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Anti-proliferative activity of *Annona muricata* extract on triple negative breast cancer cells

Heba K Alshaeri[1,2], Moudi M Alasmari[1,4], Zuhair S Natto[3] and Alejandro Pino-Figueroa[1]
[1]Boston University, USA
[2]Fakeeh College for Medical Sciences, Saudi Arabia
[3]King Abdulaziz University, Saudi Arabia
[4]King Saud bin Abdulaziz University for Health Sciences University, Saudi Arabia

Statement of the Problem: Triple Negative Breast Cancer (TNBC) cells are a subtype of breast cancer that lack of Estrogen Receptors (ERs), Progesterone Receptors (PRs) and Human Epidermal Growth Factor Receptor 2 (HER2). This type of breast cancer has poor prognosis and accounts for 15-20% of newly diagnosed Breast Cancer (BC) cases. *Annona muricata* is a tropical plant and has been used as a folk medicine to treat several diseases such as malaria, inflammation, diabetes and recently it was known to have anticancer activity on various cancer types. However, the underlying molecular mechanisms remain to be explored.

Research Question/Hypothesis: We hypothesize that *Annona muricata* Ethyl Acetate (AMEA) extract and the isolated compounds will reduce cell proliferation and produce cell death by the induction of apoptosis. Moreover, AMEA or its active ingredients will interfere with the function of EGFR signaling activity in the TNBC cell line.

Methodology: The effect of AMEA and F4 on the cell viability of BT-20 breast cancer cell line was analyzed by MTS assay. We measured caspase-3/7 activity and cytochrome C release as a marker of apoptosis. Also, the protein expression of Bax and Bcl-2 was determined using western blot. To investigate further of AMEA and F4 anti-cancer effect we measured cyclin D1 and EGFR signaling and its downstream proteins AKT, MAPK and NF-κB p65 protein expression by western blot analysis.

Results: The AMEA showed significant decrease on BT-20 cell viability. Furthermore, AMEA and F4 produced anti-proliferative effect via inhibiting the EGFR phosphorylation and the phosphorylation of its downstream signaling proteins including AKT and MAPK. These effects were accompanied with down-regulation of cyclin D1 production resulting in cell cycle arrest at G1/S phase. Moreover, this compound decreased significantly NF-κB p65 protein expression in the nuclear fraction, therefore, inhibiting its activation and preventing the induction of cell survival. Our data indicated that neither AMEA nor F4 had significant effect on apoptosis biomarkers when tested on Bcl-2, Bax, cytochrome C and caspase 3/7 activities.

Conclusion: These findings provide a scientific basis for the molecular mechanism of action of *Annona muricata* extract and its active fraction F4 in the treatment of TNBC. It has been demonstrated the anti-proliferative effect via EGFR-mediated signaling pathways which includes AKT/MAPK/NF-κB pathways and cyclin D1 inhibition.

Biography

Heba K Alshaeri has pursued PharmD degree at King Abdulaziz University, Saudi Arabia and an MPH degree at Loma Linda University, USA in 2013. In 2013 she joined MCPHS University for Doctoral program in Pharmacology and she has completed her PhD degree in 2018. She is a Member of the American Society for Pharmacology and Experimental Therapeutics and the American Association of Pharmaceutical Scientists.

halshaeri@llu.edu

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