SUPPRESSION OF 12-*O*-TETRADECANOYLPHORBOL-13-ACETATE INDUCED ORNITHINE DECARBOXYLASE ACTIVITY BY RESVERATROL DERIVATIVES

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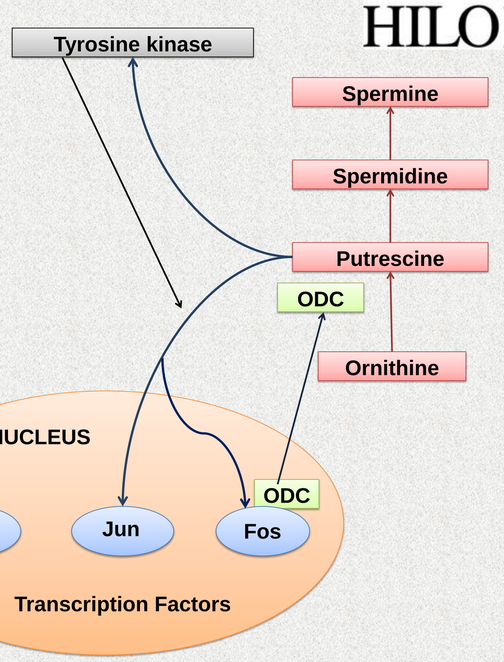
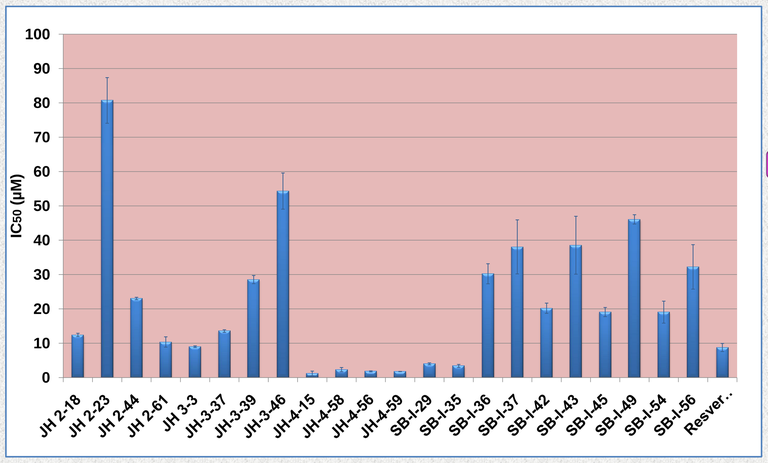
INTRODUCTION

- Resveratrol (3,4,5-trihydroxy-trans-stilbene), a phytoalexin found in grape skins, peanuts, and red wine, have a potent chemopreventive effect in multiple carcinogenesis models both *in vivo* and *in vitro.*
- Resveratrol and its analogues are known to interfere with signal transduction pathways, where they inhibit activities of various protein kinases which in turn declines the expression of nuclear proto-oncogenes and the activity of ornithine decarboxylase (ODC) is reduced.
- ODC activity and expression have been among the first biomarkers of neoplastic proliferation and catlyzes the rate- limiting step in polyamine biosynthesis.
- ODC activity is essential for cell proliferation and is required for progression into the S phase of the cell cycle.
- TPA induction of ODC mRNA expression and ODC activity may be PKC activation dependent or independent.



Possible mode of action of Resveratrol and effect of putrescine on signal transduction pathways of cell proliferation

