Details of the Project sanctioned under the Human Resource Development scheme of Department of Health Research

1. Project Title: Design, synthesis, QSAR, system pharmacology, *in-vitro* and *in-vivo* studies of Plant molecules and their derivatives for anticancer activity

2. Category of fellowship: Young Scientist Fellowship

3. PI (Name & Address):

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4. Qualifications: M.Sc. Biomedical Sciences

5. Mentor or Co.PI (Name & Address):

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6. Duration of the project: 3 Years

7. Broad area of Research: Anticancer Target/Cell line specific natural Lead Identification & Optimization.

7.1 Sub Area: *In-silico* anticancer assay/screening online tool development

8. Summary of the Project: (Give in about 300 words)

The project is based on translational research having an aim of bench to bedside. Our strategy/aim will be to develop QSAR based virtual screening tool. The screened out potential leads will be further processed for lead optimization through modern disciplines of drug discovery protocol such as molecular docking, eADMET, in silico system pharmacology. The optimized compounds will be subjected to semi-synthesis, biochemical assays, in vivo studies for pharmacodynamics and pharmacokinetics, and pathway designing etc. These strategies help to identify the on & off targets for the lead compound with minimal or no side effect. The virtual screening tool developed through this project will show a valuable drug design strategy and may recognized to reduce the time and cost involved. This study will also provide a significant approach for identification of potent anticancer compounds as well as to explore the possible mechanism of action of identified

compounds, which can be further utilized with better activity by rational modifications. This work lead us one step ahead towards anticancer drug discovery approaches and fight with cancer.

9. Objectives of the Proposal:

In short:

- Development of *in-silico* QSAR models for screening of anticancer drug like natural leads.
- Design, chemical synthesis and *in-vitro* & *in-vivo* studies for anticancer activity and system pharmacology
- Development of anticancer lead screening application online tool/database

In details:

i. Development of multiple linear regression QSAR models for screening of phytomolecules/ derivatives against human cancer cell lines/targets.
ii. Developed a QSAR based tool for virtual screening of phytomolecules/ derivatives.
iii. Prediction of cytotoxic/anticancer activity of untested compounds.
iv. Molecular docking studies of potential anticancer compounds and exploration of binding pocket/site residues of selected anti-cancer targets.
v. *In silico* pharmacokinetics (ADMET) and pharmacodynamics studies of identified compounds.
vi. Synthesis/semi-synthesis of screened out (predicted) compound and *in-vitro* experimental evaluation.
vii. Cell inhibition and other targets based evaluation of semi-synthesized derivatives.
viii. To study the adverse drug action and possible side effect of lead compounds through *in-silico* system pharmacology approach
ix. Pharmacokinetic studies of selected compound in *in-vivo* models of rabbits
x. Pharmacodynamics study of screened out compound in an *ex-vivo* system using isolated arterial tissues.
xi. Characterization of the mechanism of action of compounds founds active in the *ex-vivo* system using specific modulators/blockers/activators of signalling pathways.

10. Innovations in the project: (Give in about 100 words)

Development of computational structure-activity relationship (SAR) mathematical models for predicting anticancer biological activity by mimicking *in-vitro* and *in-vivo* target/cancer cell line based assays is proposed. Predictions will be validated by in-house studied *in-vitro* and *in-vivo* experimental data, which include biochemical assay (cytostatic/cell inhibition assay on different cancer cell lines or cell cycle analysis, and target based assays e.g., tubulin polymerization inhibition assay, DNA topoisomerase inhibition assay, apoptosis assay, signalling pathway related assays etc.). Later developed *in-silico* models will be transformed in to an online application tool/software for virtual screening and lead identification purpose. At present there is no such method or tool for predicting biological activity and screening potential leads based on structural chemical family, pharmacokinetics, pharmacodynamics, and system pharmacology. Innovative part of this proposed work is to develop a real-time

quantitative structure-activity relationship (Q-SAR) models (or simulated mathematical models) based on chemical synthesis/semi-synthesis, *in-vitro* (target/cell line specific) & *in-vivo* activity (on rabbit animal system) and *ex-vivo* (using isolated arterial tissues) experimental data, so that to predict the reliable biological activity of unknown compounds with either similar chemical family nature (derivatives/analogues) and/or pharmacokinetics (ADMET)/ pharmacodynamics/system pharmacological parameters (disease biomarkers network, drug target networks, metabolic networks, toxicity networks). These models could be used in the form of online tool for public or researchers use for quick screening of anticancer natural leads favouring pharmacokinetics/ system pharmacological/pharmacodynamics (pathways & ion-channels studies e.g., kinase, sodium, calcium, potassium ion channels) parameters as an alternate to traditional screening approaches.

11. Significance of the outcome of the project: (Give in about 150 words)

The virtual screening tool developed through this study will show a valuable application for drug like lead identification and optimization, and may recognized to reduce the time and cost involved. Although this tool is successful in generating libraries of reliable hits by screening thousands of compounds quickly with minimal effect. Apart, this study will provide a significant approach in the identification of novel and potent anticancer compounds from phytomolecules derivatives. Moreover, this study will also projected to explore the molecular mechanism by which identified compounds/derivatives can be further utilized with better activity by rational modifications. Aside from this, this study also provided a significant approach in the identification of novel and potent anticancer compounds from phytomolecules and their derivatives and can be utilized as a guide for future studies for screening and designing the structurally diverse compounds.

12. Relevance in Public Health:

Cancer is the second leading cause of death in the world and estimated about 8.2 million people die per year. An estimated 9, 79,786 cancer cases are in India, which are going to be 11, 48,757 in the year 2020. This growing incidence urge ICMR (Indian council of medical research) to make cancer a notifiable disease. Due to the high cost of cancer drugs and even resistance to existing anticancer drugs, there is a strong need of new chemical entities for cancer. So there is vital necessity of new lead identification as well as investing in technologies for high-throughput screening of anticancer compounds. The strategy used in this study will help in reducing the cost and somehow and will help in providing affordable health care to all.

Sarfaraz Alam.

Signature of the Fellow /Faculty