

## ABSTRACT

**Background and Aim :** Oxidative stress is thought to be the critical effector in hypobaric hypoxia induced cognitive dysfunctions. 12/15 Lipoxygenase (12/15 LOX) has recently been described as potent mediator of oxidative stress and is closely associated with cognitive decline. The present study was designed to decipher the underlying role of 12/15 LOX in hypobaric hypoxia induced memory impairment and neuronal damage.

**Method:** Balb/c mice were subjected to hypobaric hypoxia, simulating condition at 7620m altitude. Baicalein(12/15 LOX Inhibitor)was administered to mice . Behavioral paradigm, histopathological assessment and mitochondrial integrity were assessed to establish the involvement of 12/15 LOX in the hypobaric hypoxia neuro-pathology.

**Results:** Hypobaric hypoxia episode was accompanied by an increased level of 12/15 LOX and its metabolite 12(S) HETE. The hippocampus CA3 region was found to be mostly affected and showed sign of cellular apoptosis as characterized by elevated activity of caspase-3, 9 & 8. Working memory impairment seen in mice after hypobaric hypoxia was attenuated following baicalein treatment along with reduced level of caspase activation and HIF-1 $\alpha$ . Further, impediment of 12/15 LOX decreased NO level by down-regulating the expression of **iNOS, nNOS** but not **eNOS**. A significantly elevated level of cytochrome C was associated with increased 12/15 LOX colocalisation with mitochondria that got reversed following 12/15 LOX inhibition.

**Conclusion:** 12/15 LOX influences the hypobaric hypoxia pathology and its inhibition using baiclein was found to be neuroprotective.

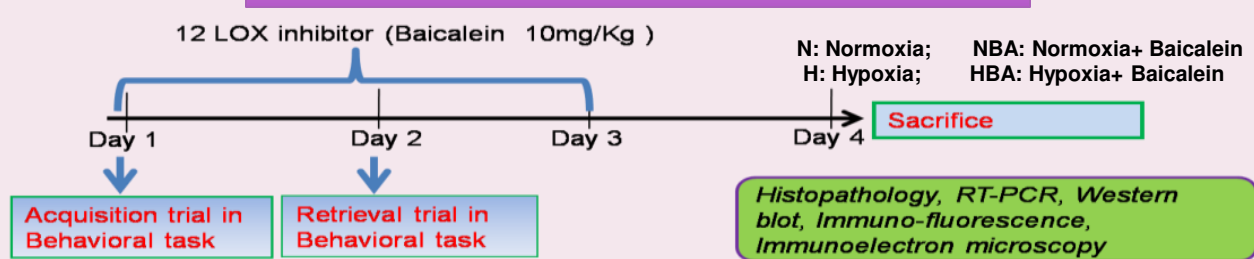
## INTRODUCTION

Decrease in partial pressure of O<sub>2</sub>/hypobaric hypoxia results in decline in memory functions associated with increased oxidative stress and neuronal apoptosis in hippocampus. Recently, 12/15-LOX emerged as an important amplifier of oxidative stress and has been found to be crucially associated with neurodegenerative conditions including stroke<sup>1,2</sup>. The present study explores the mechanistic insights into the involvement of 12/15-LOX in hypobaric hypoxia induced cognitive impairment and neuronal damage.

