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DOXORUBICIN AND CHLOROQUINE: A COMBINATION THERAPY TO OVERCOME THE MULTI DRUG RESISTANCE IN CANCER - A REVIEW

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ABSTRACT: Cancer is a genetic disorder that can happen to anybody; anytime. The treatment, where one or more chemotherapeutic agents (anti-cancer drugs) are used either to treat the cancer patients (curative intent with one or combination of anti-cancer drugs) or to prolong the life and to reduce the symptoms in cancer patients is known as Chemotherapy. But nowadays it is observed that when these chemotherapeutic agents are administered in the cancer patients for prolonged period then the drugs stop showing the required response and thus results in the failure of the treatment. This is called Multiple Drug Resistance (MDR). Various treatments are coming up recently, and combination therapy of chemotherapeutic agent and chemosensitizer molecule is one of the effective approaches to combat the Multidrug Resistance of anti-neoplastic drugs in cancer cells. This paper reviews MDR associated with cancer, therapies to overcome the resistance and studies to confirm the MDR-reversal.

INTRODUCTION: Antibiotics are the very common drugs which are known to have multidrug resistance. But recently there is an emerging problem in oncology which is multidrug resistance of the chemotherapeutics when they are administered for a prolonged period of time to the cancer patients [1]. This emerging issue is increasing the cancer death rate each year. Many therapies have been carried out to overcome this MDR but still there is no permanent solution to it [2]. Thus, a new technique that has come into light recently is combination therapy where either two chemotherapeutic drugs showing synergistic effects, are administered together or one anti-cancer drug is combined with one chemosensitizer which enhances the activity of the chemotherapeutics to overcome this MDR.

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One such combination therapy is doxorubicin (DOX) and chloroquine (CQ) nanoparticles, which are found to be potent against MCF7/Adr [3, 4] a multidrug-resistant breast cancer cell line. But Doxorubicin is also effective against many other carcinomas, one of which is lung cancer, a very common form of cancer among the male population all over the world. Thus, studies can be carried out on lung cancer cell lines [3]like A549, to check if this combination therapy is active against this specific type of cancer also.

Death Rate in India Due to Cancer: According to the current statistics it is shown that in India around 2.5 million people are suffering from cancer and over 7 lakh new cancer patients get registered every year. Amongst these people the mortality rate is around 5,56,400. Between the age group of 30-69 the total mortality rate is around 3,95,400 which is 71% of the total cancer patients. From this total population, the male population is 2,00,100 and female population is 1,95,300. Male generally suffers from oral cavity and lung cancer; females suffer from cervix and breast cancer **Fig. 1**.

Scientists all over the world are trying to find a new remedy to the disease, but still a breakthrough is yet to come. On top of that multidrug resistance of these existing drugs is making the scenario worse day by day.

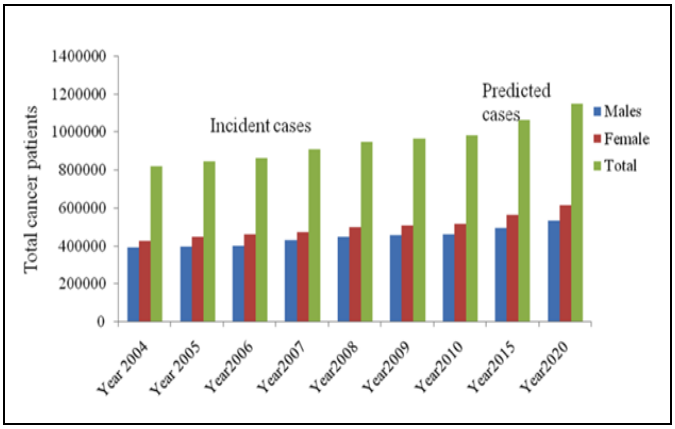

FIG. 1: YEAR WISE TOTAL CANCER PREVALENCE IN INDIA [5]

Multidrug Resistance in Cancer: MDR causes mainly because of the following reasons: a) Epigenetics, b) Drug efflux: effluxion of xenobiotics out of the cells through ATP Binding Cassette Receptors, present on the surface of the cancer cells against the concentration gradient, c) DNA damage Repair: repairing the DNA damage caused by the chemotherapeutic agents, d) Cell death inhibition: normal cell death or apoptosis is inhibited by the cancer cells, e) Epithelial mesenchymal transition, f) Drug target alteration: alteration of the drug target receptors on the cancer cell surface, thus drugs cannot bind to the cancer cells g) Drug inactivation [3] **Fig. 2**.

