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Review Article

Roadmap for Lung Cancer Treatment: Role of Natural and Synthetic Inhibitors

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Abstract

Globally cancer is the second leading reason for death. Of note, lung cancer is one of the most commonly seen cancer in different parts of the world. Despite significant advancements in the treatment and management plans, the number of mortality cases every year continue to increase. This therefore raises the need to look into novel strategies and compounds that can specifically target the key players involved in lung carcinogenesis. In the present review, we discuss the role of some of the promising naturally occurring as well as chemically synthesized compounds, namely, α-mangostin, curcumin, resveratrol and quinazolinones derivatives, in lung cancer.

Keywords: *Lung Cancer; α-Mangostin; Curcumin; Resveratrol; Quinazolinones*

Introduction

Lung cancer is a highly prevalent cancer worldwide including, India. Owing to the absence of defined clinical symptoms, lung cancers are usually diagnosed at later stages. According to the American cancer society, ~ 24.7% deaths were due to lung cancer in both men and women in United States [1], while in India and Europe deaths due to lung cancer approximated 18.1% and 20% respectively. Incidence rate and mortality patterns for lung cancer are chiefly associated with smoking history, tobacco consumption as well as the integrity of DNA repair mechanisms [2]. The various types of lung cancer are classified based on their histotypes [3]. Non-small-cell lung cancer (NSCLC) which is a major type (85% of lung cancer cases) includes histotypes of adenocarcinoma, squamous cell carcinoma, large cell carcinoma, while small cell lung cancer accounts for 15% [4]. Besides, surgical resection (a consistent and classical approach), strategies to cure lung cancer includes chemotherapy, radiotherapy, use of tumour-targeted drug conjugate etc. Despite recent developments in diagnostics and treatment strategies, the survival rate for lung cancer has not improved over the decade. This can be attributed to the late stage diagnosis, resistance towards chemotherapy and its adverse effects, local recurrences and distant metastasis. Thus, there is a need for reconsideration of treatment strategies which may incorporate the use of natural as well as synthetic compound in conjunction with the existing chemo- or radio-therapy (combinational/adjuvant therapy) [5].

Chemotherapy thus far has shown some promising results in metastatic disease but have also met with disease recurrence at a later stage. Platinum based therapy doublets are currently been appreciated, they are consisted of a combination of natural/synthetic compounds along with platinum based-compounds such as Paclitaxel, Docetaxel, Gemcitabine and Vinorelbine [6]. Besides, several other novel approaches based on protein target, immune-checkpoint-inhibitors, tumour-targeted drug conjugates such as antibody-drug conjugates, radio-immuno conjugates, small-molecule drug conjugates are also been recently considered [7]. Various naturally occurring

(polyphenolic/flavonoid) and synthetic derivatives are now being extensively employed either alone or as part of combinational/adjuvant therapy [8,9]. Towards this end, in this review we are highlighting both the role as well as the benefits of some of the naturally occurring plant derivatives (α-mangostin, curcumin and resveratrol) along with a promising synthetic anti-cancer class of compounds (quinazolinones derivatives).

Naturally occurring plant derivatives

Curcumin

Curcumin is a polyphenolic compound bearing molecular formula $C_{21}H_{20}O_6$ and a molecular weight of 368.38 Da [10]. It is an active ingredient of turmeric [11,12] which is obtained from the rhizomes of *Curcuma longa* Linn [13]. Turmeric as well its active ingredient, curcumin has been reported to possess anti-oxidant [14-18], anti-inflammatory [19-26], anti-viral [27-33], anti-fungal [34-41]. There are plethora of evidences reporting both turmeric and curcumin to prevent chemical-induced tumorigenesis [11,42]. Besides, the anti-initiating as well as anti-promoting effects of turmeric/curcumin has been well established [11,12,42].

