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POLYPHENOL - TO ENHANCE THE OVERALL EFFECTIVENESS OF LUNG CANCER TREATMENT STRATEGIES

Dr. Kazi Julekha[1], Paramita Ganguly[1]*, Sanchari Talukdar[1] and Sandip Chatterjee[2]

[1]Department of Pharmaceutical Technology, Brainware University, Kolkata-700125.
[2]Sarala Birla University, Birla Knowledge City, PO-Mahilong, Purulia Road, Ranchi 835103.

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***Corresponding Author**
Paramita Ganguly
Department of Pharmaceutical Technology, Brainware University, Kolkata-700125.

ABSTRACT

Chemotherapeutic drugs are employed to manage late-stage cancer or after surgery. Nonetheless, cancer cells can become resistant to these drugs, causing treatment failure and disease reappearance. Polyphenols, a diverse group of over 10,000 organic compounds, share a common three-membered flavone ring system. This discussion focuses on the role of specific polyphenols, primarily curcumin, resveratrol, and epigallocatechin gallate (EGCG), in addressing different facets of cancer drug resistance. Polyphenols contribute to enhancing the efficacy of chemotherapeutic agents through several mechanisms. They facilitate increased uptake of drugs by tumour cells, curbing drug metabolism catalysed by enzymes like cytochromes and Glutathione-S-transferases, and curtailing drug efflux. Consequently, these actions heighten the vulnerability of cancer cells to chemotherapeutic interventions. Furthermore, polyphenols exert influence on other vital targets that can counteract chemo resistance in cancer cells. These encompass programmed cell death processes such as autophagy and apoptosis, modulation of epithelial-mesenchymal transition (EMT), management of reactive oxygen species (ROS), facilitation of DNA repair mechanisms, regulation of cancer stem cells, and epigenetic modifications such as microRNAs (miRNAs). In summary, this abstract sheds light on the potential of polyphenols, including curcumin, resvetrol, and EGCG to combat the multi-faceted issue of chemo resistance in cancer treatment. By targeting diverse pathways that contribute to drug resistance, polyphenols offer a promising avenue for improving the sensitivity of cancer cells to chemotherapy, thereby enhancing the overall effectiveness of cancer treatment strategies.

KEYWORDS: Polyphenol, flavones, epigallocatechin gallate, Glutathione-S-transferases.

INTRODUCTION

Despite the Somber statistics, there is hope on the horizon. The medical community unwavering dedication and collaborative efforts are driving significant progress in understanding and combating lung cancer. Promising breakthroughs in targeted therapies, immunotherapy, and personalized medicine are beginning to show a glimpse of a brighter future. By Channelling resources and support into these advancements, we can aspire to uplift the spirits of patients and their familiar, transforming lung cancer from a devastating adversary into a conquerable foe. Together, We stand resolute in the fight against this formidable disease, working towards a day when lung cancer is no longer a dreaded diagnosis but a conquered challenge.[1,2,3] The burden of lung cancer is undeniably staggering, as revealed by the sobering statistics of GLOBOCAN 2018. With an estimated 2.1 million new cases reported that year, lung cancer stood at forefront as the most commonly diagnosed cancer, accounting for a troubling 11.6% of all cancer cases worldwide. Equally distressing, it held the grim distinction of being the leading cause of cancer related deaths, claiming 1.8million lives, which represented a staggering 18.4% of the total cancer deaths in 2018. These fig serve as poignant reminder of the urgent need for continued efforts in research, prevention, and innovative treatments to combat this relentless disease and improve outcomes for affected individuals and their loved once.[1,4] Despite significant strides in treatment modalities, Which encompass surgery, radiation, chemotherapy and specific targeted therapies, the prognosis for lung cancer patients remains disheartening. The crux of the issue lies in the challenge posed by late stage diagnoses frequently accompanied by the onset of metastatic disease. This unfortunate reality underscores the critical importance of heightened awareness, early screening initiatives and access to comprehensive healthcare service in order to detect and address lung cancer at its earliest and most treatable stages. By tackling the berries to timely diagnosis head on, we can

forge a path towards improved outcomes and a brighter outlook for those grappling with this formidable disease.[1,5,6] Phytochemicals, those wondrous natural compounds derived from plants, have emerged as promising agents in the battle against cancer and various other disease. The incredible potential of these substances has been underscored by a multitude of in vitro and in vivo studies, which have unveiled their remarkable ability to impact tumor proliferation, inhibit growth, and even deter metastasis. As we delve deeper into the realm of phytochemical research, we open up new avenues for therapeutic interventions that could revolutionize cancer treatment and offer hope to countless individuals worldwide.[1,7]

Natural compounds possess an irresistible appeal due to their widespread availability, exceptional tolerance in the human body, and cost- effectiveness, distinguishing them from synthetic molecules. By delving into their vast potential, we not only harness their therapeutic advantages but also create opportunities for accessible and affordable treatments, with the potential to positively impact global health.[1,8,9] Flavonoids, an enchanting subgroup of the polyphenol family, exhibit an astounding diversity with more than 4000 distinct members. Their classification is based on a captivating molecular structure, characterized by two benzene rings interconnected through a linear three-carbon chain, resulting in an oxygenated heterocycle (C6-C3-C6). What truly sets them apart is the profusion of functional groups, such as hydroxyl, methoxy, and O-glycoside, adorning the fundamental benzo-pyrone (C6-C3-C6) scaffold. This intricately orchestrated arrangement imparts them with a wide array of biological activities, making them captivating subjects for ongoing research and holding immense promise for potential therapeutic applications.[1,10]

