Dear Editors,

# Please find enclosed our manuscript titled “Docking Studies Reveal Zerumbone Targets -catenin of the Wnt--catenin Pathway in Breast Cancer” for consideration under the Original Scientific Papers category of contributions.

The present study is original research carried out in Department of Chemistry, University of Malaya, Malaysia, in collaboration with UPM\_MAKNA Cancer Research Laboratory, Institute of Bioscience, UPM, Malaysia. It is written by the first author while the other authors have helped in editing and finalisation of the manuscript. We warranty that the manuscript is not under consideration in part or whole in any other publication and will not be sent to another journal until the decision of the editor is received. It does not contain any material that violates other people’s Intellectual Property Rights. The manuscript contains twenty (21) coloured illustrations.

This study uses CHARMm based docking software, CDOCKER, to show that zerumbone binds strongly to -catenin, the key protein of the Wnt--catenin signaling pathway. It is one of the pioneering study as molecular level data about mechanism of anti-cancer action of zerumbone in the pathway is almost non-existent. The importance of the pathway lies in the fact that it is found to be active in several cancers including breast cancer with -catenin being overexpressed and aberrant destruction complex unable to control the translocation of -catenin to the nucleus. Zerumbone was found to bind strongly to -catenin in the groove used by its partner proteins like TCF4. The small molecule was able to block the crucial amino acids Lys 312 and Lys 345 of -catenin. These residues are important in anchoring TCF4 to -catenin so that it can form the transcription complex with DNA. By blocking these key proteins, it can be hypothesised that zerumbone could modulate the binding of-catenin with its partner TCF4 and thus prevent the transcription complex in cancer cells.

Regarding suitable reviewers, the following people are suggested along with their emails

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We hope that our manuscript meets your expectations and can be considered for publication. Please let me know if you require any additional information to better facilitate the understanding of the work.

Thank you

Yours Truly,

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