

## ANTI-ANGIOGENIC ACTIVITY OF *ANNONA RETICULATA* N-HEXANE SEEDS EXTRACT : *IN VIVO* STUDY

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**ABSTRACT :** Angiogenesis is the physiological process through which new blood vessels generate from pre-existing vessels and it acquired therapeutic value in cancer treatment because malignant tissue required the formation of new blood vessels to grow and metastasize. Bevacizumab is a recombinant humanized monoclonal antibody. It is the first angiogenic inhibitors used clinically. There are number of resistance mechanisms and some serious adverse effects associated with its usage. Recently, there are many studies about the anticancer activity of various extracts of *Annona reticulata* and their major active constituent's acetogenins (AGEs) against different cancer cell lines. However, to our knowledge, the antiangiogenic effect of *A. reticulata* is not verified till now. This study aimed to examine *A. reticulata* n-hexane seed extract antiangiogenic activity in *in vivo* study. The determination of LD<sub>50</sub> done by Karber method, then *in vivo* study was done, n-hexane seeds extract was tested against mammary adenocarcinoma AM3 transplanted in mice. *In vivo* results showed significant reduction in relative tumor volume (RTV) and tumor growth inhibition percentage (TGI%) and the formation of blood vessels of tumor mass in treated groups. Microarray analysis of 24 different angiogenesis factors revealed that n-hexane extract down-regulated number of proangiogenic factors like (TNF- $\alpha$ , IL- $\beta$ , MCP and VEGF-A). Chemical analysis of the extract were done by Gas chromatography-mass spectrometry (GC-MS) analysis, which revealed the presence of acetogenin compounds in extract. The study suggested that n-hexane seeds extract of *A. reticulata* can suppress angiogenesis by interfering with angiogenic factors that might reduce tumor growth and metastasis.

**Key words :** Angiogenesis, VEGF, *Annona reticulata*, bevacizumab, relative tumor volume (RTV), microarray analysis.

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### INTRODUCTION

Angiogenesis is a process of formation a new blood vessels from existing one which controlled by certain bio-molecules and stimuli, angiogenesis is a complex and multiple steps process, that is either physiological that crucial during embryo development, wound healing and collateral formation for improved organ perfusion or pathological, that associated with various disorders, including ocular neovascularization and cancer enlargement and metastasis (Rajabi *et al*, 2017; Zimna *et al*, 2015; Mahal *et al*, 2019).

Angiogenesis is play important role in cancer development and metastasis so the antiangiogenic

therapy was developed to fight cancer (Marme *et al*, 2018; Folkman *et al*, 1987). Angiogenesis process is tightly regulated by large number of pro-angiogenic factors, one of them is vascular endothelial growth factor (VEGF). Angiogenic inhibitors discovery give hope for reducing cancer mortality and morbidity (Yadav *et al*, 2015). Bevacizumab is first angiogenic inhibitors used clinically, is recombinant humanized monoclonal antibody (Krämer *et al*, 2007), act by binding to VEGF so inhibiting its binding to receptors and begin the angiogenesis process.

Bevacizumab used to treat various types of cancer like Metastatic colon or rectal cancer, non-squamous, non small cell lung cancer, Metastatic breast cancer and others