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# Delivering a Brand-new Triple Drug Combination over and over again for Improved Breast Cancer Treatment

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## Abstract

Although breast cancer is still a major worldwide health concern, new, promising therapeutic options are now available because to the development of carefully considered medication combinations and sophisticated biocompatible delivery methods. Based on the selective tumour apoptotic impact of Rosuvastatin (RST), we repurposed it here and coupled it with the antimetabolite pemetrexed (PMT) and the tumor-sensitizing polyphenol honokiol (HK). Inspired by the stealth feature of sodium alginate (ALG) and the cancer cell targeting ability of Lactoferrin (LF), this synergistic three-drug combination was combined into protein polysaccharide Nano hybrids. ALG was conjugated to PMT, combined with LF, which was conjugated to RST, and then inserted physically into core shell Nano hybrids made of genipin and LF.

The PMT-ALG/LF-RST Nano hybrids with cross-linked HK loading showed a reasonable drug loading of 7.86, 5.24, and 6.11% for RST, PMT, and HK, respectively. It showed improved cellular absorption by MCF-7 cells and an eight-fold reduction in IC50 when compared to the free drug combination. The advantage of the triple cocktail-loaded Nano hybrids was proven by their in vivo anticancer effectiveness in a breast cancer-bearing mice model. A potential, biocompatible method for efficient breast tumour suppression is provided by our rationally engineered triple drug-loaded protein/polysaccharide nano hybrids.

**Keywords:** Breast cancer treatment; Polysaccharide; Protein Nano hybrids; Sodium alginate; Lactoferrin (LF); Rosuvastatin (RST).

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## Introduction

After lung cancer, breast cancer is the second most prevalent cause of mortality in women. According to numerous sources, the number of new cases of breast cancer is expected to reach over 3.2 million by 2050. There are on-going, intensive efforts to create novel chemotherapeutics for clinical use. Traditional anticancer therapy is still a significant therapeutic concern, but novel approaches are currently being used to get beyond chemotherapy's fundamental drawbacks, which range from random bio distribution to systemic toxicity. Numerous delivery systems based on nanoparticles (NP) have been created in this area to deliver individual anticancer drugs or a combination of them. A successful method for chemotherapy treatment is the adoption of a combined strategy. Some Nano drug delivery systems have been created by fusing nanotechnology with multi-drug chemo sensitization in order to combat multi-drug resistance (MDR) and improve drug effectiveness against both drug-resistant and drug-sensitive cancer cells. A potent multidirectional antifolate cytotoxic chemotherapeutic medication used to treat cancer, including breast cancer, is pemetrexed (PMT). However, its poor therapeutic outcomes related to the difficulty to achieve adequate intracellular concentrations at the dose limits permitted, while raising the PMT dose results in systemic toxicity and MDR, limit the clinical benefits. Additionally, PMT has poor selectivity and bioavailability [1].

As a result, numerous attempts have been undertaken to increase PMT's anticancer activity, including pairing it with other chemotherapeutic drugs or phytomedicines, Additionally,

by combining medications with enhancer peptides or nanoformulations, several targeted drug delivery systems have increased the bioavailability of PMT and decreased side effects. One of the statins used to treat hypercholesterolemia is Rosuvastatin (RST). It works by inhibiting the mevalonate (MVA) pathway and suppressing -hydroxy -methylglutaryl-CoA (HMG-CO A) reductase. In addition to lowering cholesterol synthesis, it has been noted that suppressing the MVA pathway also causes specific tumour cell death events. Additionally, HK, an herbal extract made from the seeds of Magnolia grand flora, has drawn a lot of interest due to its beneficial anticancer properties[2].

According to the projected synergy between the three medications caused by their various molecular pathways, the combination of PMT, RST, and HK was suggested. In order to restore equilibrium, RST inhibits the MVA route, which causes the sterol regulatory element-binding protein 2 (SREBP2) to become activated. On the other side, HK has the ability to stop SREBP2 processing. As a result, HK improves RST's capacity to cause cancer cells to undergo apoptosis. RST may also work in concert with PMT's apoptotic effect to increase its cytotoxicity by blocking the Ras-Raf-1-MAPK signalling pathway. Additionally, as HK inhibits the P-glycoprotein efflux pumps to render drug-resistant tumour cells susceptible to chemotherapeutic agents, HK improves the effectiveness of PMT by reducing the occurrence of MDR [3].

A number of benefits come with the delivery of chemotherapeutics using Nano sized polymeric carriers, including effective drug loading, targeted release, and enhanced accumulation of medications in tumour cells, which decreases adverse effects, as well as improved circulation times and bioavailability. Protein- and polysaccharide-based NPs are among the most advantageous nanocarriers due to their biodegradability, biocompatibility, and simplicity of functionalization, low toxicity profiles, and improved bio distribution. Because natural proteins and polysaccharides include several reactive functional groups, such as carboxylic, thiol, and amino groups, they can be used in chemical coupling [4].

To avoid reticuloendothelial detection and subsequent removal, the NP shell needs to have stealth characteristics. This enables a passive build-up in the tumour cells. Polysaccharides, like sodium alginate (ALG), can give nanoparticles stealth characteristics and lessen the plasma protein adsorption. All varieties of brown algae contain alginic acid, a harmless, naturally occurring polymer, and ALG is its hydrophilic salt. ALG is also a biodegradable polymer that is widely used in the healthcare, food, and pharmaceutical sectors. ALG has been employed to prepare the sustained release delivery systems for a number of different medications, as reported in earlier investigations [5].