The far-reaching impact of flavonoids on human health is indisputable, as they manifest countless beneficial effects. These versatile compounds serve as an inspiring molecular template for the development of novel therapeutics agents, holding promise for diverse diseases including lung cancer. Initially, flavonoids biological effects were primarily linked to their capability to inhibit reactive oxygen species production, thereby influencing a multitude of pivotal cellular processes and impacting several molecular mechanisms altered in tumor cells. As our understanding of flavonoids deepens, their potential to revolutionize cancer treatment became increasingly evident, inspiring hope for more effective and targeted therapeutics strategies in the fight against lung cancer and other malignancies.[1,7,11]

2. Role of polyphenol in lung cancer treatment

A. As per Qingyu Zhou et.al describe, The exploration of bioactive natural polyphenol as a therapeutics avenue for cancer prevention and intervention continue to evolve, holding promising prospects in the field of cancer management. A comprehensive understanding of their mechanism of action is essential to seamlessly integrate these polyphenols into standard oncology care. This section focuses primarily on the recent strides made in comprehending the antitumor effects of natural polyphenol in the context of lung cancer. Only original studies that extensively investigated the molecular mechanisms underpinning the antitumor potential of natural polyphenol and their analogues were included, ensuring a robust foundation for the exploration of their therapeutics potential. Mechanism was describing in table no 1.[12]

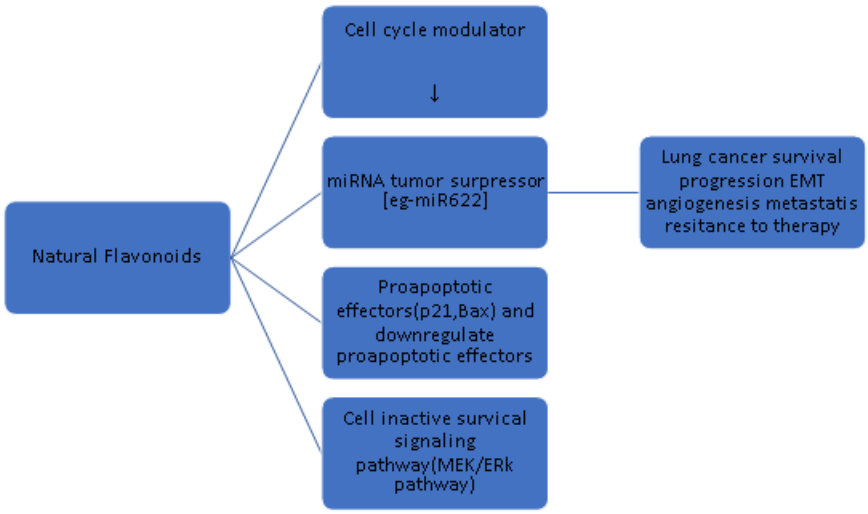

Table-01: Natural flavonoids in cancer therapy.

B. Giusibriguglio et.al describe, Smoking is the leading cause of lung cancer, responsible for a significant proportion of cases globally.[13,14] Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) together account for about 15% and 85% of all cases, respectively. The consumption of fruits, vegetables, and natural products is considered beneficial in the prevention and combat against lung cancer. Certain natural polyphenols have shown promising anticancer activities due to their anti-proliferative, anti-migratory,

anti-metastasis, anti-angiogenic, and pro-apoptotic properties. A recent comprehensive review has summarized preclinical studies investigating the molecular mechanisms of these natural polyphenols or analogues, with resveratrol (RES), curcumin (CUR), and epigallocatechin gallate (EGCG) emerging as the most extensively studied compounds with potential roles in lung cancer.[13,15] Recently, there have been significant advancements in research, leading to a deeper understanding of the mechanisms by which resveratrol (RES) inhibits cell proliferation, induces apoptosis, and causes cell cycle arrest, while also suppressing invasion and metastasis in cancer cells. Resveratrol (RES) has demonstrated its ability to induce apoptosis through multiple signalling pathways, involving various kinases such as AKT, STAT3, PKC, p38, JNK, ERK, AMPK, and PFK, along with cell cycle regulators like cyclins A, D, E, and CDK. Additionally, numerous growth and transcription factors, including VEGF, FGF, TGFβ, EGFR, AHR, Nrf2, NF-KB, and p53, have been implicated in RES's pro-apoptotic effects. Similar pathways have been identified to contribute to the anti-cancer properties of curcumin (CUR) and epigallocatechin gallate (EGCG). Furthermore, exciting findings from several studies have shown that RES's antitumor activity in lung cancer involves the modulation of over 70 miRNAs associated with apoptosis, cell cycle regulation, and differentiation, with significant changes in their expression levels observed in RES-treated A549 cells.[13,15] CUR has demonstrated its anticancer potential in lung cancer through its ability to induce epigenetic alterations and modulate the expression of miRNAs. These mechanisms play a crucial role in the anticancer effects of curcumin, making it a promising therapeutic agent against LC.[13,14] As research on polyphenols in lung cancer (LC) progresses, it is becoming evident that apoptosis is a primary mechanism driving their antitumor effects. However, emerging evidence suggests the involvement of additional pathways that contribute to inhibiting tumour survival and progression. For example, resveratrol (RES) has been found to induce a significant reduction and imbalance in the pools of deoxyribonucleoside triphosphates (dNTPs), leading to the suppression of DNA synthesis. This inhibition of DNA synthesis hampers the progression through the S phase in A549 cells, which partially accounts for the cytotoxic effect of RES. These discoveries highlight the diverse and multifaceted mechanisms by which polyphenols exert their anticancer activities, emphasizing their potential as effective agents against lung cancer. Further studies in this field are essential to fully comprehend the therapeutic potential of these natural compounds.[13,16] Both in vivo and in vitro investigations have consistently demonstrated the potential of EGCG, a polyphenol abundant in green tea, to exert profound inhibitory effects on lung cancer cells (A549 and H1299). EGCG's actions include the inhibition of proliferation and migration, as well as the induction of apoptosis. These effects are, in part, achieved through the inhibition of the NF-κB signalling pathway, adding to EGCG's therapeutic promise.