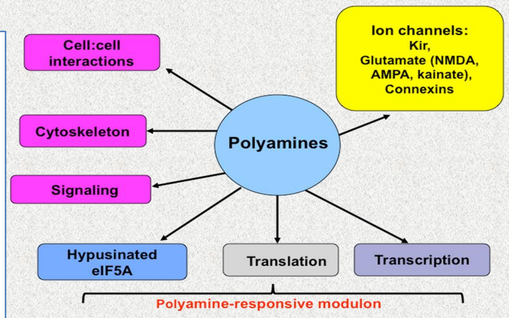
RESULTS

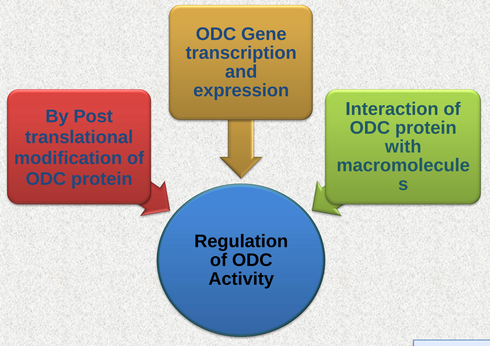


Compounds	Inhibition (%)	Survival (%)
JH 2-18	94.27 0.55	68.2 14.3
JH 2-23	90.55 4.49	71.9 17.2
JH 2-44	98.15 0.08	99.5 4.1
JH 2-61	97.85 0.66	56.6 16.7
JH 3-3	96.17 1.3	60.5 19.1
JH-3-37	95.07 0.97	67.0 18.6
JH-3-39	90.8 2.15	66.4 22.9
JH-3-46	96.2 0.44	78.1 11.4
JH-4-15	95.12 0.41	74.4 8.7
JH-4-58	93.52 0.14	73.8 3.1
JH-4-56	97.27 0.03	84.4 17.5
JH-4-59	91.07 2.7	89.6 7.1
SB-I-29	90.34 6.5	48.1 12.0
SB-I-35	95.42 0.23	58.0 2.6
SB-I-36	95.35 1.15	64.1 8.0
SB-I-37	95.80 0.58	79.8 5.2
SB-I-42	94.87 2.39	52.9 9.2
SB-I-43	92.26 0.34	58.7 25.0
SB-I-45	93.49 3.92	77.7 6.3
SB-I-49	97.86 0.45	94.9 30.2
SB-I-54	47.62 7.2	53.4 10.5
SB-I-56	97.78 0.24	62.6 14.9
Resveratrol	96.09 1.82	99.1 11.7

Inhibition of TPA induced Ornithine decarboxylase activity

- JH 4-15 showed maximum inhibition of ODC activity at IC50 1.21μM
- The IC_{50} values for the resveratrol derivatives were found to be in the following order: JH 2-23>JH 3-46> SB I 49>SB I 43>SB I 37> SB I 56> SB I 36>JH 3-39>JH 2-44> SB I 42>SB I 45> SB I 54> JH 3-37>JH 2-18>JH 2-61>JH 3-3>SB I 29>SB I 35>JH 4-58>JH 4-56> JH 4-59>JH 4-15.





EXPERIMENTAL REFERENCES

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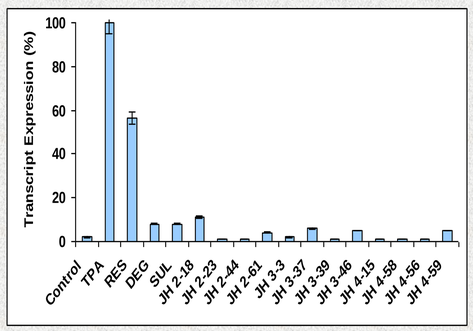
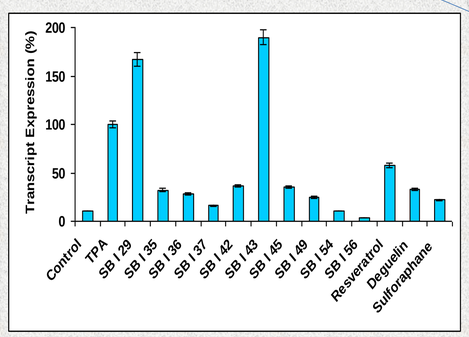
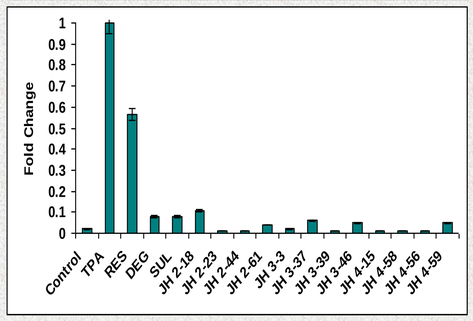
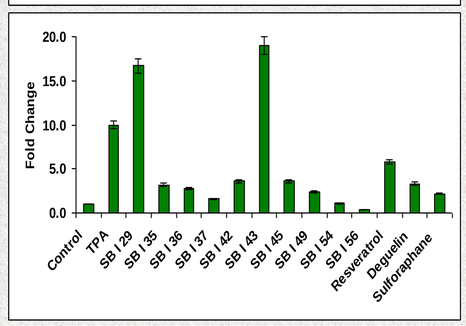