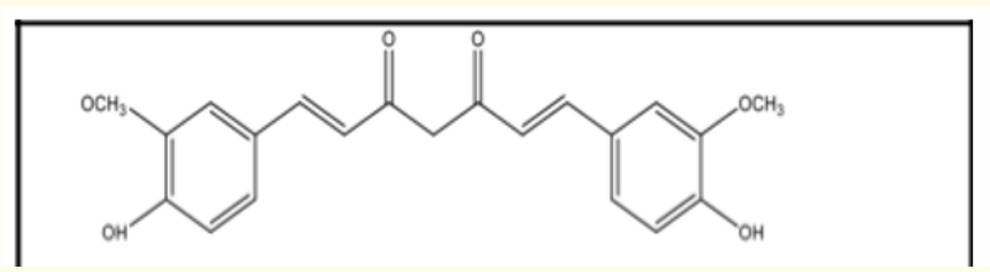

Figure 1: *1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6 heptadiene-3,5-dione (Curcumin).*

Curcumin has been shown to reduce the carcinogen-induced DNA adduct formation in lung, liver and skin tissues of mice [12]. In the table 1, we have summarized the effects of curcumin on lung cancer.

Cell line	Cellular	Mechanism	References
A549	Proliferation, apoptosis	Regulation of Bcl-2/Bax, mitochondrial apoptotic pathway	[43]
SCLCNCI-H446, NCI-1688	Proliferation, migration, invasion	Inhibits phosphorylation of STAT3, downregulation of cyclin B1 and cyclin D1	[44]
A549	Invasion, metastasis	Intervention of PKCα/Nox2/ROS/ATF-2 pathway	[45]
95D (highly metastatic lung cancer cell line)	metastasis	Inhibition of miR-34a-5p/miR-34c-5p/miR-302b-3p-LEF1-CCND1/WNT1/MYC axis	[46]
A549 and H2170	Cancer stem cells	Inhibition of CD166+/EpCAM+ subpopulation of cells	[47]
A549	Proliferation, apoptosis, invasion and migration	Curcumin co-treatment with carboplatin and cisplatin downregulated MMP-9 and BCL-2 while it increased caspase-3 and caspase-9 expression. Suppressed NF-kB, Akt/IKK a signalling	[48]
A549	Migration, invasion	Inhibition of adiponectin receptor-1 via NF-κB/MMP pathway	[49]
A549	Invasion, metastasis	Inhibit the expressions of GLUT1, MT1-MMP and MMP2	[50]

NCI-H292 LSCC	Proliferation	STAT3 inhibition, increased FOXA2 expression	[51]
Beas-2B cell, A549	Cell survival	Induction of UBE1L expression, EGFR downregulation and its downstream signalling events	[52]
CL1-5, H1975 and A549	Tumor growth and apoptosis	Decreased expression of EGFR, c-MET, cyclin D1. Induction of apoptosis, increased expression of caspase-8, caspase-9 and PARP	[53]
H1299 and A549	Cancer stem cells	Acts on Wnt/ß-catenin and hedgehog pathway. Decreased expression of lung cancer stem cell markers and CD133 positive cells.	[54]
NCI-H446 and NCI-1688	Cell proliferation, cell cycle, migration, invasion and angiogenesis	Inhibition of STAT3 phosphorylation	[44]
PC-14, H1299	Apoptosis	Inhibition of COX-2, EGFR and p-ERK1/2	[55]
A549, PC-9	EMT and angiogenesis	Inhibition of HGF-activated migration	[56]
A549, H1299	Apoptosis	Regulation of IP3R phosphorylation, calcium accumulation, apoptosis by mitochondrial pathway	[57]

Table 1: *Anti-carcinogenic effects of curcumin in lung cancer.*

Notably, curcumin has also been reported to cross blood-brain barrier due to its lipophilicity [10]. It undergoes a keto-enol tautomerism, of which the enol form is chiefly responsible for the anti-oxidant nature [10]. However, major issues with the drug ability of curcumin has been related to its low bioavailability [13]. This has been attributed to the high rate of first pass metabolism *via* glucuronidation and sulfation, thereby hampering its therapeutic efficacy [13]. Though efforts have been directed towards this end via the development of nano-curcumins, there are still various problems associated with delivery and absorption. Studies are ongoing towards the betterment of nano-formulations and their delivery in order to enhance the usage of curcumin in most efficacious manner [10].

