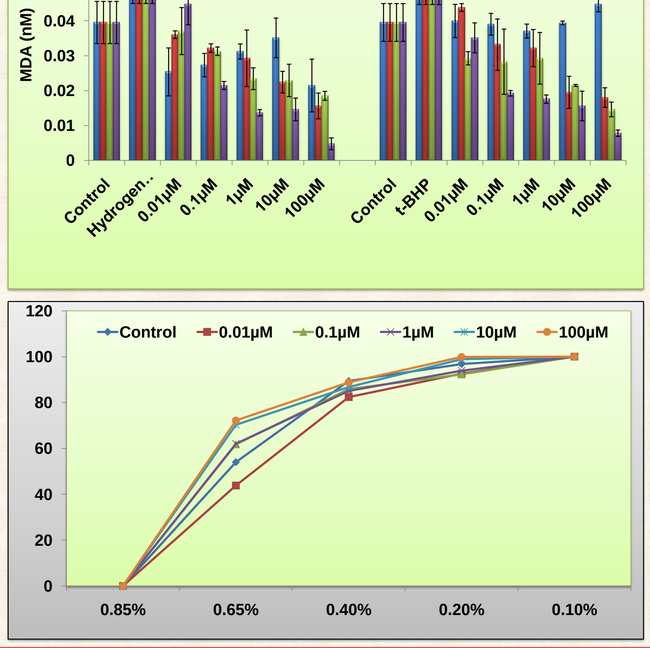


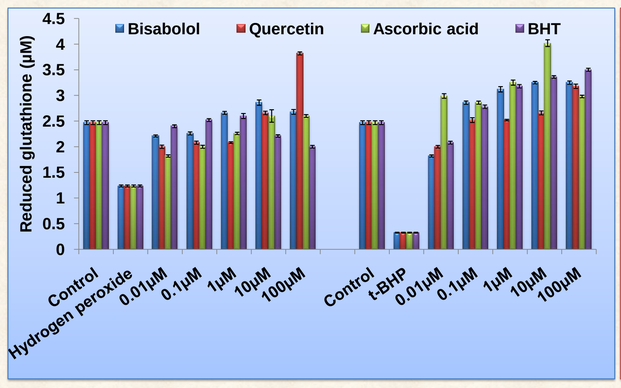


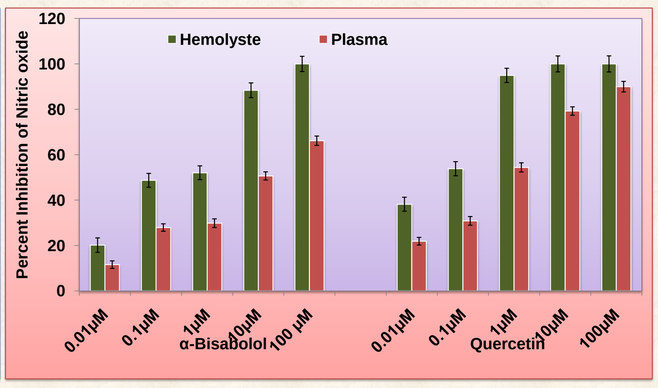
Toxicity Analysis of α-(-) bisabolol

Parameters	Control	5 mg/kg	50 mg/kg	300 mg/kg
Body weight (g)	20.88±0.51	21.38±1.02	20.32±0.77	21.40±0.60
Total RBC count (millions/mm^3)	2.06±0.07	2.24±0.15	2.15±0.10	1.98±0.01
Total WBC count (thousands/mm^3)	5.19±0.46	5.93±0.77	5.57±0.43	5.49±0.37
Hb (g/dL)	12.24±0.58	10.23±0.95	11.61±0.89	12.69±0.69
SGOT (U/L)	33.55±2.56	32.70±2.21	34.28±2.68	34.19±1.55
SGPT (U/L)	10.78±1.42	13.26±1.42	15.47±1.90	11.99±1.63
Triglycerides (mg/dL)	92.86±6.59	89.50±3.13	83.72±4.85	89.28±6.16
Cholesterol (mg/dL)	92.16±5.98	99.61±8.04	97.88±8.14	101.32±8.81
Creatinine (mg/dL)	0.11±0.02	0.10±0.02	0.13±0.03	0.16±0.01









- α-(-)-Bisabolol inhibits activity of Ornithine decarboxylase and Cathepsin D, Nitric oxide content in a dose-dependent manner.
- The IC_{50} value for ODC and Nitric oxide content scavenging was found to be 10nM and 100nM respectively.
- At 100μM, α-(-)-Bisabolol inhibits Cathepsin D activity by 28%.
- α-(-)-Bisabolol also protects GSH and MDA content in stressed erythrocytes by enhancing the activity of Superoxide dismutase and Catalase.
- No significant toxicity was observed for the molecule when tested *in vivo* in Swiss albino mice.

CONCLUSION: α-(-)-Bisabolol exerts inhibitory action on ODC activity and in turn channels the arginine towards the nitric oxide formation pathway. When nitric oxide in excess, the molecule enhances the nitric oxide scavenging and reduces the PKC activity, regulating the polyamines biosynthesis in the cell.
Our work provides a possibility of further exploration of α-(-)-bisabolol as a cancer chemopreventive agent.

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