## OBJECTIVES

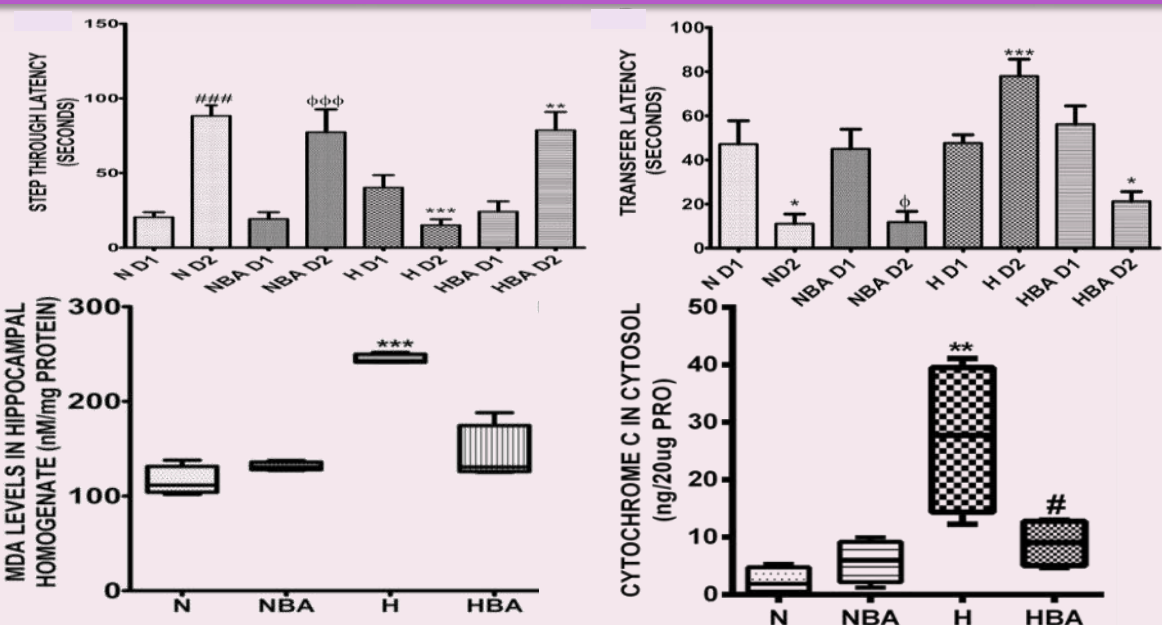
- ❖ To evaluate the involvement of 12/15 LOX in hypobaric hypoxia induced working memory deficits and neuronal damage.
- ❖ To estimate the relative expression and activity of 12/15-LOX in hippocampus during hypobaric hypoxia and its modulation by baicalein.
- ❖ To elucidate the role of 12/15-LOX in modulation of hippocampal hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) expression and its targeted genes viz. NOS isoforms during hypobaric hypoxia.
- ❖ To investigate the association of 12/15-LOX in executing mitochondria dependent cell death cascade during hypobaric hypoxia.