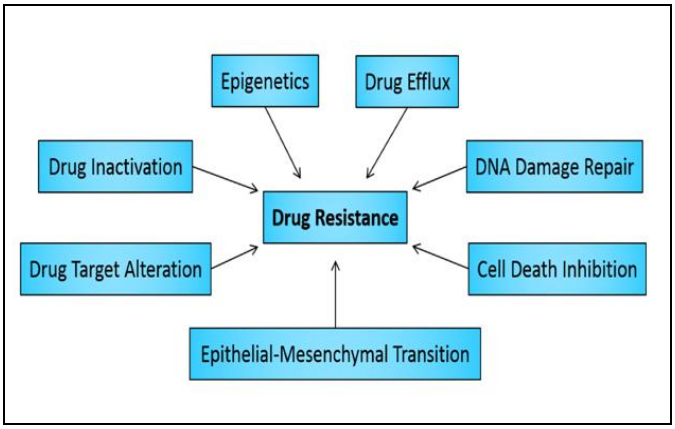

FIG. 2: TYPES OF MECHANISMS ENABLING OR PROMOTING DIRECT AND INDIRECT DRUG RESISTANCE IN HUMAN CANCER CELLS. THESE MECHANISMS CAN ACT INDEPENDENTLY OR IN COMBINATION AND THROUGH VARIOUS SIGNAL TRANSDUCTION PATHWAYS [6]

The main reasons behind MDR in cancer patients are because of the following: (a) increased expression of drug efflux pumps like permeability glycoprotein (P-gp), multidrug resistance-associated protein (MRP), and breast cancer resistance protein (BCRP) (b) altered lipid metabolism (ceramide pathway) (c) toxicity removing system which eliminates drugs (d) reduction of drug uptake because of altered surface receptors/carriers (e) glutathione-mediated reduction causing drug inactivation (f) over-expression of thymidylate synthase (g) changed drug targets such as topoisomerase II (h) increase in DNA repair capacity (i) reduced apoptotic ability (j) hypoxia up-regulated expression of MDR-linked genes such as ABC transporters, Bcl-2 family genes, glutathione by transcription factor HIF1 activation (k) abnormal chromosomes in tumor cells causing over-expression of anti-apoptotic genes (l) integrin receptors and growth factor receptors governed altered signal transduction pathways in cancer cells leads to blockage of apoptosis and expression of MDR-linked genes which are involved in repairing of DNA and drug-efflux pumps **Fig. 3**.

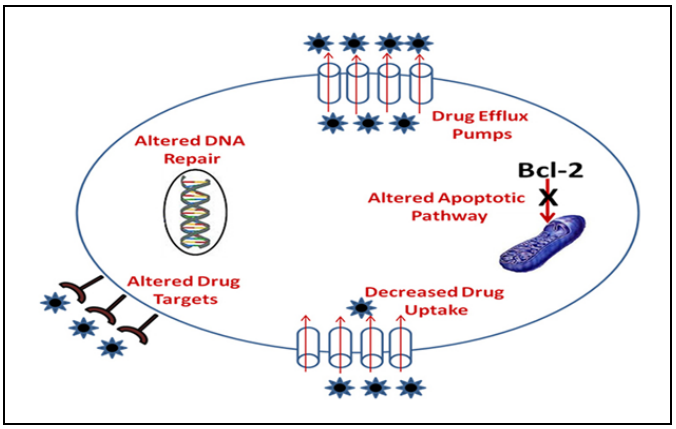

FIG. 3: MECHANISM OF MULTI DRUG RESISTANCE IN TUMOUR CELLS [7]

MDR is generally of two types: Active Multidrug Resistance, Passive Multidrug Resistance [8]. Active MDR happens when the cells naturally possess some receptors which are involved in drug effluxion from the cells against the concentration gradient. These receptors include P-glycoprotein and Multi-Drug Resistant Protein (MRP), which are present on the cell membrane of the cancer cells and are responsible for the Active MDR. Passive MDR happens when the same chemotherapeutic agents are administered into the patients for a

prolonged period of time due to: a) decreased drug uptake mechanisms, such as altered folate carriers, b) inactivation of drugs via glutathione-mediated reduction, c) overexpression of target enzymes, such as upregulated thymidylate synthase, d) altered drug targets, such as topoisomerase II, e) increased DNA repair capacity, f) reduced ability to undergo apoptosis [1, 9].

