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REPOSITIONING OF NSAIDS FOR LUNG CANCER TREATMENT AND AUGMENTATION BY QUERCETIN

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ABSTRACT

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are widely used analgesics. NSAIDs can inhibit cyclooxygenase (COX) enzyme, thereby targeting the prostaglandin (PG) pathway resulting in the prevention and treatment of cancer. Five NSAIDs were selected belonging to different classes based on the literature survey. The study aims to investigate the cytotoxic effect of NSAIDs and its synergism with quercetin, on lung cancer cell line A549 for repositioning. Cytotoxic assay and *in-silico* screening of NSAIDs was the methodology employed to attain the objective. The significance of repositioning of NSAIDs is cost-effectiveness and non- invasive cancer management.

KEYWORDS; Repositioning, NSAIDs, Cyclooxygenase enzyme, *In-silico* Docking, Synergistic effect.

INTRODUCTION

Lung cancer is bronchial (airway) cancer. The etiological cause of lung cancer is the inhalation of carcinogens through the air into the lungs. Lung cancer is responsible for a huge number of deaths in Asia, and a total of 160,068 lung cancer cases were reported in Asian countries in 2018.[1] The two main types of lung cancer are small cell and non-small cell lung carcinoma (NSCLC)[3][4], a majority (85%) being the cases of NSCLC.[5] Adenocarcinoma is a common subtype of NSCLC (around 40% of the total NSCLC), and it originates in peripheral lung tissue.[6],[7] Drug repositioning is the application of already approved drugs and compounds for the treatment of another indication. Generally, it takes around 7 to 12

years for the de novo manufacture and marketing of any drug. However, drug repositioning can minimize the time and cost of development.[22,12,13,16,21]

The present study tried to demonstrate a drug repositioning strategy for lung cancer using NSAIDs and augmentation by quercetin. Most lung cancer patients become immuno-suppressed due to radiotherapy and chemotherapy, which leads to serious complications in lung cancer patients.[21] In such situations, a drug repositioning regime can prove to be beneficial in the management of lung cancer. One of the pharmacological actions of NSAIDs is to inhibit cyclooxygenase (COX). Cyclooxygenase enzyme catalyzes the formation of prostaglandins H2 (precursor for the synthesis of prostaglandins).[12,13] NSAIDs reduce COX-2 catalyzed formation of specific prostaglandins (particularly PGE-2), which promote key cellular processes in cancer development including mitogenesis, mutagenesis, angiogenesis, deregulation of apoptosis, immune- suppression and metastasis, thereby acting as chemo-preventive agents.[13,15] The goal of this study was to find evidence of antiproliferative activity of selected NSAIDs (Diclofenac, Naproxen, Tolfenamic acid, Ibuprofen, and Celecoxib), determine an effective dosage and study synergism with quercetin on lung cancer cell line A549. The selection criteria of NSAIDs were based on previous literature. Also, NSAIDs of five different classes were incorporated, which were as follows.

NSAID Class	Compound used in the Study
anthranilic acid derivatives	Tolefenamic Acid
phenylacetic acid derivative	Diclofenac
propionic acid derivative	Naproxen
pyrazole derivative	Celecoxib
monocarboxylic acid	Ibuprofen

Diclofenac is a potent inhibitor of COX2, resulting in a decrease of prostaglandins E2 synthesis, thus having antiproliferative activity.[15] Naproxen inhibits PGE2 synthesis and therefore reducing the COX activity in colorectal cancer.[16,19] Tolfenamic acid activates the p38 mitogen-activated protein kinase (MAPK) pathway in pancreatic and colorectal cancer.[23,20] Celecoxib can suppress tumor growth, lung metastasis, and angiogenesis at high doses.[19] Ibuprofen is found to inhibit COX 1 and COX 2.[12] The selected phytochemical quercetin (3,30,40,5,7- pentahydroxyflavone (30,40,5,7 tetrahydroxyflavonol or 3,30,40,5,7-pentahydroxy-2- phenylchro- men-4-one) exhibits antiproliferation in cancer cells by induction of growth arrest in G1or G2 phase, apoptosis and inhibition of angiogenesis.[18,19] Also, molecular docking on cyclooxygenase enzyme was investigated in this study. Computer-based simulation of the binding interactions of the protein-ligand complex was

performed to understand binding affinities of drugs and compounds (ligand) and COX1 and COX2 enzyme (protein). Autodock was employed to compute energetically stable conformation(s) that model(s) the structure of the complex[27,28] as ligands for docking studies.