Moreover, promising findings have emerged from studies combining EGCG with BAY11-7082, which revealed a synergistic effect, presenting a potential novel therapeutic strategy for lung cancer. The anti-proliferative activity of EGCG has been attributed to the suppression of key phosphorylation events in proteins like EGFR, ALK, ROS1, and their downstream counterparts Akt and ERK. In a xenograft tumour model, the observed growth inhibition was associated with reduced expression of HIF-1α and tumour angiogenesis, underscoring the influence of the tumour microenvironment on the tumour response to EGCG.

The accumulating evidence on EGCG's multifaceted actions provides valuable insights into its potential as a promising natural compound for lung cancer treatment, warranting further exploration and research to translate these findings into effective therapeutic interventions.[13,15,17]

Dieckol, a polyphenolic compound extracted from brown algae, has been attracting considerable attention due to its intriguing anticancer properties. A recent in vitro study conducted by Wang et al. revealed its significant impact, particularly in A549 cells. Dieckol displayed impressive efficacy by inhibiting the invasive and migratory properties of these cells and inducing apoptosis through the targeted inhibition of the PI3K/AKT/mTOR signalling pathway. Moreover, the study observed that dieckol effectively activates the E-cadherin tumour suppressor protein, further bolstering its anticancer potential. These compelling findings strongly suggest that dieckol may emerge as a potent and natural anticancer drug for the treatment of non-small cell lung cancer (NSCLC). However, further research and exploration of dieckol's mechanisms and overall efficacy are essential to fully validate its promise as a therapeutic option in the ongoing battle against NSCLC. Continued scientific investigation will pave the way for potential clinical applications and contribute to advancing treatment options for patients with NSCLC.[13,18]

C. Miguel Asensiet,al describe, As of 2008, lung cancer remains the most prevalent cause of cancer-related deaths globally, claiming the lives of approximately 1.5 million men and women each year (www.cancer.gov). The disease is primarily categorized into two types: small-cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). While NSCLC may, in certain cases, be treated with surgery, SCLC typically exhibits a more favourable response to chemotherapy and radiation therapy. The staging of NSCLC ranges from IA (indicating the best prognosis) to IV (indicating the worst prognosis), while SCLC is divided into limited stages, confined to one-half of the chest within a single radiotherapy field, and extensive stage when it spreads beyond these parameters. These staging distinctions play

a pivotal role in guiding treatment strategies and determining patient outcomes in managing lung cancer.

Non-small cell lung cancer (NSCLC) typically carries a poor prognosis. After undergoing complete surgical resection for stage IA disease, the 5-year survival rate stands at 67%. For stage IB disease, the 5-year survival rate drops to 57%, and for stage IV disease, the survival rate plunges to approximately 1%. In the case of small-cell lung cancer (SCLC), the overall 5-year survival rate for patients is only around 5%. For patients with extensive-stage disease, the average five-year survival rate drops to less than 1%. In contrast, for patients with limited-stage disease, the median survival time is 20 months, and the 5-year survival rate improves to 20%. These statistics underscore the challenging nature of both NSCLC and SCLC, with low overall survival rates, particularly in advanced stages of the disease. Improving treatment outcomes for lung cancer remains a critical area of research and focus in the medical community.[19,20] Initial studies investigating the oral administration of flavone-8-acetic acid have yielded disappointing results, as it did not effectively inhibit the growth of early-stage Lewis lung tumours growing in the lungs. Further research is necessary to explore alternative treatment approaches or combination therapies to address this challenge effectively.[19,21] The effects of flavone-8-acetic acid varied across different tumour types, showing interesting discrepancies. While no response was observed in ascitic and lung-growing human ovarian carcinomas, the compound exhibited notable growth inhibition in subcutaneous and liver-growing tumours. These distinct outcomes suggest the potential influence of tissue- and organ-specific factors on the response to flavone-8-acetic acid. As such, further research is warranted to gain a deeper understanding of its mechanism of action and explore its potential as a therapeutic option for specific tumour types. Such investigations hold promise for advancing our knowledge and optimizing the application of flavone-8-acetic acid in cancer treatment.[19,22] Emerging research indicates that orally administered green tea polyphenols may offer protective effects against chemical carcinogen-induced pulmonary neoplasia. Early reports highlight the potential of these compounds in mitigating the risk of lung cancer development induced by exposure to certain carcinogens. Further investigation is necessary to fully elucidate the extent and mechanisms of this protective effect, potentially paving the way for new preventive strategies against lung cancer.[19,23,24] Furthermore, in a spontaneous metastasis system, the oral administration of green tea infusion was found to reduce the number of lung colonies formed by mouse Lewis lung carcinoma cells. This suggests that green tea may hold promise in inhibiting the metastatic spread of lung cancer cells and could be a potential therapeutic option for preventing lung cancer progression and metastasis. However, more research is needed to fully understand the underlying mechanisms and optimize the use of green tea compounds as an adjunctive treatment for lung cancer patients.[19,25] Intriguingly, the administration of black tea polyphenols, starting 16 weeks after exposure to a single dose of a tobacco carcinogen [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone], displayed a noteworthy ability to impede the progression of lung adenoma to adenocarcinoma. This promising discovery suggests that black tea polyphenols might hold chemo preventive potential against the development and transformation of lung tumours triggered by tobacco carcinogens. Nevertheless, to harness the full therapeutic benefits and understand the underlying mechanisms behind this inhibition, further research is indispensable. Exploring the feasibility of incorporating black tea polyphenols into preventive strategies for lung cancer warrants in-depth investigation to potentially augment preventive and therapeutic approaches for this lethal disease.[19,26] While tea components have shown the ability to inhibit human lung cell growth and signal transduction pathways, it is important to note that the concentrations required to produce these effects were higher than what can typically be achieved in vivo tissues. These findings suggest that while tea compounds may have potential therapeutic benefits, their effectiveness as standalone treatments for lung cancer may be limited due to the challenges in attaining sufficiently high concentrations within the body. Therefore, further research is essential to explore innovative drug delivery strategies or combination therapies to maximize the anticancer potential of tea components for lung cancer patients.[19,27] In a mouse model with Lewis lung cancer, the combination of genistein and cyclophosphamide demonstrated an additive antiangiogenic effect, while there was no significant cytostatic effect observed. These findings suggest that the combination of these two compounds may have the potential to inhibit the growth of new blood vessels that support tumour growth, offering a promising approach for antiangiogenic therapy in lung cancer. However, further studies are required to elucidate the precise mechanisms and optimize the dosage and timing of this combination therapy to effectively target lung cancer progression.[19,28] In both in vitro and in vivo studies, the combination of docetaxel and flavopiridol has been reported to enhance the efficacy of radiation. This promising finding suggests that the synergistic effect of these two compounds may potentiate the effectiveness of radiation therapy in treating lung cancer. Further research is warranted to explore the underlying mechanisms and assess the feasibility of incorporating this combination therapy into clinical settings for improved outcomes in lung cancer patients.[19,29] Silibinin, when administered orally, exhibited the ability to inhibit lung tumour growth in athymic nude mice. Furthermore, it formed a novel chemo combination with doxorubicin, specifically targeting NF-κB-mediated inducible chemoresistance. This exciting discovery reinforces the notion of combining polyphenols with chemotherapy for synergistic therapeutic effects. Such combination approaches hold significant promise in improving treatment outcomes for lung cancer patients and merit further exploration to fully harness their