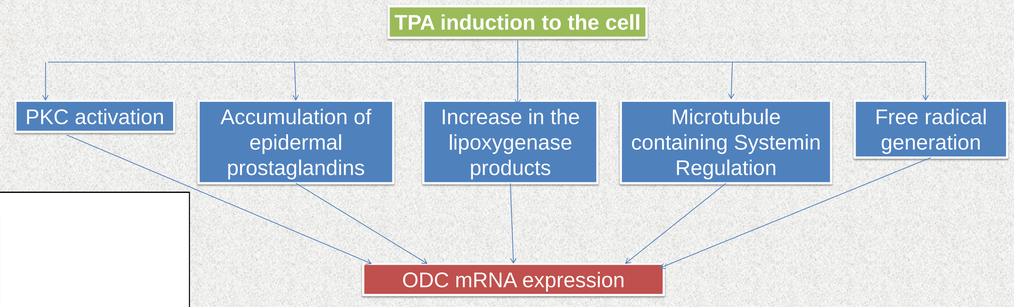




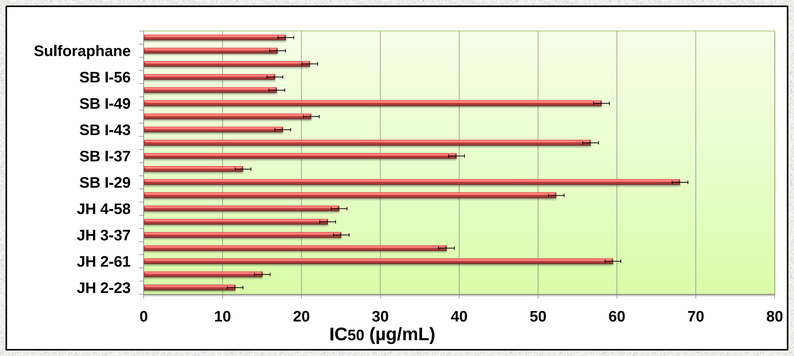


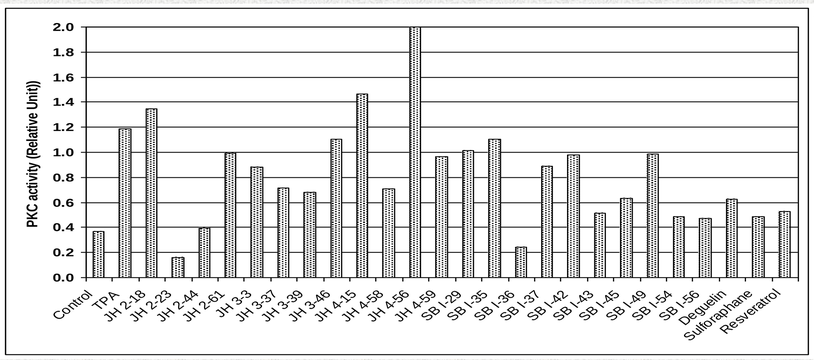
mRNA Expression Analysis

- JH 2-23 showed highest inhibition (99.0 ± 5.0 %) and Resveratrol lowest (58.0 ± 2.6 %).
- The order of inhibition for other samples was as follows: JH 2-44= JH 3-39= JH 4-15> JH 4-58> JH 4-56> JH 3-3> SB I-56> JH 2-61> JH 4-59> JH 3-46> JH 3-37> SB I-54> JH 2-18> SB I-37> SB I-49> SB I-36> SB I-35> SB I-45> SB I-42.



Molecular Mechanisms For ODC induction by TPA





Inhibition of PKC activity

- JH 2-23 showed maximum inhibition of PKC activity
- The inhibition of PKC activity: SB I-36> JH 2-44>SB I-56= SB I-54=SB I-43> SB I-45> JH 3-39= JH 3-37= JH 4-58> JH 3-3 = SB I-37 > JH 4-59=SB I-42= SB I-49=JH 2-61=SB I-29> SB I-35=JH 3-46.

CONCLUSION

- Our studies depicts potential metabolites having greater activity [tetrabutylammonium (E)-4-(3,5-dihydroxystyryl)phenyl sulfate (IC50 1.2 μM), resveratrol tripotassium 3,5,4'-trisulfate (IC50 1.8 μM), resveratrol tripotassium 3,4'-disulfate (IC50 1.8 μM), and resveratrol tripotassium 3,5-disulfate (IC50 2.3 μM)], than the resveratrol on human bladder epithelial carcinoma HTB-24 cells in culture
- TPA-increased amount of ODC mRNA may be the result of enhanced ODC gene transcription and/or decreased degradation of ODC mRNA.
- During ODC induction by TPA, the increase in its mRNA is usually much less than the observed activity, suggesting that some regulation of ODC activity occurs posttranscriptionally.
- Some of the resveratrol derivatives, doesnot show any significant inhibition of PKC activity although inhibiting the ODC activity at very low concentration of 1.2μM, suggesting their mode of action which is PKC independent.

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