## EXPERIMENTAL PLAN

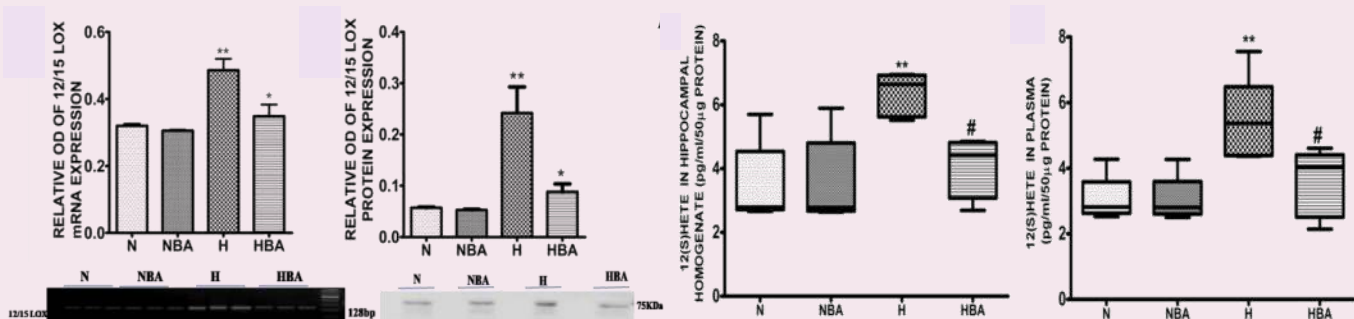


## RESULTS

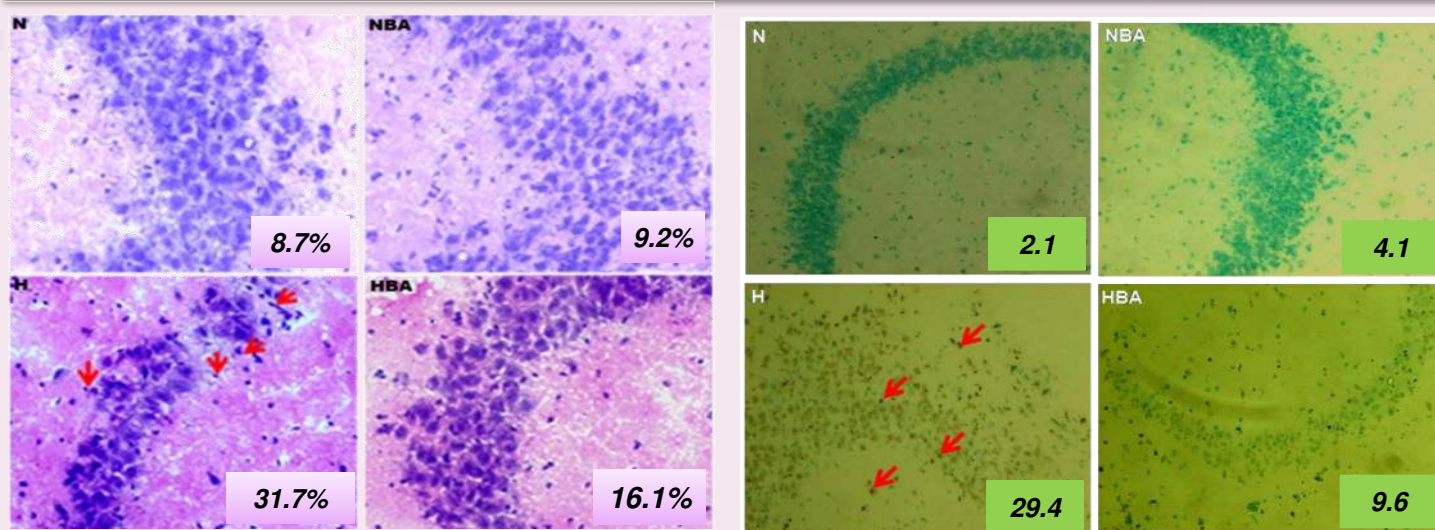
Baicalein ameliorates hypobaric hypoxia induced memory dysfunction/oxidative stress and prevents Cytochrome C release in cytosol