Therapies to Overcome MDR: Many attempts have been made to reverse this Drug Resistance like:

- Drug efflux transporter inhibitors development.
- Active drug analogs synthesis.
- Use of advanced drug delivery systems.

But these above therapies need the development of a new drug which is a very much time consuming and costly affair. Thus, an alternative therapy has been introduced recently which is known as Combination Therapy [10].

Combination Therapy: Combination Therapy is the treatment which involves the administration of one or more drugs in the patients together to get a synergistic effect to overcome the MDR.

The combination therapies which were already tried are as follows:

- Dual doxorubicin- and verapamil-loaded liposomes, designed to reverse the P-gp-mediated drug efflux of doxorubicin [11].
- Vincristine and verapamil co-encapsulation in poly (D, L lactide-co-glycolide) nanoparticles
- Liposomes for treatment of MDR cancer, as well as the combination of doxorubicin- and quinine-based drugs to overcome MRP-1-mediated MDR.
- Verapamil and Quininecombination therapy to overcome P-gp mediated MDR [12].

Drugs Showing MDR: P-glycoprotein (Pgp) is a plasma membrane protein, encoded by the MDR1 gene [10, 13] which is mostly overexpressed in multi-drug-resistant cell lines. Many chemotherapeutics are substrate of P-gp and it acts on the absorption, permeability, retention and finally effluxion of the drug out of the cells [14]. If P-glycoproteins are Overexpressed in cancer cells, it results in reduced accumulation of chemotherapeutic agents inside the cell, leading to development of resistance against many of the currently available anti-cancer drugs such as taxanes (paclitaxel), vinca alkaloids (vinblastine), and anthracyclines (daunorubicin/ doxorubicin) **Fig. 4**.

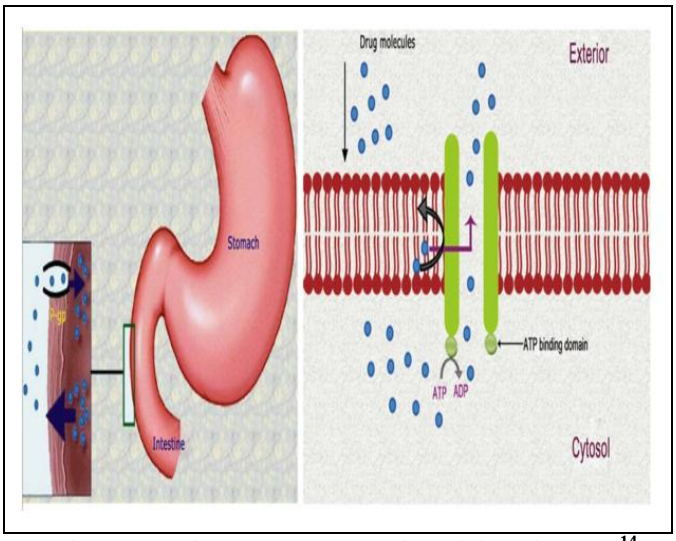

FIG. 4: DRUG EFFLUX BY P-GLYCOPROTEIN [14]

Doxorubicin (DOX): which is an anthracycline antibiotic and are used to cure many cancers such as breast cancer, liver cancer, Kaposi's sarcoma, lymphoma, and acute lymphocytic leukemia but always comes with various side effects such as myelosuppression, dose-limiting toxicity, leukopenia more common than thrombocytopenia or anaemia, nausea and vomiting, mucositis and diarrhoea, cardiotoxicity, extravasation, alopecia.