potential in clinical settings.[19,30] In murine models, the intravenous administration of liposomal QUER (quercetin) demonstrated significant efficacy in efficiently suppressing the growth of solid tumours, including Lewis lung carcinoma. This finding highlights the potential of liposomal QUER as a promising therapeutic agent for combating lung cancer and other solid tumours. Further research and clinical studies are essential to explore its safety, optimal dosage, and potential benefits in human cancer patients to advance its translation into effective anticancer treatments.[19,31] Oral administration of QUER (quercetin) was shown to effectively inhibit A549 lung carcinoma cell proliferation. This inhibitory effect was found to be associated with the activation of the ERK (extracellular signal-regulated kinase) signalling pathway. These encouraging results suggest that QUER holds potential as a therapeutic agent for targeting lung cancer cells and may warrant further investigation for its clinical application in lung cancer treatment. Understanding the underlying mechanisms of its action could pave the way for the development of novel and targeted therapies for lung carcinoma.[19,32] Quercetin-induced apoptosis was found to be specifically dependent on the activation of MEK1/2 (mitogen-activated protein kinase 1/2) and the downstream ERK (extracellular signal-regulated kinase) pathway. Inhibition of MEK1/2, but not PI3 kinase, p38 kinase, or JNK (c-Jun N-terminal kinase), abolished the apoptotic response triggered by quercetin. These findings strongly suggest that MEK-ERK activation plays a critical role in mediating the apoptotic effects of quercetin, highlighting the significance of this signalling pathway as a potential therapeutic target in lung cancer treatment. Further exploration of this mechanism may open new avenues for developing targeted therapies harnessing the apoptotic potential of quercetin against lung carcinoma.[19,33] Moreover, there have been reports of synergistic effects between tea polyphenols and atorvastatin in inhibiting chemically induced lung tumorigenesis in mice and suppressing the growth of lung cancer cells (H1299 and H460). These combined treatments appeared to enhance apoptosis, providing a potential avenue for their application in lung cancer therapy. These promising findings underscore the significance of exploring the therapeutic potential of tea polyphenols and atorvastatin as a synergistic combination for lung cancer treatment, warranting further investigation and potential translation into clinical applications.[19,34] Numerous epidemiological studies have revealed an intriguing inverse association between flavonoids, such as epicatechin, catechin, quercetin (QUER), and kaempferol, and lung cancer specifically among tobacco smokers. However, this inverse relationship was not evident among nonsmokers. These findings highlight the potential protective effects of flavonoids against lung cancer, especially in the context of tobacco smoke exposure. Nevertheless, further research is essential to understand the underlying mechanisms and to ascertain whether flavonoid consumption could serve as a preventive strategy for lung cancer in high-risk populations.[19,35] Recent preclinical studies in mice with pulmonary fibrosis have unveiled promising results for naringenin's potential in reducing lung metastases and improving overall survival. This positive outcome can be linked to naringenin's ability to alter the immunosuppressive microenvironment by down-regulating TGF-β (transforming growth factor-beta) and decreasing the number of regulatory T cells. These compelling findings provide a strong rationale for further research and exploration to validate the effectiveness and safety of naringenin as a potential therapeutic option for lung cancer treatment in human subjects. The continued investigation of naringenin's anticancer properties could pave the way for innovative and improved treatment strategies in the fight against lung cancer.[19,36] An intriguing recent report has highlighted the potential synergy between epicatechin and curcumin (CURC) in enhancing growth inhibition and inducing apoptosis in human lung cancer cells. This compelling finding suggests that the combination of these two compounds may hold promise as a novel and potent therapeutic strategy for lung cancer treatment. Further investigations are necessary to fully comprehend the underlying mechanisms of this synergy and to explore the translational potential of this combination therapy in preclinical and clinical settings. The research on epicatechin and curcumin presents exciting possibilities for developing effective and targeted therapies for lung cancer patients. Additionally, a noteworthy report indicates that the combination of epigallocatechin gallate (EGCG) and luteolin has been shown to exhibit enhanced anti-tumor activity, possibly through a p53-dependent mechanism. This intriguing finding adds to the growing body of evidence supporting the potential benefits of combining natural compounds to develop more effective therapeutic approaches for lung cancer and other malignancies. Further investigations are needed to elucidate the precise molecular pathways involved and to determine the optimal dosage and treatment regimens for this combination therapy. The study of EGCG and luteolin combination therapy presents an exciting avenue for advancing lung cancer treatment strategies and warrants further exploration in preclinical and clinical studies.[19,37]