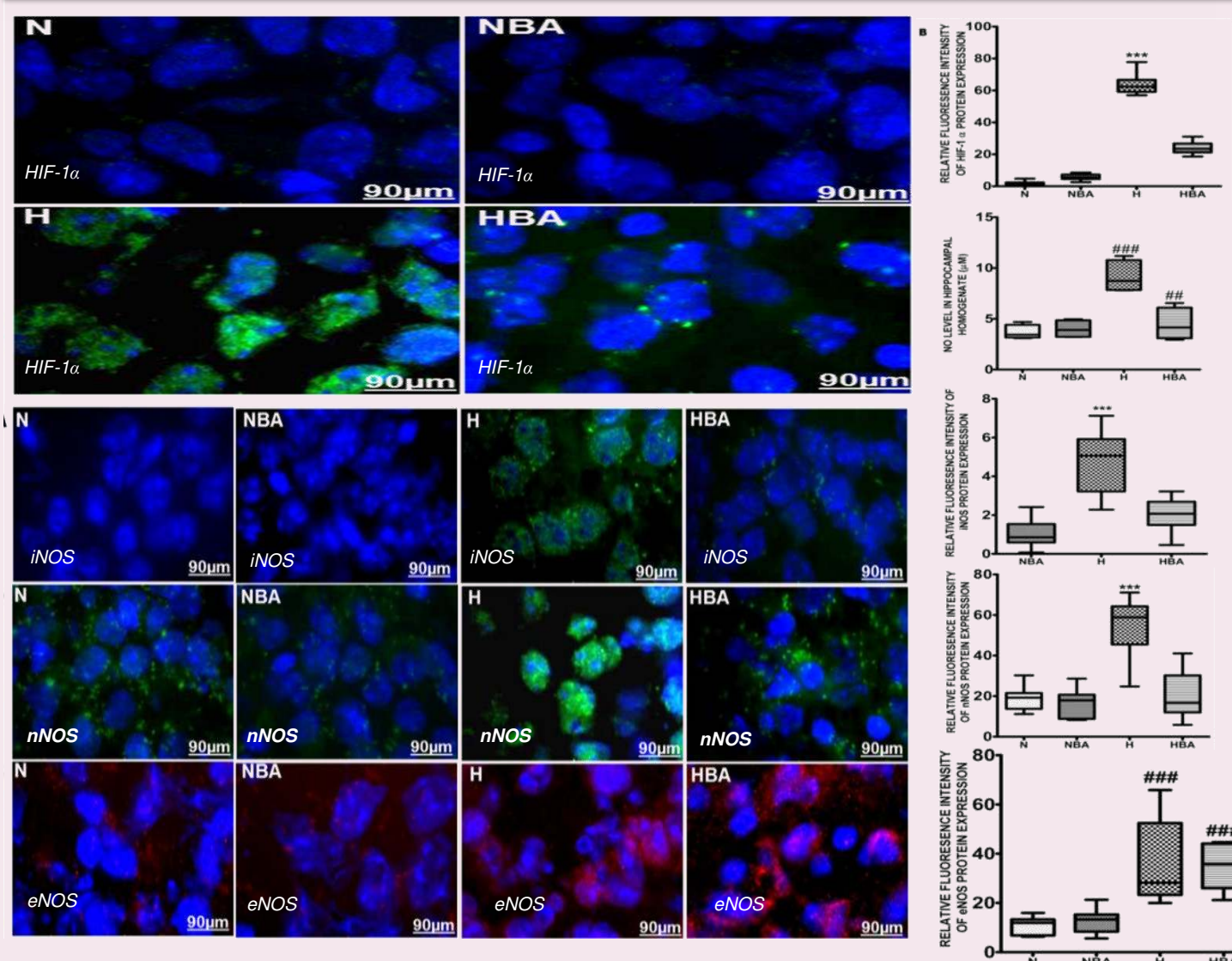
## Baicalein reverses alteration in 12/15-LOX and HETE in hypobaric hypoxia