The main mechanism of action of DOX involves inhibiting the progress of DNA topoisomerase II enzyme, the enzyme which relaxes supercoils in DNA for transcription. DOX stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the process of replication. But it has been noticed that DOX, when administered repeatedly, shows huge Multi-Drug Resistance. To overcome this situation, it was recommended to administer DOX in higher concentrations, but the main problem with this is its increased toxicity, resulting in severe side effects [15].

Chemosensitizers to Overcome 'Drug Efflux' MDR: Many drugs which are not chemotherapeutics show the synergistic effect when administered along with the anticancer drugs. Thus, recently these chemosensitizers are widely used along with chemotherapeutics as a combination therapy. Chloroquine is one such drug which is known to have chemosensitizing property.

Chloroquine is a quinolone derivative which is a potent anti-malarial agent that generally works by inhibiting the conversion of Heme (harmful for malarial parasite) to Hemozoin. It is also occasionally used for amebiasis that is occurring outside the intestines, rheumatoid arthritis, and lupus erythematosus. But the main reason why chloroquine is combined with chemotherapeutic agents is because of its radiosensitization and chemosensitization properties.

Chemo sensitization is the property that induces the chemotherapeutic agents to stay in the cells for a longer period without getting efflux [16]. Chloroquine generally gets bind to the ATP Binding Cassettes which are present on the wall of the cancer cells with higher P-Glycoprotein expression [17], which are mainly responsible for the MDR. Thus, this prevents cancer drugs to go out of the cells. Thus, the anti-cancer drugs stay inside the cells for a longer period and can show better effect **Fig. 5**.

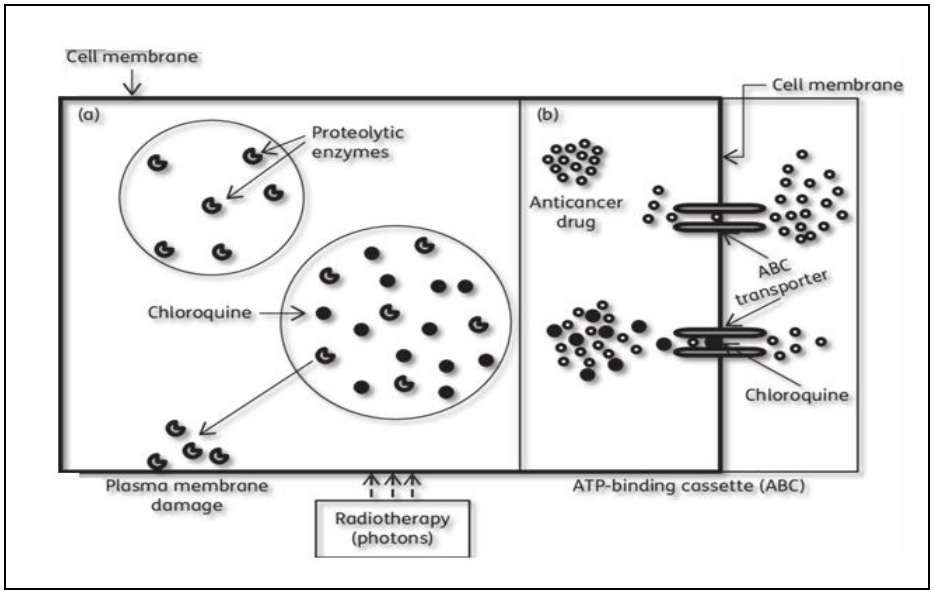

FIG. 5: MODE OF ACTION OF ANTICANCER ACTIONS OF CHLOROQUINE ANALOGUES. (A) RADIOSENSITIZING EFFECT: PROTEOLYTIC ENZYMES THAT CAN DAMAGE MEMBRANES ARE RELEASED AND LYSOSOMAL PERMEABILITY IS INCREASED AS A RESULT OF RADIATION AND THE EFFECT OF CHLOROQUINE. (B) CHEMOSENSITIZING EFFECT: ANTICANCER DRUG EXTRUSION IS PREVENTED *VIA* BLOCKADE OF ABC TRANSPORTERS WITH CHLOROQUINE AND INTRACELLULAR DRUG AVAILABILITY IS INCREASED AND CELLS DAMAGED [18]

Dox-Chloroquine Nanoparticles: Both Doxo-rubicin and Chloroquine can be given together because DOX is anthracycline antibiotics, which mainly works by preventing the action of DNA Topoisomerase II during DNA replication and Chloroquine is also a quinolone derivative antibiotic, and the quinolones act mainly by inhibiting the DNA Topoisomerase IV in the bacterial cells. Thus, when they are given together, then they show some synergism, and Chloroquine enhances the activity of DOX. The combination therapy can also be delivered to the targeted cells by preparing the nanoparticles.