α-mangostin

α-mangostin (1,3,6-trihydroxy -7 -methoxy-2,8-bis(3-methyl-but-2-en -1-yl)-9H-xanthene -9-one) is a xanthone derivative isolated from the pericarp of Mangosteen fruit (*Garcinia mangostana* Linn.) [58]. α-mangostin has been reported to show various physiological effects including anti-inflammatory, antifungal and antidiabetic [59]. Notably, several studies have also highlighted the anticancer effect of alpha mangostin in breast cancer, head and neck cancer, leukaemia, lung cancer.

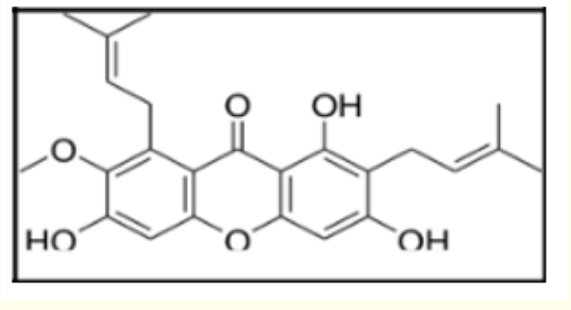

Figure 2: *Chemical structure of α-mangostin.*

α-mangostin has been shown to inhibit the invasive and migratory potential of lung cancer cells [60]. It has been shown to suppress phorbol 12- myristate 13 -acetate induced MMP-2/MMP-9, αvβ3 integrin and FAK/ERK/NF-κB signalling pathway in human lung adenocarcinoma cells [60]. Kieu., *et al.* demonstrated thatα-mangostin exerts anti-metastatic activity by the reduction of actin cytoskeleton in lung cancer cells. α -mangostin has been shown to induce apoptosis and ROS-mediated cytotoxicity in NSCLC (non-small cells lung cancer) cells [61]. The table 2 lists the effects of α-mangostin on lung cancer.

Sr. No.	Cell lines	Cellular effect	Mechanism	Reference
1.	A549	Migration and invasion	Antimetastatic activity	[62]
2.	A549, WI-38	Metastasis and cell adhesion	Downregulated MMP-2 and MMP-9 expression via αvβ3 integrin	[60]
3.	A549, WI-38 and hPBMC	Cell survival	ROS mediated cytotoxicity	[61]

Table 2: *Anticancer effect of α-mangostin.*

Resveratrol

Resveratrol (3,5,4'- trihydroxy-stilbene) is a natural polyphenolic phytoalexin isolated from grapes, peanuts, mulberries, and legumes [63]. It is also known to be produced due to stress, injury, fungal infection, or UV exposure. Resveratrol has been reported to induce anti-oxidant and anti-inflammatory effects in different cancer cells such as breast, cervical, uterine, blood, kidney, liver, colon, head and neck, and lung cancer.