MATERIALS AND METHODS

Cell Culture and Media

The A549 lung cancer cell line was procured from NCCS, Pune. Cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) with 10% FBS and 1% penicillin/streptomycin. The cells were maintained in T25 vented type of adherent tissue culture flasks at 37oC in CO2 incubator with 5% CO2 concentration. Cells were harvested by trypsinization when the culture reached confluency.

TREATMENT IN CELL CULTURE

1. Single Compound study

NSAIDs and quercetin were prepared with suitable solvents for the treatment of the cell culture. According to the solubility, Tolfenamic acid and Diclofenac were dissolved in distilled water, Naproxen and Celecoxib were dissolved in DMSO (50%), Ibuprofen and Quercetin were dissolved in Ethanol (100%). On the other hand, cells were seeded onto 96 titer well plate, after counting the cells using a hemocytometer (improved Neubauer chamber). The seeded cells were treated with NSAIDs and quercetin in amounts ranging from 25 micromoles to 100 micromoles and 10 micromoles to 100 micromoles respectively.[29]

2. Synergistic Study with varied combinations of drugs

A novel approach to study the synergistic potential of drugs was employed in this study. A cocktail of two, three, and four NSAIDs were prepared. The dose of NSAIDs to study synergism was as follows, 100 micromoles of Tolfenamic acid, Celecoxib, Diclofenac and Quercetin, 75 micromoles of Ibuprofen and, 60 micromoles Naproxen.

Cell viability assay (MTT assay)

Cytotoxic assessment of A549 cell line post-treatment was performed by MTT assay. MTT assay was based on the reduction of tetrazolium dye (MTT) by metabolically active cells turning the dye purple. Therefore, the viable and unviable cells were differentiated based on purple color, which was assessed using a spectrophotometer.

Cell viability was determined post-treatment at regular 24-hour time intervals for 96 hours. This was done by adding 100 microliters media with MTT dye to each well in the plate. The plate was wrapped in an aluminum foil and incubated for 4 hours in a humidified atmosphere at 37°C to allow the formation of the formazone crystals (purple product). After the incubation period, the media and MTT were carefully removed. DMSO was added to each well. Absorbance was recorded immediately in a 96 well-plate reader at 570 nanometers.

Statistical analysis

The cell viability results were statistically analyzed using one- way ANOVA method. $P<0.05$ was considered to be significant. The statistically significant concentrations of NSAIDs and quercetin were shortlisted for further studies.

***In-silico* study**

In-silico study was done using the *Autodock Software* to corroborate with the findings of *in-vitro* demonstration of repositioning efficiency. A computer-generated representation of the five NSAIDs (Tolfenamic acid, Naproxen, Celecoxib, Ibuprofen, and Diclofenac) and Quercetin were used as ligands, to study binding affinities with the target proteins i.e., Cyclooxygenase 1 and Cyclooxygenase 2 (prostaglandin-endoperoxide synthase) (PTGS) enzyme.