The main reasons behind nanoparticle formulation are threefold: Firstly, it escapes the first-pass metabolism which mostly all drugs go through when they are administered orally. Secondly, the cytotoxicity of both of these drugs, when administered independently is very high. So, the concentration at which these drugs to be given must be very low. Thus, when they are given in the nanomolar concentrations then the toxic effect of these drugs can also be reduced, and the delivery of the anti-cancer drugs will be specific to the cancer cells only by passive targeting of the nanoparticles.

Finally, Endosome formation is the main method for the cancer cells to take in the nanoparticles. Chloroquine has the special property of escaping the endosomal formation by proton sponge effect **Fig. 6**.

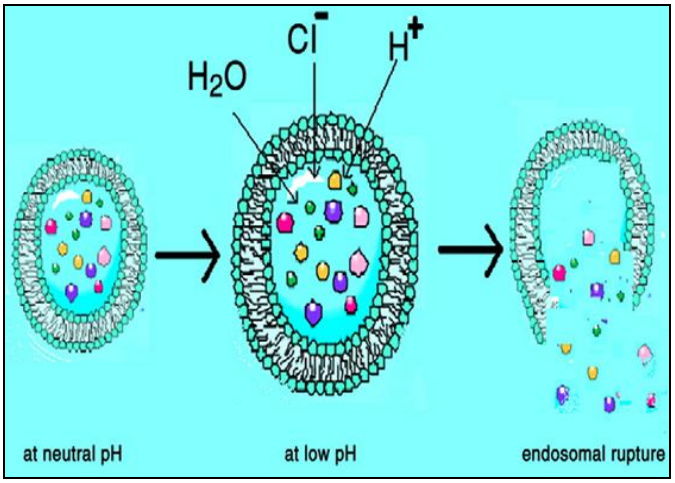

FIG. 6: AN ARTISTIC REPRESENTATION DEPICTING THE PROTON SPONGE HYPOTHESIS. THE LOW PH IN ENDOSOMAL ENVIRONMENT LEADS TO PROTONATION OF THE ENTRAPPED AGENTS WITH A HIGH BUFFERING CAPACITY. PROTONATION LEADS TO INFLOW OF H+ AND CL− AND WATER INTO THE ENDOSOMES, RESULTING IN OSMOTIC SWELLING AND ENDOSOME RUPTURE [19]

Proton sponge effect is mainly the pH buffering capacity of some chemicals, which when administered in a low pH environment causes the ions and water molecules to go inside the endosomes, causing osmotic swelling of the same. This results in bursting of the endosomes and helps the molecules to escape from the endosomes. So, pH is one of the most important criteria for the release of drugs from nanoparticles [20].

P-glycoprotein or its isoforms mainly induce MDR by transporting the hydrophobic chemotherapeutic drugs out of the tumor cells. Thus, when DOX, which is a hydrophobic drug, is administered along with CQ, a chemosensitizer in the form of liposomes, then the effect of P-gp on the drug gets reduced to a great extent [21]. According to some studies, nanoparticles preparation by nano-precipitation using PLGA [22] or formulating liposome [23] using cholesterol with various concentrations of DOX and CQ and it was found to be very much stable at certain pH. MDR breast cancer cell lines (MCF7/ADR) and normal breast cancer cells (MCF7) when treated with these liposomes and *in-vitro* cytotoxicity assay was performed, it showed the improved activity of the chemotherapeutics in comparison to the free drug. DOX and CQ [24, 25] PLGA or PEG nanoparticles are the new formulations understudy to overcome MDR.