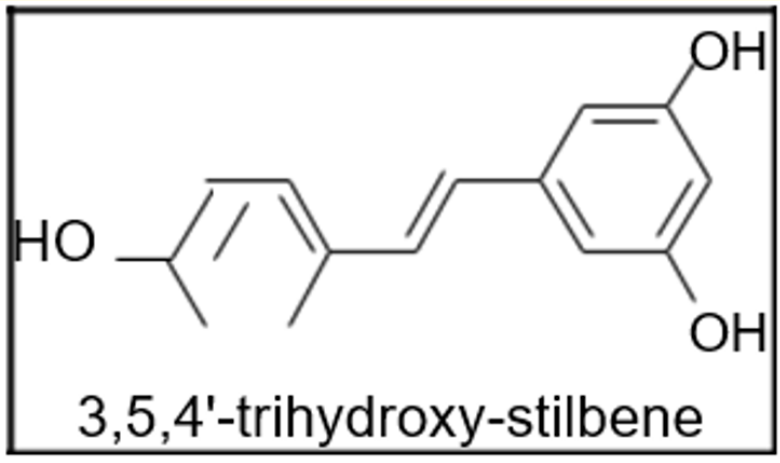

Figure 3: *Chemical structure of resveratrol.*

Resveratrol has been reported to decrease cell viability and proliferation of lung cancer cells while it induced apoptosis [63]. This was associated with an increased hydrogen peroxide production and activation of Bid, PARP and caspase 8. Resveratrol was found to cause significant downregulation of pEGFR, pAkt, c-FLIP and NF-kB protein expression [63,64]. It has also been shown to induce autophagy by increasing beclin - 1, LC3 II/I and SIRT1 expression and decreasing p62 expression and activating p38/MAPK and inhibiting Akt/mTOR signalling in NSCLC [65]. Bae., *et al.* showed that resveratrol treatment induced apoptosis via Bak mediated AIF-dependent mitochondrial apoptotic signalling pathway in ASTC-a-1 and A549 lung cancer cells [66] and alters miRNA expression in NSCLC cells [67]. Resveratrol

showed synergistic cytotoxic effect in combination with pemetrexed in NSCLC cells by downregulating MKK3/6-p38 MAPK -ERCC1 signalling [68]. Treatment with resveratrol supressed lung cancer cell adhesion, metastasis, invasion and inhibited TGF-β1-induced epithelial to mesenchymal transition [69,70]. It has also been shown to induce GADD45a [70], inhibit XRCC1 expression and enhance etoposide - induce cell death in lung cancer cells [71]. It inhibited invasiveness in lung cancer cells via decreasing MMP-2 and MMP- 9 expression through HO-1 mediated NF-kB pathway [72]. In another study, resveratrol was shown to induce premature senescence with increase in DNA double strand breaks (DSBs) and reactive oxygen species (ROS) production in lung cancer cells [73]. The treatment of resveratrol in co-cultured A549 and mesenchymal stem cells resulted in suppression of the release of IL-6 and VEGF [74]. Furthermore, resveratrol treatment arrested the cells in the G0/G1 phase via p53 independent pathway, this was accompanied by the downregulation of cyclin D1, CDK4 and CDK6 expression whilst there was upregulation of CDK inhibitors, p21 and p27 [75]. Resveratrol has been reported to enhance ionizing radiation induced cell killing in NSCLS through apoptosis independent mechanism [76]. Table 3 below lists the effects of resveratrol on lung cancer.

Synthetic derivatives

In the last decade, significant advancements in the therapeutics of lung cancer has been seen, majorly, where the drugs having been synthesized to act on the specific target or pathway. This had been possible as a result of the molecular studies that have dissected the underlying mechanism and/or identified the specific target dysregulated in cancer. This has ultimately led to the development of efficient and targeted chemotherapy. Table 4 below lists the drugs that are currently recognised as therapeutics for lung cancer, with their current advancements with respect to the clinical [78,79].

Targets	Drugs	Clinical trial (phase)
Epidermal growth factor receptor (EGFR)	Gefitinib	Approved
	Erlotinib	Approved
	Afatinib	Approved
	Osimertinib	Approved
	Necitumumab	Approved
Anaplastic lymphoma receptor tyrosine kinase (ALK)	Rociletinib	Phase III
	Crizotinib	Approved
	Alectinib	Approved
	Ceritinib	Approved
	Lorlatinib	Phase II
	Brigatinib	Phase II
Mesenchymal-to-epithelial transition (MET) erbB2 receptor tyrosine kinase 2 (HER2)	Crizotinib	Phase II
	Cabozantinib	Phase II
	Trastuzumab emtansine	Phase II
	Afatinib	Phase II
	Dacomitinib	Phase II