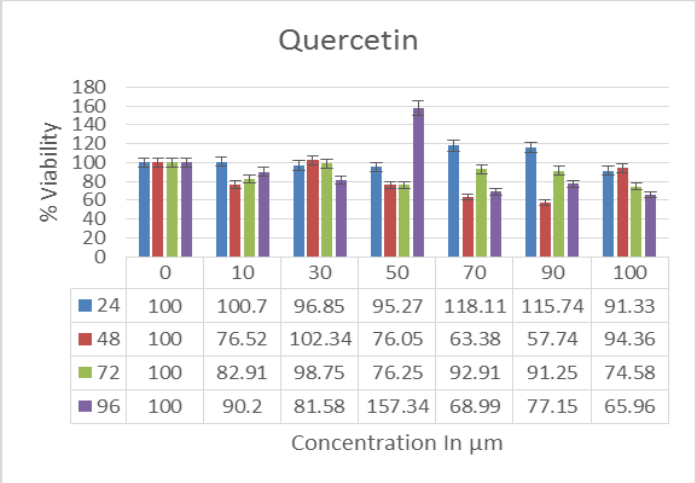
Protein structure and ligand preparation for Docking.

The biological macromolecular protein structure of COX2 (PDB Id: 5F19) was obtained by sequences from the RCSB protein databank. Ligplots were obtained from PDBSum-Generate. Protein structure server SWISS-MODEL was used for homology- based modeling of COX1 (PDB Id-a147) because the PDB structure was not available in the RCSB protein databank. Ligand structure drugs and phytochemicals were obtained from PubChem

RESULT AND DISCUSSION

The present study investigated the synergistic and augmented effects of selected non-steroidal anti-inflammatory drugs (NSAIDs) viz., Tolfenamic acid, Celecoxib, Diclofenac, Naproxen and Ibuprofen and Quercetin on Lung cancer A549 cell line. MTT assay was performed to gauge the cytotoxicity of each treatment. Finally, the in-vitro results were corroborated with the molecular interaction of COX-1 and COX-2. The molecular interactions were studied using *in-silico* molecular docking.

Our findings indicate that tolfenamic acid was most cytotoxic to cells at a dose of 25 micromoles and 100 micromoles at all time-points until 96 hours. Naproxen was found to be most cytotoxic at 25 micromoles, 50 micromoles, 60 micromoles, and 75 micromoles. Ibuprofen and diclofenac were most cytotoxic at 75 micromoles, 60 micromoles, 100 micromoles, and 50 micromoles, respectively, at all-time points. Celecoxib was cytotoxic to cells at 25 micromoles, 75 micromoles, and 100 micromoles at all time-points.[29] Quercetin has indicated cytotoxicity at 100 micromoles, 90 micromoles, 70 micromoles, 50 micromoles and 10 micromoles at all the time-points as indicated in Graph 1.

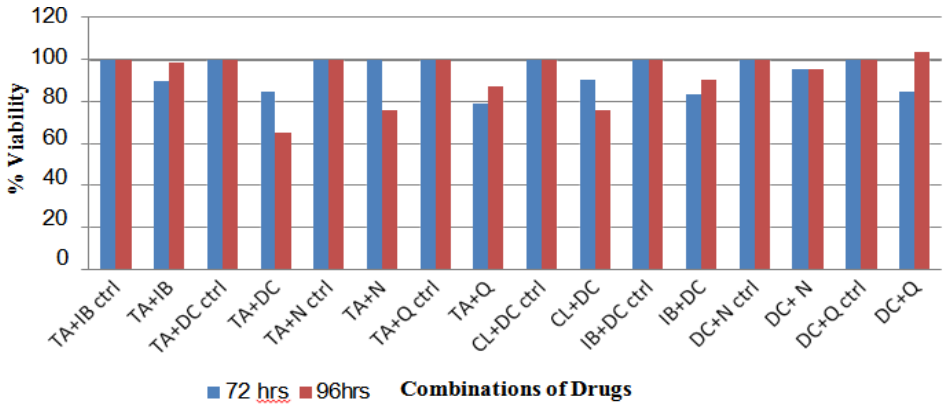


	0	10	30	50	70	90	100
24	100	100.7	96.85	95.27	118.11	115.74	91.33
48	100	76.52	102.34	76.05	63.38	57.74	94.36
72	100	82.91	98.75	76.25	92.91	91.25	74.58
96	100	90.2	81.58	157.34	68.99	77.15	65.96

Graph 1: % viability against Quercetin.