Effect of polyphenol nanoparticle in lung cancer

The anticancer activity of polyphenol nanoformulations is achieved through a number of cellular mechanisms, including induction of cell cycle arrest at various stages of the cancer cell cycle, activation of caspase enzymes, reduction of tumour vascularization, reduction of tumour cell invasion and metastasis, induction of mitochondrial damage, and induction of apoptosis in the neoplasm. One of the primary functions of nanoformulated polyphenols in cancer cells is to induce apoptosis, a crucial sign for anticancer therapy. Many natural substances work to prevent cancer by causing apoptosis, or the planned cell death that rids the body of cancerous cells. Bcl-2 and Bax are two members of the Bcl-2 family of proteins that control apoptosis and have opposing effects on the

process. Bax encourages apoptosis whereas Bcl-2 inhibits it.

The induction of apoptosis in cancer cells is thought to be one of these medications' primary mechanisms, and the rise of the Bax/Bcl-2 ratio has a significant impact on this process.

Since ancient times, natural cures have been widely used as complementary and alternative treatments to treat a variety of cancers and promote healthy bodily function. Conventional medications only partially combat cancer when administered in the dosage forms that are now on the market. As a result, it is predicted that there will be restrictions in the treatment of cancers. In order to create focused, safe drug delivery medications with increased therapeutic action, it is necessary to investigate novel drug delivery techniques. The most significant enhancement of nanoformulated polyphenols over their free molecules is their enhanced bioavailability and increased anti-neoplastic action, which can enhance passive targeting of cancer cells.

In the meanwhile, this scenario avoids the pharmacokinetic issues with standard formulations by using lower dosages of medication to achieve the best result. Numerous studies have suggested that phytochemicals, especially polyphenols, have anticancer capabilities that can be used intelligently, i.e., demonstrating cytotoxicity only against neoplasms, not against normal cells, in contrast to traditional anticancer drugs, which have not been shown to exhibit this intelligence.

Polyphenol nanoparticles in lung cancer is an area of active research, and there might have been further developments beyond that date.

Polyphenol nanoparticles are nanoparticles composed of polyphenols or loaded with polyphenols. They hold promise in cancer research due to their potential to enhance the delivery and targeting of therapeutic agents to cancer cells while minimizing damage to healthy cells. Polyphenol nanoparticles can be utilized as carriers to deliver anti-cancer drugs directly to lung cancer cells. By encapsulating therapeutic agents within nanoparticles, the drugs can be protected from degradation, have prolonged circulation time, and achieve targeted delivery to tumor sites, improving their effectiveness and reducing side effects. Polyphenols themselves have shown anticancer properties, including inhibiting tumor growth, inducing apoptosis (programmed cell death) in cancer cells, and suppressing cancer cell proliferation. When these properties are combined with the advantages of nanoparticles for targeted delivery, it may lead to more potent and efficient lung cancer treatment. Polyphenol nanoparticles can also be employed as imaging agents to detect lung tumors. By loading nanoparticles with contrast agents or other imaging molecules, researchers can improve the visualization and early detection of lung cancer. Using polyphenol nanoparticles may help reduce the toxicity associated with certain chemotherapy drugs. By delivering drugs directly to the tumor site, the exposure of healthy tissues to toxic agents is minimized, leading to fewer adverse effects. Polyphenol nanoparticles can potentially be used in combination with other therapeutic modalities, such as radiation therapy or immunotherapy, to enhance their effectiveness and achieve synergistic effects against the lung. Clinical application of polyphenol nanoparticles in lung cancer treatment is still in its early stages. Further studies, including preclinical and clinical trials, are needed to fully understand their safety, efficacy, and potential role in lung.

Majumdar D et al reported that luteolin nanoparticles have anticancer activity in lung cell line H292 (38). Qiu N et al. researched that nanoformulation of honokiol caused an anticancer effect in the mouse Lewis lung cancer LL/2 cell lines by induction of cell cycle arrest at the G0/G1 phase (39). SabyaSachi Das et al reported that flavonoids have therapeutic potentiality in lung cancer.

Role of protein kinase signaling in carcinogenesis

Protein kinases play a critical role in cell signaling pathways, including those involved in carcinogenesis, which is the process of cancer development. Carcinogenesis is a complex and multifaceted process that involves the transformation of normal cells into cancer cells. Protein kinases are enzymes that regulate various cellular processes by transferring phosphate groups from ATP to specific target proteins, thereby modulating their activity. Dysregulation of protein kinase signalling pathways can contribute to the initiation, promotion, and progression of cancer. Here's an overview of how protein kinase signalling is involved in carcinogenesis:

1. **Cell Growth and Proliferation:** Many protein kinases are involved in controlling cell growth and division. Dysregulation of these kinases can lead to uncontrolled cell proliferation, a hallmark of cancer. For instance, the Ras-Raf-MAPK pathway is a key signalling pathway that regulates cell proliferation and survival. Mutations or overexpression of kinases in this pathway can lead to continuous activation, contributing to cancer development.
2. **Apoptosis Resistance:** Apoptosis is programmed cell death that helps remove damaged or abnormal cells. Protein kinases are involved in regulating the balance between cell survival and apoptosis. Dysfunctional kinase signalling can lead to reduced apoptosis, allowing damaged cells to survive and accumulate genetic mutations that contribute to cancer.
3. **Angiogenesis:** Angiogenesis is the process by which new blood vessels are formed to supply nutrients and oxygen to growing tumors. Protein kinases such as vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) play a role in promoting

angiogenesis, which supports tumor growth and metastasis.