ROS proto-oncogene 1 (ROS1)	Crizotinib	Approved
	Cabozantinib	Phase II
	Ceritinib	Phase II
	Lorlatnib	Phase II
	DS-6051b	Phase I
B-Raf proto-oncogene (BRAF)	Vemurafenib	Phase II
	Dabrafenib	Phase II
Ret proto-oncogene (RET)	Cabozantinib	Phase II
	Alectinib	Phase II
	Apatinib	Phase II
	Vandetanib	Phase II
	Ponatinib	Phase II
Neurotrophic tyrosine kinase receptor type1 (NTRK1)	Lenvanib	Phase II
	Entrectinib	Phase II
	LOXO-101	Phase II
	Cabozantinib	Phase II
Phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3KA)	DS-6051b	Phase I
	LY3023414	Phase II
	PQR 309	Phase I
Mitogen-activate protein kinase 1 (MEK1)	Trametinib	Phase II
	Selumetinib	Phase III
	Cobimetinib	Phase I

Table 4: *Current therapeutic drugs targeting lung cancer.*

Quinazolinones

Quinazolinones are heterocyclic synthetic molecule that have recently been appreciated for their activity against multiple cancer. Figure 4 shows a typical structure of a quinazolinone. Quinazolinones are known to possess wide range of activities like: anti -microbial, anti-malarial, anti-convulsant, anti-histaminic, anti -hyperlipidemic, anti-influenza and so on [80]. Thus far, as an anti- cancer agent, it has mainly been employed in targeting epidermal growth factor (EGFR) with some potential shown towards inhibition of histone deacetylase (HDAC), hedgehog (Hh), PI3K/Akt/mTOR and NF-κB pathway, as discussed below.

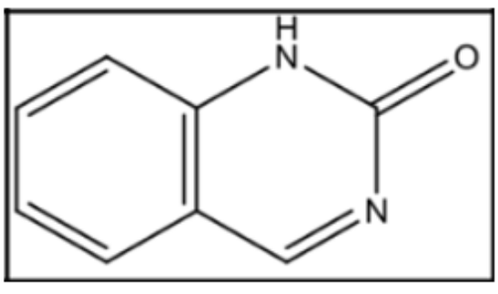

Figure 4: *Chemical structure of quinazolinone.*

Quinazolinone as EGFR inhibitor

EGFR is an important target in lung cancer, since this receptor is found to be over-expressed in > 60% of NSCLC [81]. It is a transmembrane receptor belonging to tyrosine kinase family. As a result of its phosphorylation/activation, various intracellular signalling pathways are activated including ERK/MAPK, PI3K/AKT and JAK/STAT. This in turn leads to decreased apoptosis with a concomitant enhancement in cell proliferation, angiogenesis, and metastasis, thereby contributing to pulmonary carcinogenesis. Phosphorylation of EGFR also plays essential role in the maintenance of tumor microenvironment [81].

Several synthetic tyrosine kinase inhibitors (TKIs) based on quinazolinone pharmacophore and monoclonal antibodies targeting EGFR are currently being employed as a therapeutic strategy. TKIs have majorly been designed to block the phosphorylation site of EGFR, resulting in inhibiting its activity. Erlotinib and Gefitinib (quinazolinamine derivatives) are two classic EGFR targeting drugs that are currently been used for the NSCLCs therapy. Table 5 enlists some of the known quinazolinones-based drugs targeting EGFR that are being used against lung cancer.

Generation	Drugs	Targets
First generation	Gefitinib	EGFR TKIs
	Erlotinib	EGFR TKIs
Second generation	Afatinib	EGFR, HER2
	Dacomitinib	EGFR, HER2, vascular endothelial growth factor receptor (VEGFR) 2, FLT-4, and EphB4 (irreversible inhibitor of EGFR and HER2)
	HKI-272	
	XL647	
	BIBW2992	

Table 5: *Quinazolinone derivatives targeting EGFR.*

Many more derivatives of the quinazolinones have shown effects in lung cancer *in vitro* and are yet to enter the market. Mahdavi., *et al.* documented that a novel quinazolin-4(3H) - one molecule linked to 1,2,3-triazoles show anti-cancer effects in A549 lung cancer cells, comparable to the existing drug, erlotinib.