The results of cell cytotoxicity of the cocktail preparation of the drugs to study the synergistic potential of drug repositioning of NSAIDs are shown in graphs 2-5. Amongst the two-drug combinations, the cocktail of Tolfenamic acid and Diclofenac was most cytotoxic, reducing the cell viability to 65 % at 96 hours.

Synergistic cytotoxicity: 2 Drug Combination

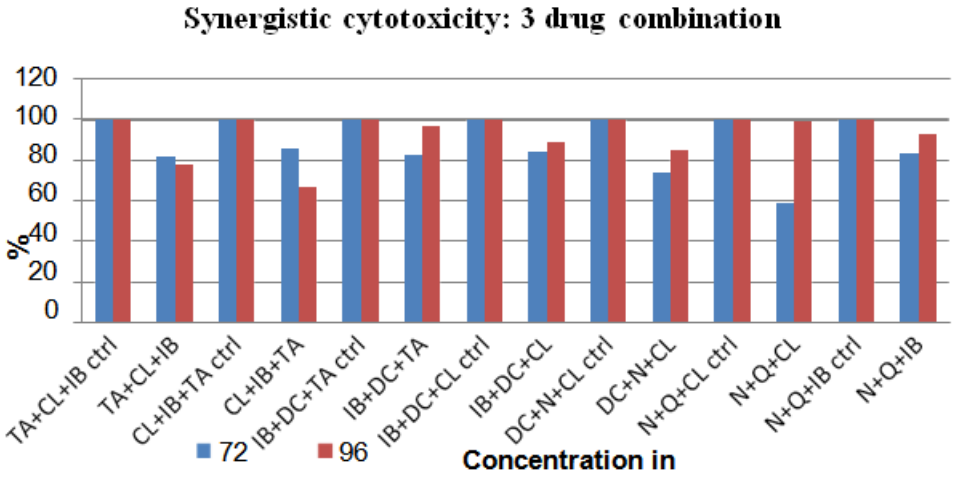


Graph 2: MTT assay combination of 2 drugs.

TA: (Tolefenamic Acid); IB: (Ibuprofen); CL: (Celecoxib); N: (Naproxen); DC: (Diclofenac) CU: (Curcumin)

Amongst the three-compound combinations, a cocktail of Naproxen, Quercetin and Celecoxib was most cytotoxic, reducing the cell viability to 59% after 72 hours of treatment.

Synergistic cytotoxicity: 3 drug combination

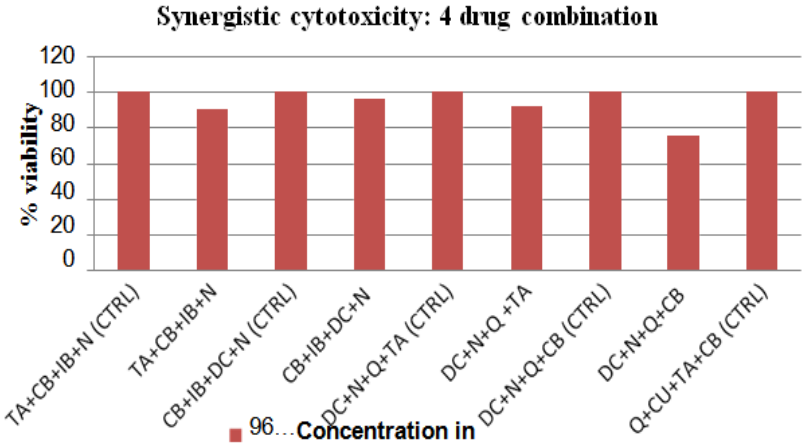


Graph 3: MTT assay combination of 3 drugs.

TA: (Tolefenamic Acid); IB: (Ibuprofen); CL: (Celecoxib); N: (Naproxen); DC: (Diclofenac) CU: (Curcumin**)**

A preparation of diclofenac, naproxen, quercetin and celecoxib was found to exhibit the highest synergistic effect in case of four-drug combinations. Diclofenac, naproxen, quercetin and celecoxib reduced the cell viability to 76%.