4. **Metastasis:** Metastasis is the spread of cancer cells from the primary tumor to other parts of the body. Protein kinases are involved in regulating the migration and invasion of cancer cells. For instance, kinases like focal adhesion kinase (FAK) and Src kinase are implicated in promoting cancer cell motility and invasiveness.
5. **Cell Signalling Crosstalk:** Protein kinase pathways often interact and cross-regulate each other, forming complex networks. Dysregulation of one pathway can lead to unintended effects on other pathways, contributing to cancer development. These interconnected pathways can amplify oncogenic signals.
6. **Cell Cycle Control:** Protein kinases regulate the cell cycle, ensuring proper progression from one phase to another. Cyclin-dependent kinases (CDKs) are key players in this process. Dysregulation of CDKs can result in abnormal cell cycle progression and genomic instability, which are factors in cancer development.
7. **DNA Damage Response:** Protein kinases are involved in the DNA damage response, which helps maintain genomic stability by repairing DNA damage. Dysfunctional DNA repair due to kinase abnormalities can lead to the accumulation of mutations that contribute to cancer initiation.
8. **Inflammation and Immune Response:** Inflammation is associated with cancer development. Protein kinases play a role in mediating inflammatory responses and immune evasion by cancer cells. Kinases like IKK and JAK-STAT are involved in these processes.
9. **Targeted Therapies:** The dysregulated protein kinase signalling pathways in cancer cells have led to the development of targeted therapies. These therapies aim to specifically inhibit the activity of mutated or overactive kinases, thereby disrupting cancer cell survival and proliferation.

In summary, protein kinases play a crucial role in various aspects of carcinogenesis, from cell proliferation and survival to invasion, angiogenesis, and metastasis. Dysregulation of protein kinase signaling pathways can lead to the development and progression of cancer.

Understanding these pathways is essential for developing targeted therapies and interventions to manage and treat cancer effectively.

Chemistry of Polyphenol

Polyphenol structure-activity relationships (SAR) with respect to their anticancer activities

Polyphenols are a class of naturally occurring compounds found in various plants and foods, known for their potential health benefits, including antioxidant and anticancer properties. The structure-activity relationships (SAR) of polyphenols refer to the relationship between the chemical structure of these compounds and their biological activities, such as their anticancer effects and their ability to target specific kinases, which are enzymes that play crucial roles in cell signalling and regulation.[40]

The SAR of polyphenols in terms of their anticancer activities and kinase targeting can be quite complex due to the diversity of polyphenolic compounds and the intricate mechanisms underlying their effects. It involves understanding how different structural elements of these compounds influence their biological effects. Polyphenols have been studied extensively for their potential to inhibit various kinases, which are enzymes that play crucial roles in cell signalling and regulation. Here, I'll provide an overview of the SAR of polyphenols with respect to their anticancer activities and kinase targeting.

Structural Elements and Anticancer Activities

Hydroxyl Groups: Polyphenols contain multiple hydroxyl (-OH) groups, which contribute to their antioxidant and anticancer properties. The number and position of hydroxyl groups on the polyphenol molecule influence its bioactivity. More hydroxyl groups generally enhance the compound's antioxidant and anticancer potential.

Aromatic Rings: The presence of aromatic rings in polyphenols contributes to their stability and ability to scavenge free radicals, which are involved in cancer development. A higher number of aromatic rings can enhance the anticancer activity.

Conjugation: Polyphenols often possess conjugated double bonds, which stabilize the molecule and influence its electronic properties. Enhanced conjugation generally improves the anticancer potential by increasing the ability to interact with cellular components.

Functional Groups: Various functional groups, such as methoxy (-OCH3) and glycoside (-O-Glc), can be present in polyphenols. These groups can affect solubility, stability, and interactions with cellular components, impacting the compound's anticancer activity.

Kinase Targeting and Mechanisms

Protein Kinases: Polyphenols can modulate the activity of protein kinases, enzymes that regulate cell signalling pathways involved in cancer progression. For example, polyphenols like resveratrol and quercetin have been shown to inhibit kinases such as PI3K, Akt, and MAPK, which are implicated in cancer cell survival and proliferation.

Tyrosine Kinases: Certain polyphenols target tyrosine kinases, such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR), which are associated with angiogenesis and tumor growth.[41]

Kinase Inhibition: Polyphenols can inhibit kinase activity by competing with ATP binding, interfering with kinase activation loops, or modulating downstream signalling pathways. This disruption can lead to inhibited cancer cell growth and apoptosis (programmed cell death) Fig1.

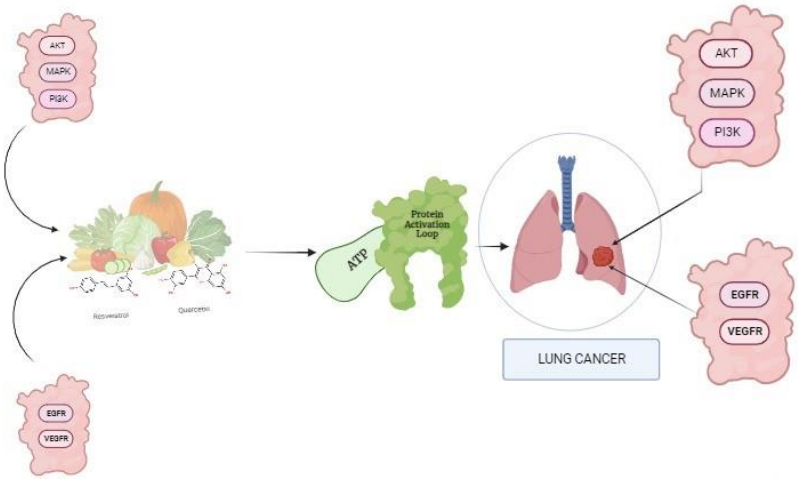

Figure 1: Kinase Targeting & Inhibition.