Through molecular docking analysis they showed that this novel compound interacted with EGFR [82]. Adel S., *et al.* synthesized 2-substituted mercapto-3-(3,4,5-trimethoxybenzyl)-4(3H)-quinazolinone analogues and showed significant anti-tumour activity with EGFR interaction using multiple lung cancer cell lines [83]. Hour., *et al.* synthesized 2-aryl-6-substituted quinazolinones and showed its anti- cancer effects on lung squamous carcinoma: CH27 and lung non-small carcinoma: H460 cell lines [84].

Quinazolinones as histone deacetylase inhibitors (HDACi)

Histone Deacetylase (HDAC) acts as an important regulator of gene expression. For a gene to be expressed, the acetylation of the histone group plays essential role, which in turn influences the gene transcription, while deacetylation causes its transcriptional repression [85]. As the name suggests, HDACi remove the acetyl group from the histone or non-histone proteins enzymatically and modulates various downstream biological events such as cell proliferation, angiogenesis, cell cycle arrest, immune suppression which in turn helps in tumorigenesis. Till date, 11 different types of HDACi have been designed targeting three different classes of HDACs. In cancer, aberrant changes in the expression level of HDACs have been reported, which make them important target for the anti-cancer therapy [85].

In lung cancer, quinazolinones derivatives have also found their application as histone deacetylase inhibitor and SAHA (suberoylanilide hydroxamic acid, vorinostat) is commonly used as a standard molecule. JW Chern., *et al.* designed and synthesized quinazolin-2,4-dione-based hydroxamic acids which acts as HDACi, selectively acting on HDAC6. The synthesized compound was studied both on the LL2, lung cancer cell line and in xenograft syngeneic non-small cell lung cancer mouse model, where it showed significant anti-tumour properties [86]. Similarly, SB Han., *et al.* synthesized N -hydroxybenzamides/N-hydroxypropenamides incorporating quinazolin-4(3H) -ones which acted as HDACi when evaluated on NCI-H23 lung cancer cell line. Some of these compounds were found to be even more potent than SAHA [87].

Quinazolinones as Hedgehog (Hh) pathway inhibitors

Hedgehog signalling pathways plays a vital role in cellular growth and differentiation during development [88]. This signalling pathway is initiated when Hh ligand binds to the PATCHED1 (PTCH1) protein, which also has the ability to repress smoothened (SMO) in the absence of Hh ligand. SMO is a G-coupled protein coupled -like receptor and is considered to play an important role in the Hh pathway. Upon the activation of signalling events, SMO is disassociated and translocated to primary celium. Transcription factors like GL1, GL2 (activators) and GL3 (repressors) are known key players regulating the transcription of Hh target genes. Studies have shown that aberrant activation of hedgehog pathway results in the increased expression of anti- apoptotic proteins, causes epithelial-to-mesenchymal transition, cell-cycle arrest and cell differentiation, ultimately resulting in carcinogenesis [88].

Hyuk Wan Ko*., et al*. utilized structure hopping approach to design and synthesize quinazolinones derivatives targeting Hh pathway. The compounds were tested biologically on fibroblast cell lines NIH3T3 by luciferase assay. It will be of interest to see if these modified quinazolinones may also show promising effect on the lung cancer cells [89].

Conclusion

Lung cancer is a major cause of death worldwide and its prevalence has been increasing. The major cause of poor survival rate for lung cancer patient is its late stage diagnosis. There had been use of several chemo/radio-based therapeutic strategies, however, there are many limitations/side-effects/problems related to disease recurrence/metastases. Therefore, research is getting diverted towards developing synthetically derived chemical compounds as well as naturally occurring plant derivatives. Focusing on these derivatives, our review draws attention specifically towards compounds like curcumin, resveratrol and α -mangostin and synthetic derivatives of quinazolinone class.

For a successful therapy, a combination of these naturally occurring and/or synthesised compounds may help in decreasing toxicity whilst increasing the efficacy. Also, structural modifications of quinazolinones may further can increase their efficacy. Overall, the information will be help in development of improved therapeutic strategy.

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Conflict of Interest

Authors declare no conflict of interest.

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Volume 9 Issue 4 March 2020