Studies to Confirm MDR Reversal: In some studies, it was shown that they have already used the Doxorubicin Resistant Cell lines where expression of P-glycoprotein is more and cytotoxicity assay was performed with various concentrations of free drug and the nanoparticles and the effect of the chemosensitizers on the anti-neoplastic drugs was observed. It was reported that the IC_{50} value of DOX had decreased with the increased concentration of chloroquine up to a certain concentration, which is mainly because chloroquine goes and binds to the drug efflux receptors, preventing the chemotherapeutics to get efflux out of the cells again, doxorubicinis known to have fluorescence activity [26]. In several studies, they have performed cell internalization assay **Fig. 7** and flow cytometry [27] to evaluate the effluxion and accumulation of the drug. In the cellular internalization assay, they had observed the time of accumulation of doxorubicin inside the cells. It was observed that DOX when administered along with CQ in the form of nanoparticle, the former drug had shown better cell internalization and remained accumulated for longer period of time when compared to free DOX, not only in normal but also in resistant MCF-7 cell lines. The reversal of MDR can also be proved without using the drug-resistant cell lines, with the help of the cell internalization assay.

P-glycoprotein is an energy-dependent drug efflux pump whose substrates include naturally occurring, lipophilic agents with a complex ring structure such as vinca alkaloids, anthracyclines, epipodo-phyllotoxins and certain rhodamine dyes [28]. When tumor cells are exposed to either of these substrates, can cause increased expression of P-gp, resulting in the MDR phenotype which can be confirmed by Northern Hybridisation and Immunoblot analysis. This is a passive way to induce MDR in cancer cells. Thus, when the normal breast cancer cells are treated with these substrates for a long period, nearly 100 days [29] then the cells get naturally over-expressed with P-gp or any other drug efflux transporters.