Structure-Kinase Relationship

Binding Sites: The three-dimensional structure of polyphenols and kinases determines the binding interactions. Complementary shapes and electrostatic properties enable polyphenols to bind to kinase active sites or allosteric sites.

Key Residues: Specific amino acid residues within the kinase active site are critical for polyphenol binding. Polyphenols form hydrogen bonds, hydrophobic interactions, and π-π stacking with these residues, influencing kinase inhibition.[42]

CONCLUSION

The structure-activity relationships of polyphenols in terms of anticancer activities and kinase targeting involve intricate interactions between the chemical structure of polyphenols and the molecular properties of kinases. Understanding these relationships helps in designing and developing novel polyphenol-based compounds with enhanced anticancer potential and kinase inhibition.

REFERENCES

1. Oana Zanoaga, Cornelia Braicu, AncutaJurj, AlexandruRusu, RaresBuiga and IoanaBerindan-Neagoe. Progress in Research on the Role of Flavonoids in Lung Cancer. international journal of medical science, 2019; 20: 4291.
2. Allemani, C.;Weir, H.K.; Carreira, H.; Harewood, R.; Spika, D.;Wang, X.S.; Bannon, F.; Ahn, J.V.; Johnson, C.J.; Bonaventure, A.; et al. Global surveillance of cancer survival Analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (concord-2). Lancet, 2015, 1995–2009: 385: 977–1010.
3. Chae, D.K.; Ban, E.; Yoo, Y.S.; Kim, E.E.; Baik, J.H.; Song, E.J. Mir-27a regulates the tgf-beta signaling pathway by targeting smad2 and smad4 in lung cancer. Mol. Carcinog. 2017; 56: 1992–1998.
4. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin, 2018; 68: 394–424.
5. Altorki, N.K.; Markowitz, G.J.; Gao, D.; Port, J.L.; Saxena, A.; Stiles, B.; McGraw, T.; Mittal, V. The lung microenvironment: An important regulator of tumour growth and metastasis. Nat. Rev. Cancer 2019; 19: 9–31.
6. Vauzour, D.; Rodriguez-Mateos, A.; Corona, G.; Oruna-Concha, M.J.; Spencer, J.P. Polyphenols and human health: Prevention of disease and mechanisms of action. Nutrients, 2010; 2: 1106–1131.
7. Budisan, L.; Gulei, D.; Zanoaga, O.M.; Irimie, A.I.; Sergiu, C.; Braicu, C.; Gherman, C.D.; Berindan-Neagoe, I.Dietary intervention by phytochemicals and their role in modulating coding and non-coding genes in cancer. Int. J. Mol. Sci., 2017; 18: 1178.
8. Ng, C.Y.; Yen, H.; Hsiao, H.Y.; Su, S.C. Phytochemicals in skin cancer prevention and treatment: An updated review. Int. J. Mol. Sci., 2018; 19: 941.
9. CojocneanuPetric, R.; Braicu, C.; Raduly, L.; Zanoaga, O.; Dragos, N.; Monroig, P.; Dumitrascu, D.; Berindan-Neagoe, I. Phytochemicals modulate carcinogenic signaling pathways in breast and hormone-related cancers. Oncotargets Ther, 2015; 8: 2053–2066.
10. Braicu, C.; Pilecki, V.; Balacescu, O.; Irimie, A.; Neagoe, I.B. The relationships between biological