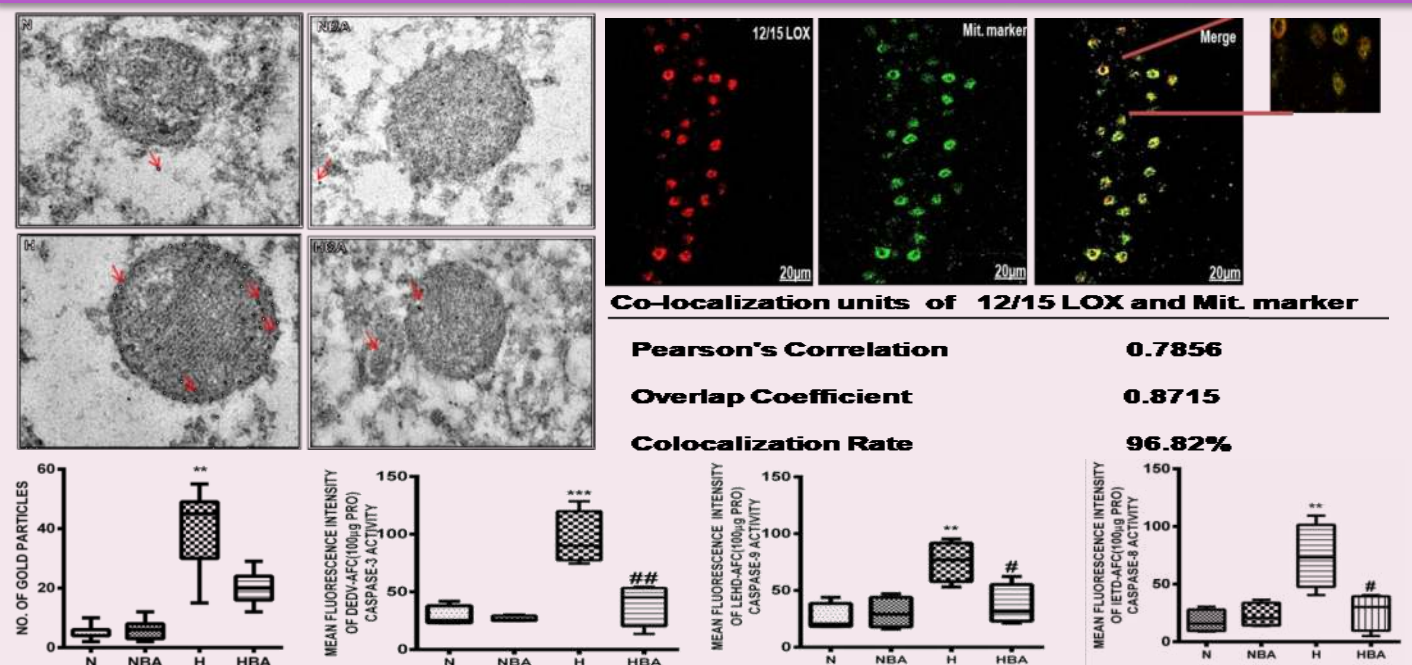
## Baicalein mitigates hypobaric hypoxia induced neurotoxicity



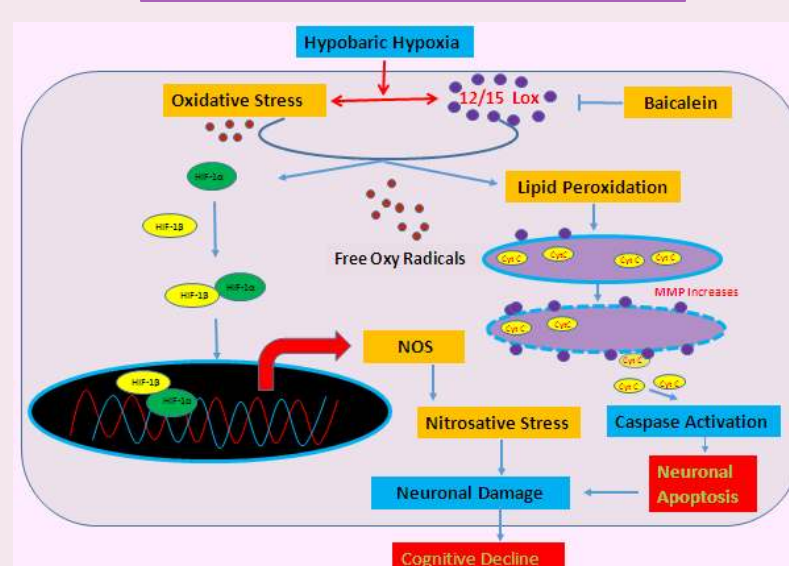
## Role of 12/15-LOX in modulation of HIF-1 $\alpha$ and targeted genes (NOS)



## 12/15-LOX attacks on the periphery of mitochondria promoting apoptosis



## CONCLUSION



## REFERENCES

- 1) van Leyen K, Kim HY, Lee SR, Jin G, Arai K, Lo EH.. Stroke. 37(2006):3014-8.
- 2) Praticò D et al., Am J Pathol.164(2004):1655-62.

## ACKNOWLEDGEMENT

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