Synergistic cytotoxicity: 4 drug combination

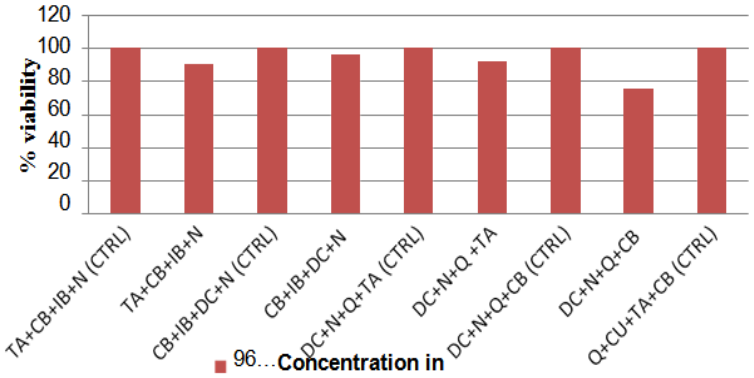


Graph 4: MTT assay combination of 4 drugs at 96 hour.

TA: (Tolefenamic Acid); IB: (Ibuprofen); CB: (Celecoxib); N: (Naproxen); DC: (Diclofenac) CU: (Curcumin).

The five-compound synergistic effect of tolefenamic acid, celecoxib, diclofenac, naproxen and quercetin was found to be most potent, thereby reducing the cell viability to 52.4% at 96-hour time-point.

Synergistic cytotoxicity: 5 drugz combination



Graph 5: MTT assay combination of 5 drugs.

T: (Tolefenamic Acid); I: (Ibuprofen); C: (Celecoxib); N: (Naproxen); D: (Diclofenac) CU: (Curcumin).

Table 1: Synergistic potential of repositioning.

	% Viability		Best outcome
Time of Incubation	**72 hours**	**96 hours**	
Two NSAIDs Combination Treatment			
TA+Q	79%	87%	TA+DC
TA+IB	90%	98%	
TA+DC	84%	66%	
TA+N	100%	76%	
CL+DC	90%	76%	
IB+DC	83%	91%	
DC+N	95%	95%	
DC+Q	85%	104%	
TA+CL	175%	78%	
CL+IB	109%	83%	
Three NSAIDs Combination Treatment			
TA+CL+IB	82%	78%	N+Q+CL
TA+CL+N	105%	67%	
CL+IB+TA	85%	66%	
CL+IB+N	111%	89%	
IB+DC+TA	83%	97%	
IB+DC+CL	84%	89%	

IB+DC+Q	115%	98%	
DC+N+TA	90%	145%	
DC+N+CL	74%	85%	
DC+N+IB	148%	78%	
N+Q+TA	125%	95%	
N+Q+CL	59%	99%	
N+Q+IB	84%	93%	
N+Q+DC	142%	83%	
TA+CL+Q	97%	114%	
Four NSAIDs Combination Treatment			
DC+N+Q+CL	-	76%	DC+N+Q+CL
TA+CB+IB+N	-	91%	
CL+IB+DC+N	-	96%	
DC+N+Q+TA	-	92%	
Five NSAIDs Combination Treatment			
TA+CL+IB+DC+Q	150%	83.2%	TA+CL+DC+N+Q
CL+IB+DC+N+Q	106%	90.3%	
IB+DC+N+Q+TA	71.9%	116%	
TA+CL+DC+N+Q	52.4%	105%	

T: (Tolefenamic Acid); IB: (Ibuprofen); CL: (Celecoxib); N: (Naproxen); D: (Diclofenac); Q: (Quercetin)

Table 2: Comparison of Dock Score of Standard Chemotherapeutic Drugs, With Nsaids and Quercetin For Cox-1 And Cox-2 Binding.