activities and structure of flavan-3-ols. Int. J. Mol. Sci., 2011; 12: 9342–9353.
11. Budisan, L.; Gulei, D.; Jurj, A.; Braicu, C.; Zanoaga, O.; Cojocneanu, R.; Pop, L.; Raduly, L.; Barbat, A.; Moldovan, A.; et al. Inhibitory e_ect of cape and kaempferol in colon cancer cell lines-possible implications in new therapeutic strategies. Int. J. Mol. Sci., 2019; 20: 1199.
12. Qingyu Zhou 1, Hua Pan and Jing Li, Molecular Insights into Potential Contributions of Natural Polyphenols to Lung Cancer Treatment, Cancers, 2019; 11: 1565: 05.
13. Giusibriguglio, chiara costa, manuelapollicino, federicagiambo, stefaniacatania and concettinafenga. Polyphenols in cancer prevention: New insights (Review). international journal of functional nutrition, 2020; 1: 9: 06.
14. Wan MohdTajuddin WNB, Lajis NH, Abas F, Othman I and Naidu R: Mechanistic understanding of curcumin's therapeutic effects in lung cancer Nutrients, 2019, 11: 2989.
15. Zhou Q, Pan H and Li J: Molecular insights into potential contributions of natural polyphenols to lung cancer treatment. Cancers (Basel), 2019; 11: 1565.
16. Amararathna M, Hoskin DW and Rupasinghe HPV: Anthocyanin-rich haskap (LoniceraCaerulea L.) berry extracts reduce nitrosamine-induced DNA damage in human normal lung epithelial cells in vitro. Food ChemToxicol, 2020; 141: 111404.
17. Zhang L, Xie J, Gan R, Wu Z, Luo H, Chen X, Lu Y, Wu L and Zheng D: Synergistic Inhibition of Lung Cancer Cells by EGCG and NF-κB Inhibitor BAY11-7082. J Cancer, 2019; 10: 6543-6556.
18. Wang CH, Li XF, Jin LF, Zhao Y, Zhu GJ and Shen WZ: Dieckol inhibits non-small-cell lung cancer cell proliferation and migration by regulating the PI3K/AKT signaling pathway. J BiochemMolToxicol, 2019; 33: e22346.
19. Miguel Asensi, Angel Ortega, Salvador Mena, Fatima Feddi, and José M. Estrela, Natural polyphenols in cancer therapy. Critical Reviews in Clinical Laboratory Sciences, 2011; 48(5-6): 208-209.
20. Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med, 2008; 359: 1367–1380.
21. Finlay GJ, Smith GP, Fray LM, Baguley BC. Effect of flavone acetic acid on Lewis lung carcinoma: Evidence for an indirect effect. J Natl Cancer Inst, 1988; 80: 241–245.
22. Pratesi G, Manzotti C, Tortoreto M, Audisio RA, Zunino F. Differential efficacy of flavone acetic against liver versus lung metastases in a human tumour xenograft. Br J Cancer, 1991; 63: 71–74.
23. Katiyar SK, Agarwal R, Mukhtar H. Protective effects of green tea polyphenols administered by oral intubation against chemical carcinogen-induced forestomach and pulmonary neoplasia in A/J mice. Cancer Lett, 1993; 73: 167–172.
24. Komori A, Yatsunami J, Okabe S, Abe S, Hara K, Suganuma M, Kim SJ, Fujiki H. Anticarcinogenic activity of green tea polyphenols. Jpn J ClinOncol, 1993; 23: 186–190.
25. Sazuka M, Murakami S, Isemura M, Satoh K, Nukiwa T. Inhibitory effects of green tea infusion on in vitro invasion and in vivo metastasis of mouse lung carcinoma cells. Cancer Lett, 1995; 98: 27–31.
26. Yang G, Wang ZY, Kim S, Liao J, Seril DN, Chen X, Smith TJ, Yang CS. Characterization of early pulmonary hyperproliferation and tumor progression and their inhibition by black tea in a 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis model with A/J mice. Cancer Res, 1997; 57: 1889–1894.
27. Yang CS, Yang GY, Landau JM, Kim S, Liao J. Tea and tea polyphenols inhibit cell hyperproliferation, lung tumorigenesis, and tumor progression. Exp Lung Res, 1998; 24: 629–639.
28. Wietrzyk J, Boratynski J, Grynkiewicz G, Ryczynski A, Radzikowski C, Opolski A. Antiangiogenic and antitumour effects in vivo of genistein applied alone or combined with cyclophosphamide. Anticancer Res, 2001; 21: 3893–3896.
29. Kim JC, Saha D, Cao Q, Choy H. Enhancement of radiation effects by combined docetaxel and flavopiridol treatment in lung cancer cells. RadiotherOncol, 2004; 71: 213–221.
30. Singh RP, Mallikarjuna GU, Sharma G, Dhanalakshmi S, Tyagi AK, Chan DC, Agarwal C, Agarwal R. Oral silibinin inhibits lung tumor growth in athymic nude mice and forms a novel chemocombination with doxorubicin targeting nuclear factor kappaB-mediated inducible chemoresistance. Clin Cancer Res, 2004; 10: 8641–8647.
31. Yuan ZP, Chen LJ, Fan LY, Tang MH, Yang GL, Yang HS, Du XB, et al. Liposomal quercetin efficiently suppresses growth of solid tumors in murine models. Clin Cancer Res, 2006; 12: 3193–3199.
32. Hung H. Dietary quercetin inhibits proliferation of lung carcinoma cells. Forum Nutr, 2007; 60: 146–157.
33. Lu G, Xiao H, You H, Lin Y, Jin H, Snagaski B, Yang CS. Synergistic inhibition of lung tumorigenesis by a combination of green tea polyphenols and atorvastatin. Clin Cancer Res, 2008; 14: 4981–4988.
34. Cui Y, Morgenstern H, Greenland S, Tashkin DP, Mao JT, Cai L, Cozen W, et al. Dietary flavonoid intake and lung cancer–a population-based case-control study. Cancer, 2008; 112: 2241–2248.
35. Du G, Jin L, Han X, Song Z, Zhang H, Liang W. Naringenin: A potential immunomodulator for inhibiting lung fibrosis and metastasis. Cancer Res, 2009; 69: 3205–3212.
36. Saha A, Kuzuhara T, Echigo N, Suganuma M, Fujiki H. New role of (-)-epicatechin in enhancing the

induction of growth inhibitionand apoptosis in human lung cancer cells by curcumin. Cancer Prev Res (Phila), 2010; 3: 953–962.
37. Amin AR, Wang D, Zhang H, Peng S, Shin HJ, Brandes JC, Tighiouart M, et al. Enhanced anti-tumor activity by the combination of the natural compounds (-)-epigallocatechin-3-gallate and luteolin: Potential role of p53. J BiolChem, 2010; 285: 34557–34565.
38. Liu A, Wang W, Fang H, et al. Baicalein protects against polymicrobial sepsis-induced liver injury via inhibition of inflammation and apoptosis in mice. Eur J Pharmacol, 2015; 748: 45–53.
39. Qiu N, Cai LL, Xie D, et al. Synthesis, structural and in vitro studies of well-dispersed monomethoxy-poly(ethylene glycol)-honokiol conjugate micelles. Biomed Mater, 2010; 5(6): 065006.
40. Forni C, Facchiano F, Bartoli M, Pieretti S, Facchiano A, D'Arcangelo D, Norelli S, Valle G, Nisini R, Beninati S, Tabolacci C. Beneficial role of phytochemicals on oxidative stress and age-related diseases. Biomed Res Int., 2019; 2019: 8748253.
41. Piwowarczyk L, Stawny M, Mlynarczyk DT, Muszalska-Kolos I, Goslinski T, Jelińska A. Role of curcumin and (−)-epigallocatechin-3-O-gallate in bladder cancer treatment: a review. Cancer, 2020; 12(7): 1801.
42. Williams SA, Anderson WC, Santaguida MT, Dylla SJ. Patient-derived xenografts, the cancer stem cell paradigm, and cancer pathobiology in the 21st century. Lab Invest, 2013; 93(9): 970–82.