MECHANISTIC INSIGHTS INTO THE BIOACTIVITY AND BIOAVAILABILITY OF NATURAL COMPOUNDS AGAINST CANCER

SEYAD SHEFRIN N

DEPARTMENT OF BIOCHEMICAL ENGINEERING AND BIOTECHNOLOGY
INDIAN INSTITUTE OF TECHNOLOGY DELHI

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by

Seyad Shefrin N

Department of Biochemical Engineering and Biotechnology

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CERTIFICATE

This is to certify that the thesis entitled **'Mechanistic insights into the bioactivity and bioavailability of natural compounds against cancer'** being submitted by Mr. Seyad Shefrin N to the Indian Institute of Technology Delhi for the award of the degree of **'Doctor of Philosophy'**, is a record of the bonafide research work carried out by him, which has been prepared under my supervision in conformity with the rules and regulations of Indian Institute of Technology Delhi. The research reports and the results presented in the thesis have not been submitted for any degree or diploma in any other University or Institute.

Prof. D. Sundar

Institute Chair Professor

Department of Biochemical Engineering and Biotechnology

Indian Institute of Technology Delhi

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ABSTRACT

Cancer can be defined as the uncontrolled cell proliferation and migration of such cells into the nearby tissues. Understanding the molecular mechanism and developing a therapeutic strategy is a cumbersome process due to the increased number of complex pathways and factors that drives the normal cells to become cancerous. Targeted therapy, including monoclonal antibodies and small-molecule drugs, fail in clinical trials multiple times due to the heterogeneous nature of the tumor cells and various other micro-environmental factors. Side-effects such as vomiting, diarrhoea, high blood pressure and fatigue are commonly observed in patients treated with chemotherapy or targeted therapy using synthetic drugs. Radiation therapy and surgery can remove the tumor cells; however, there are higher chances of regeneration of the cancer stem cells that can grow back the tumor during the post-treatment phase. In this premise, there is a need for alternative drugs to conventional synthetic cancer drugs that can reduce side effects in the patients undergoing treatment. Natural resources have emerged as a crucial source of pharmaceutically relevant novel secondary metabolites, several of which are already approved, and many are under development or in clinical trials. Traditional medicinal system like *Ayurveda* that uses whole plant extract for treating various diseases including cancer, Alzheimer's and other neurodegenerative diseases, are in practice for many years in India due to their lesser side effects. However, their individual compound's mechanism of action is not completely understood for use in treatment. With this background, this PhD thesis aimed to bring the mechanistic understanding of natural compounds and their mode of action by studying their bioactivity and bioavailability inside the cell.

Keywords: Natural compounds, Drug discovery, Molecular mechanism, Natural metabolites, Cancer drug

सार

कैंसर को अनियंत्रित कोशिका प्रसार के रूप में परिभाषित किया जा सकता है और ऐसी कोशिकाओं, आस-पास के ऊतकों में प्रवास करके उनको भी प्रभावित कर देती है । आणविक तंत्र को समझना और एक चिकित्सीय रणनीति विकसित करना एक बोझिल प्रक्रिया है क्यूंकि जटिल मार्गों और कारकों की संख्या बध रही है जो सामान्य कोशिकाओं को कैंसर बनने के लिए प्रेरित करती है। ट्यूमर कोशिकाओं की विषम प्रकृति और विभिन्न अन्य सूक्ष्म-पर्यावरणीय कारकों के कारण मोनोक्लोनल एंटीबॉडी, छोटे-अणु दवाऐ और लक्षित चिकित्सा कई बार नैदानिक परीक्षणों में विफल हो जाती है। उल्टी, दस्त, उच्च रक्तचाप और थकान जैसे दुष्प्रभाव आमतौर पर कीमोथेरेपी या सिंथेटिक दवा के जरीए लक्षित थेरेपी का उपयोग करके रोगियों में देखे गए थे। विकिरण चिकित्सा और सर्जरी ट्यूमर कोशिकाओं को हटा सकती है; हालाँकि, कैंसर स्टेम कोशिकाओं के पुनर्जन्म की संभावना अधिक होती है। ये ट्यूमर कोशिकाऐ उपचार के चरण के बाद ट्यूमर को पुन: विकसित कर देती है। इस आधार पर, पारंपरिक सिंथेटिक कैंसर दवाओं के लिए वैकल्पिक दवाओं की आवश्यकता है जो रोगी के इलाज में होने वाले दुष्प्रभावों को कम कर सके। प्राकृतिक संसाधन, फार्मास्युटिकल में प्रासंगिक उपन्यास माध्यमिक मेटाबोलाइट्स के लिये एक महत्वपूर्ण स्रोत के रूप में उभरे हैं, जिनमें से कई पहले से ही अनुमोदित हैं, और कई विकास के अधीन हैं या नैदानिक परीक्षणों में हैं। आयुर्वेद जैसी पारंपरिक औषधीय प्रणाली जो कैंसर, अल्जाइमर और अन्य न्यूरोडीजेनेरेटिव रोगों सहित विभिन्न बीमारियों के इलाज के लिए पूरे पौधे के अर्क को उपयोग में लाया जाता है। ये पारंपरिक औषधीय अपने कम दुष्प्रभावों के कारण कई वर्षों से प्रचलन में है। हालाँकि, उपचार में उपयोग के लिए उनके व्यक्तिगत यौगिक की क्रिया का तंत्र पूरी तरह से समझा नहीं गया है। इस पृष्ठभूमि के साथ, इस पीएचडी थीसिस का उद्देश्य कोशिका के अंदर की जैव सक्रियता और जैव उपलब्धता का अध्ययन करके विभिन्न प्राकृतिक यौगिकों और उनकी क्रिया के तरीके की यंत्रवत को समझना है।

कीवर्ड: प्राकृतिक यौगिक, दवा की खोज, आणविक तंत्र, प्राकृतिक मेटाबोलाइट्स, कैंसर की दवा

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LIST OF ABBREVIATIONS

ADME	Absorption Distribution Metabolism Excretion
ADP	Adenosine Di Phosphate
AKT1	Ak strain Transforming
APL	Area Per Lipid
ARC	Artipillin-C
ATP	Adenosine Tri Phosphate
CAPE	Caffeic Acid Phenethyl Ester
Cuc-B	Cucurbitacin-B
HDM2	Human Double Minute 2 Homolog
hnRNP-K	Heterogeneous nuclear Ribonucleoprotein K
LUAD	Lung Adeno Carcinoma
NGS	Next Generation Sequencing
PARP1	Poly [ADP-ribose] Polymerase 1
PMF	Potential Mean Force
POPC	1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine
QSAR	Quantitative Structure Activity Relationship
RMSD	Root Mean Square Deviation
RMSF	Root Mean Square Fluctuation
SMD	Steered Molecular Dynamics
WHAM	Weighted Histogram Analysis Method
Wi-A	Withaferin-A
Wi-N	Withanone