Ligand	**Cycloxygenase 1**		**Cycloxygenase 2**	
NSAIDs	**Binding Energy**	**Interacting Sites**	**Binding Energy**	**Interacting Sites**
Tolfenamic acid	-8.82	Asn 381, His 385 Tyr 384	-8.56	Asn 375, Asn 376
Ibuprofen	-7.56	Trp 386	-6.96	Asn 537, Val 228 Gly 533
Diclofenac	-7.78	Asn 381, Tyr 384 His 206	-8.08	Gly 225, His226 Val 228, Asn375
Naproxen	-8.23	Met 390, Trp 386 Asn 381	-7.96	Val 228, Asn 537
Celecoxib	-6.94	Tyr 403,His 387	-8.44	Gln 374,Arg 376
Quercetin	-9.57	His 387, Thr 205, Asn 381	-9.19	Arg 376, Asn 375 Val 228, Asn 537 Gln 374, Tyr 37, Gly 533
Standard Chemotherapeutic Agents	**Binding energy**		**Binding Energy**	
Etoposide	-10.35		**-12.45**	
Irinotecan	-13.23		**-13.73**	
Paclitaxel	-7.39		**-11.45**	

The interactions of NSAIDs and quercetin with cyclooxygenase 1 and 2 was considered to be based on the binding of ligand with the proteins COX 1 and 2. The binding energy was assigned with a docking score. Dock score is a function of the binding energy of ligands-proteins. Table 2 represents the *in silico* analysis represented by a docking score as a mathematical function and putative interacting amino acids in the binding site. The NSAIDs and phytochemicals were compared with standard chemotherapeutic drugs, Etoposide, Irinotecan, and Paclitaxel. A ligand's lower negative dock score indicates a higher binding affinity with the protein.

Tolefenamic acid had the highest *in silico* binding potential with three interacting amino acids asparagines, histidine, and tyrosine for COX 1 and two interacting amino acids, both asparagines for COX 2. A slightly higher binding potential of tolefenamic acid for COX 1 complies with the presence of three interaction units in COX 1. The phytochemical quercetin had higher binding potential than NSAIDs, and quercetin has three interacting amino acids (histidine, threonine, and asparagines) with COX 1 and seven interacting amino acids (valine, glycine, glutamine, tyrosine, arginine, and two asparagine) with COX 2. Naturally, the NSAIDs, and phytochemical had a lower binding potential as compared to standard chemotherapeutic drugs. However, a few like tolefenamic acid and quercetin hold potential. Also, the chemotherapeutic drugs have multiple cellular targets to inhibit cell division or induce cell death, although, the NSAIDs solely target the prostaglandin pathway. Therefore, the chemopreventive action of NSAIDs should be seen as a potential for further development, which holds future promise, and the *in silico* findings surely suggest the NSAIDs to be an active specific binding agent.

CONCLUSION

Lung cancer is the result of an aggressively proliferating group of lung cells. The study has demonstrated an effective repositioning strategy for lung cancer. The repositioning of NSAIDs and quercetin has been able to induce cytotoxicity in A549 lung cancer cells. Thus, it can be concluded that a combination of NSAIDs works better than single NSAIDs in inducing cytotoxicity. Previous repositioning strategies focused on using a single compound for treating an indication, yet the present study was focused on creating a regime of compounds for better success in repositioning. Therefore, a study to find out the synergistic potential of the NSAIDs was performed. It was found that synergism was effective against A549 cells. In The synergistic study, this two-drug, three-drug, four-drug, and five-drug

cocktails showed potential cytotoxic effects. Furthermore, the results show that the augmentation of NSAIDs by phytochemical quercetin always works better than a non-augmented combination. The results of synergistic potential and augmentation demonstrate a promising novel repositioning strategy that has never been done before. The results of *in silico* studies for the binding of compounds proved the interaction NSAIDs and quercetin with cyclooxygenase enzyme. Tolefenamic acid had the highest *in silico* binding affinity. Also, quercetin, a proven antiproliferative agent, had a high binding affinity with cyclooxygenase. Lung cancer is a complex phenomenon. Thus, the present study was focused on helping find a non-invasive management strategy, rather than to claim a replacement of conventional cancer therapies. The study demonstrated the potential of repositioning NSAIDs for lung cancer management augmented with quercetin.

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