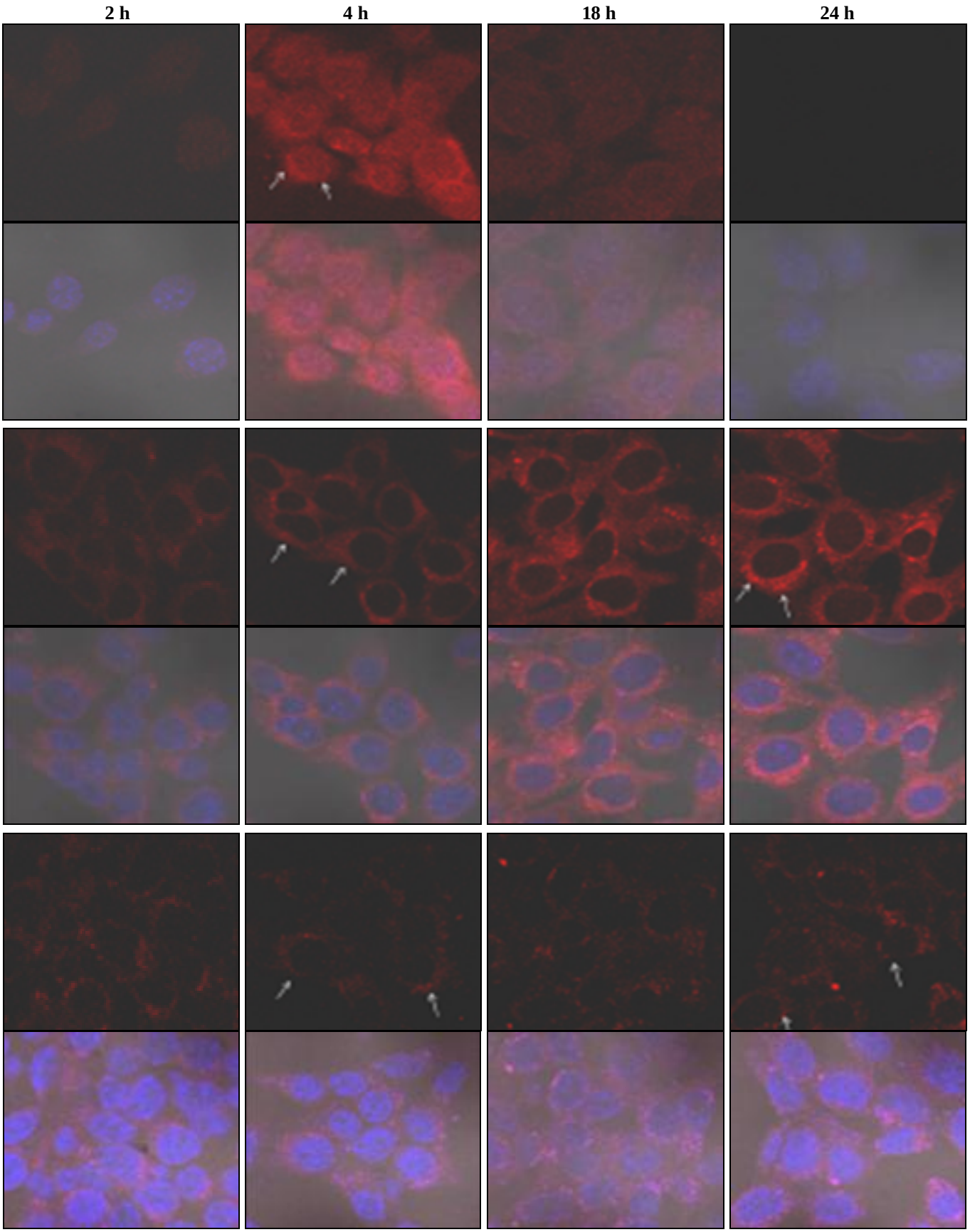

FIG. 7: KINETICS OF CELLULAR UPTAKE AND INTERNALIZATION OF FREE DOX (A), PEG–GTS–DOX (B) AND PEG–DOX–NAG (C) AT 2, 4, 18 AND 24 H USING MCF 7 HUMAN CANCER CELLS, RESPECTIVELY. THE INTENSITY OF THE REPRESENTATIVE CONJUGATE INSIDE THE CELLS IS ONLY QUALITATIVE, ESTIMATED BY VARIED AMOUNT OF DRUG DOX AND NAG IN EACH CONJUGATE. THE ARROW INDICATES RETENTION OF DOX INTO THE PERINUCLEAR REGION [5, 32]

This expression of P-gp happens in the mRNA level as revealed by reverse transcriptase PCR analysis [26]. Thus, studies can be performed on these cells and decrease in the IC_{50} value of the xenobiotics before and after addition of the chemosensitizers can be proved by MTT Assay and the proportion of apoptotic cells can be measured by flow cytometric analysis [30, 31] to prove MDR reversal doxorubicin is an anthracycline antibiotic which is one of the substrates causing overexpression of P-gp and therefore, when the cells are treated with DOX for a longer period of time, it may result into overexpression of P-gp which is one of the main reasons behind Drug-efflux MDR.

And this DOX treated cell lines can be used as an alternative to actual drug-resistant cell lines (MCF7/ADR in case of Human Breast Cancer Cell Lines) when the resistance cell lines are unavailable and further studies can be carried out on these cells to conclude reversal Multi-Drug Resistance of DOX.

CONCLUSION: Cancer is the deadliest disorder with an increasing number of mortalities each year among the human population. Anti-cancer drugs already in the market are generally administered to the first stage cancer patients mainly to reduce the side effects of cancer and to increase the life period of certain cancer patients. But sometimes this chemotherapeutics are also not showing the appropriate response due to multidrug resistance of the drugs to the cancer cells. Thus, it can be stated that the multidrug resistance which is one of the threats for the cancer patients can be overcome by using these chemosensitizers which actually not only cause the reversal of MDR but also causes the lowering of the IC_{50} value of the anti-cancer drugs resulting in reduction of side effects which generally comes along with the drugs. Thus, it can be concluded that combination therapy is a time saving and cost-effective method to overcome MDR as it does not involve the discovery of totally new formulation. When these anti-cancer drugs with some chemosensitizers are incorporated into a cancer patient in the form of a nanoparticle can overcome the MDR.

Chloroquine not only helps in reducing the IC_{50} value of the Doxorubicin but also helps the drugs to come out of the nanoparticles by endosomal escape method. Thus, the combination therapy is useful in reducing the side effects of the chemotherapeutics, as very less concentration of antineoplastic drugs can also show greater effect when they are administered along with the chemosensitizers, and the nanoparticles also show the target specificity to the cancer cells, increasing the overall efficiency of the therapy.

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