عنوان المشروع باللغة العربية - Title of the proposed project in Arabic	كمضاد للسرطان عن طريق تحوير PACدراسة تقييم تأثير المركب التناظري للكركمين الـ الضرر التالف لمسار التعبير الجيني للحمض النووي في سرطان الثدي البشري
Title of the proposed project in English	In Vivo and in vitro studies for assessing the anti-carcinogenic effect of curcumin analog (PAC) by modulating DNA damage signaling pathway gene expression in Human Breast cancer
المشرف الرئيس - PI	Dr Abdelhabib Semlali
التخصص الدقيق للمشرف الرئيس - Specialty of PI	Molecular and cell biology
المشرف المساعد - Co-PI	Dr Sooad Al-Daihan
المدة المتوقعة لإنجاز البحث منذ الحصول على موافقة عمادة الدراسات العليا (بالشهور) - Expected time in month to finish	10
Abstract of the proposal (No more than 200 words)	Breast Cancer is a multi-factorial disorder with genetic and environmental components leading cause of cancer-related mortality worldwide (1). De novo and acquired resistance to chemotherapeutics and targeted therapies and the toxicity to normal cells are the major causes of treatment failure. Activating mutations in epidermal growth factor receptors (EGFRs) and/or their downstream signaling pathways as well as constitutive activation of ubiquitous transcription transcription factors, nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) (2-5), constitutes major pathways by which breast cancer cells neutralize cytotoxic effects of therapeutic regimens (5). Therefore, it is necessary to search for new and better treatments for Breast cancer. To these end, attention could be drawn to curcumin and their analogues due to their anti cancer effect and their safety (6,7). Curcumin is widely used in traditional medicine. It possesses wide pharmacological actions and, importantly, has low toxicity (4), which led the support to the rationale behind its therapeutic uses. Curcumin has been found to exhibit anti-oxidant and anti-inflammatory activities, to inhibit the proliferation of various tumor cells in culture and to prevent carcinogen induced tumors in rodents. Curcumin's anti-carcinogenic, anti-inflammatory, and growth-modulatory effects have been ascribed to the deactivation of NF-κB and AP-1 and their asscociated signaling molecules (3). Despite these studies, no report has yet addressed the effect of Pac a new analogue of Curcumin on breast cancer treatment. The current study will be carried out to evaluate the effect of PAC on both ER-and ER+ breast cancer cell line (MCF-7 and MDA 231) and to elucidate the molecular mechanism of action. We hypothesized that curcumin analog can to active the genes involved in DNA repair damage to contribute to anti-cancer effect. We tested this by studying DNA damage genes related gene expression in breast cancer cells induced by PAC.

Hypothesis of the proposal	We hypothesized that curcumin analog can to active the genes involved in DNA repair damage to contribute to anti-cancer effect.
Specific objectives	The purpose of our study is to investigate the molecular mechanism by which the Curcuma analogues; PAC exerts its inhibitory effects on colon cancer cells, and to provide the scientific rationale for using PAC as a therapeutic agent against colon cancer. We hypothesize that the PAC might exert this role by modulating activity of key molecules involed in DNA repair proteins. We will investigate the effect of the PAC on the following parameters: i- Controlling proliferation in vivo on MCF-7 and MDA-231 cells by MTT assay and in vitro by the variation of size of tumor before and after 1 month of PAC treatment ii- Induction of apoptosis in MCF-7 and MDA-23cells by low cytometry and by Modulating expression of anti-apoptotic / pro-apoptotic proteins (Bcl-2, Bax) by real time PCR and western Blotting, iii- Modulating expression of DNA repair signaling pathways by real-time PCR using RT2 Profiler PCR Array. Relative gene expression will be calculated using ΔΔCt method. Real time for with primer will be used to validate select genes with ≥2 fold change expression in the array expression profile.
Methodology & Major Techniques to be used	To chieve these goals, we will utilize MTT assay, Low cytometry, apoptotic, qRT-PCR and Western blotting assays assay to study the anti cancer effect of PAC on MCF-7 and MDA-231 cells. DNA damage differential gene expression was examined in vivo on breast cancer cells and in vitro on tumor tissues from breast cancer animal model stimulated by Curcuma analog (PAC) compared to control cells or compared to breast tumor no treated by PAC. Following total RNA extraction, 84 key genes in DNA Damage pathway will be examined by real-time PCR using RT2 Profiler PCR Array. Relative gene expression was calculated using ΔΔCt method. Real time for with primer was used to validate select genes with ≥2 fold change expression in the array expression profile. We hypothesize that because of its substantially wide range of activities, it would allow targeting of multiple molecular and cellular pathways involved in the process of breast carcinogenesis. The data generated by this study may lead to the design of more effective drug against breast cancer, as well as other neoplastic growths
Availability of Samples	Yes
Availability of Chemicals	Yes
Availability of Instruments	Yes
Ethical Approval	Not needed

Recent References	1- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30. 2- Schulz et al, 2007 3- Schaffer M1, Schaffer PM, Zidan J, et al 2011 4- Parthasarathy Seshacharyulu, et al 2013 5- Normanno N,et al 2005 6- Alok Vyas, 2013 7- Mosley CA, 2007