Synergy to Fight the Monster

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It is time to change gear and approach to kill the monster. The monster I am referring to is cancer. One of the deadliest diseases that mankind has faced, and with the passage of time, it has taken various forms. To name a few, brain cancer, lung cancer, skin cancer and stomach cancer, etc. But being a female what concerns me the most and my colleagues around the globe is that, the almighty has further burdened us with an unbearable pain of breast cancer. As per WHO statistics, breast cancer impacts about 2.1 million women worldwide every year and accounted for 627,000 deaths in 2018 that is approximately 15% of all cancer deaths among women.

Treatment modules are there, but the statistical data clearly indicates that it's time for a change and we need to adopt a more ruthless approach towards the disease but a more caring approach for our female colleagues. It's like killing the disease without affecting the quality of life for the patient after the treatment is over. A modern day approach which has been adopted for treatment of chronic disease is, treating the disease with some mixture of ingredients which has the capacity to fight the disease along with providing nutritional value with health benefit. It's like a single sword for killing and for healing.

Being a country of cultural diversity, we provide an excellent platform for such combinatorial approach, i.e., mixing the synthetic with the natural (also nutritional value) healing molecules. Prime Minister Narendra Modi's initiative of producing 'neem coated urea' to improvise the agricultural sector further strengthened the objective of our research work to use a natural and a

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* Ms. Sobiya Zafar, Ph.D. Scholar from School of Pharmaceutical Education & Research, Jamia Hamdard, Delhi, is pursuing her research on "Nanocarrier Approach for Combinatorial Delivery of Docetaxel and a Nutraceutical Agent for Solid Tumor Management." Her popular science story entitled "Synergy to Fight the Monster" has been selected for AWSAR Award.

synthetic agent that provides a platform to test the efficacy of the two agents from varied sources in order to bring reforms in the area of cancer treatment.

Nutraceuticals have gained immense interest from the scientific community for their potential in cancer chemoprevention and therapy. In our previous study, our group evaluated the efficacy of curcumin (a natural molecule obtained from *Curcuma longa* sp.) and paclitaxel (another taxane commonly used for breast cancer treatment) in an animal model of the solid tumor. The study revealed enhance anti-cancer effects due to synergism between the two therapeutic molecules and was published in Pharmacological Research entitled as "*Enhanced anti-tumor efficacy of paclitaxel with PEGylatedlipidicnanocapsules in presence of curcumin and poloxamer: In vitro and in vivo studies*". Taking the reference of our previous study, we assessed the anti-cancer effects of docetaxel (a synthetic drug) and thymoquinone (a nutraceutical) for effective treatment of breast cancer.

Docetaxel, marketed as Taxotere, is a widely used anti-cancer agent for the treatment of breast cancer but the poor water solubility, dose-limiting toxicity, and unwanted side effects present a great challenge with the docetaxel chemotherapy. And also, just as mutations in bacteria create infections which are resistant to antibiotics, the mutations in cancer cells create tumors resistant to previously effective treatments, a phenomenon commonly called multi-drug resistance (MDR). This is another very common issue with docetaxel therapy. Cancer has become such a complex disease that a single drug or even a stand-alone molecularly targeted therapeutic agent may not suffice and has become the major limitation of anti-tumor clinical treatment.

Thymoquinone (THQ)', a bioactive principle of the *Nigella sativa* oil (commonly called as black cumin or kalonji), well known in Indian traditional system has shown to possess anti-cancer, antioxidant and anti-inflammatory properties. THQ can also protect against the toxicity caused by conventional chemotherapeutics. Considering the potential benefits of THQ, it was selected to be combined with docetaxel, however, the poor water solubility, the non-selective distribution in the human body and the inadequate accessibility to the tumor tissue, on intravenous administration of the two agents impedes their successful translation to the clinic.

Loading multiple drugs at the right ratio in an impeccable delivery system such as nanoparticles is an innovative approach to deliver the therapeutic agents to the site of action. The researchers worldwide are searching for the "magic bullet" (a concept proposed in medicine by Paul Ehrlich) to selectively target the cancerous cells with precision facilitating disease diagnosis and therapy. The lipid nanoparticles developed in the lab of Prof. (Dr) Farhan Jalees Ahmad explored the very approach of 'magic bullet' for targeting the breast cancer cells.

In order to improve breast cancer outcomes and survival, a combination therapy approach wherein two therapeutic agents with profound anti-cancer effects was simultaneously incorporated in a nanocarrier system for delivering the drugs in the right amount at the right place at the right time to obtain the maximum clinical therapeutic effect.

Optimization using statistical design was carried out for the development of chitosan-coated lipid nanoparticles. The spherical shape, the small particle size in the sub-micron range and the presence of two drugs in the developed nanoformulation were checked using several physicochemical characterization techniques. The nanometric size of the particles facilitated their

effective localization to the tumor cells while the chitosan coating on the surface of nanoparticles enhanced their uptake inside the tumor cells via CD44 receptors, which are highly expressed on the surface of breast cancer cells. This process is popularly known as active targeting approach for cancer treatment. The chitosan-coated nanoparticles could be degraded in the acidic microenvironment of the tumor and eventually accumulated in the interior of the cell producing the cytotoxic effect.

We further collaborated with the lab of Dr Angamuthu Selvapandiyan (Team Lead, JH Institute of Molecular Medicine, New Delhi) to evaluate the cytotoxic i.e. cell-killing effects of the developed nanocarrier system and the individual drugs in the breast cancer cell lines. We could observe enhanced cytotoxicity with the lipidic nanoparticles compared to individual drugs. This could be ascribed to the small particle size and the presence of chitosan on the surface of nanoparticles, which could facilitate the efficient delivery of nanoparticles to the cancer cells via passive and active targeting approaches, respectively. The presence of THQ helped to overcome the multi-drug resistance associated with the taxane therapy which leads to retention of docetaxel inside the tumor cells and hence produced the synergistic anti-cancer effects. We are now further studying how this system works in the real scenario using a tumor model.

Cancer is a complex series of fatal diseases, posing a huge health crisis on both the developed and developing countries. Researchers in Dr Farhan's Lab are constantly striving to bring about a better alternative for successful cancer treatment with the combination chemotherapy-nanotechnology approach that could play a pivotal role in the augmentation of therapeutic response in cancer. Combination therapy may increase the [patients'] chances to live longer, without cancer recurrence, and to live a better quality of life.