# Materials and Method

## Making Alginate/Lactoferrin Nano hybrids (ALG/LF NHs).F1

The carboxyl groups of the ALG and LF amino groups were used in a carbodiimide coupling procedure to create the Nano hybrids. In 7 mL of double-filtered, distilled water, 0.05 g of sodium alginate was dissolved. By adding in situ (0.01 g, 0.05 mmol) EDC for 5 minutes, the carboxylic acid groups of ALG were reactivated. For five minutes, the HCl and K. Oxyma (0.009 g, 0.05 mmol) at room temperature (RT) were constantly stirred. The reaction mixture received a drop wise addition of Lactoferrin (0.10 g, 0.00125 mmol) in an aqueous solution (5 mL). Overnight, the reaction mixture was stirred [6].

## Alginate/Lactoferrin-Rosuvastatin Nano hybrids with Honokiol Loaded (HK-Loaded ALG/LF-RST NHs) are made. F4

ALG, 0.05 g of sodium alginate, was dissolved in 7 mL of double-filtered, distilled water. The in situ addition of 0.009 g (0.05 mmol) of K. Oxyma and 0.01 g (0.05 mmol) of EDC was used to activate the carboxylic group of ALG. For five minutes, the HCl at RT was constantly stirred. The activated ALG solution was then gradually supplemented with the produced aqueous LF-RST conjugate solution. For 24 hours, the reaction was agitated at RT. To get the ALG/LF-RST NHS F3, the resulting Nano hybrids were dialyzed against double-filtered distilled water. The physical loading of HK into the core of the ALG-LF-RST NHs was done using the solvent evaporation method [7].

## Cross-linked PMT-ALG/LF-RST NHs: Physical and Chemical Characterization

To assess the physicochemical properties of the produced Nano hybrids, a variety of approaches have been used. DSC, HPLC, FT-IR, and 1H-NMR spectroscopy were used to investigate the loading and conjugation of medications. The zeta potential, particle size, and particle morphology were assessed using a Malvern Zetasizer, and the release of pharmaceuticals was examined using the dialysis membrane method and HPLC. The stability and dispensability of the produced Nano hybrids were also carefully examined. Also carried out as described were the lyophilization, redispersibility, physical stability tests, in vitro haemolysis, and serum stability [8].

## Creation of Cross-linked PMT-ALG/LF-RST NHs Loaded with HK

HK was physically loaded inside the hydrophobic core of the PMT-ALG/LF-RST NHs via a straightforward solvent evaporation method as opposed to PMT and RST, which were covalently attached to the ALG-LF backbone. There may be a wealth of co-acting intermolecular interactions between the carrier material and the drug in the loading process, such as van der Waal forces, hydrophobic interactions, and hydrogen bonds. Effective HK loading and stabilisation of Nano hybrids can be influenced by each of these forces. Finally, it appears that using genipin to crosslink the polymeric Nano hybrids will improve their structural stability and guard against premature disintegration and rapid drug release. This work showed that the size of the monohybrid and the drug release profile were significantly reduced by genipin, which also successfully cross-linked the amine groups of LF. A vivid blue hue was produced by the genipin crosslinking process. As a result of the Nano hybrids being more compact and dense after crosslinking, the particle size significantly dropped from 389 nm to 258.7 nm. ALG-LF Nano hybrids were cross-linked using various concentrations of genipin during our initial research [9, 10].

## Discussion

In order to administer a combination of weakly soluble RST and HK and highly soluble PMT anticancer medications for a targeted breast cancer treatment, cross-linked HK-loaded PMT-ALG/LF-RST NHS F10 was developed. Through a carbodiimide conjugation procedure, the PMT and RST medicines were joined to the ALG and LF polymers, respectively, to create an ester bond between ALG and PMT and an amide bond between LF and RST. To prevent systemic side effects, the medications' leakage when injected into the blood stream was stopped since the conjugation of the drugs sustained an in vitro release. By physically packing the hydrophobic drug HK inside the hydrophobic core of the NHs, the hydrophobic drug's release pattern was improved. To increase the stability of the NH structure, maintain drug release, and prevent early disintegration, genipin was used to crosslink the NHs. The cross-linked HK/PMT-ALG/LF-RST NHS F10 demonstrated excellent serum stability and hemocompatibility, a narrow PDI, an adequate size, an enhanced negative zeta potential, and a high percentage drug loading of PMT, RST, and HK [11].

Additionally, cross-linked HK/PMT-ALG/LF-RST NHS F10 demonstrated higher cytotoxicity and improved cellular absorption into the MCF-7 breast cancer cell line. Cross-linked HK/PMT-ALG/LF-RST NHS F10 decreased tumour size in vivo by preventing ki-67 and VEGF-1 expression levels, which could stop tumour growth. Additionally, the expression of active caspase-3 was increased, and the cross-linked HK/PMT-ALG/LF-RST NHS F10 was successful in inducing apoptosis in the tumour tissue of EAT-bearing mice. Cross-linked HK/PMT-ALG/LF-RST NHS F10 is a promising nanocarrier for a focused cancer treatment, according to our findings [12].

## Conclusion

The current study has demonstrated that proteome analysis is an effective method for characterising phosphorylation patterns and may contribute to a better understanding of TNBC cells that are resistant to treatment. According to our findings, resistant TNBC cells had selectively active PML, AP-1, and HSF-1, which may have encouraged the activation of vimentin and other downstream signals. Our research also provided evidence that Cdk5 might encourage vimentin and LMNB1 activation, which would boost EMT in the resistant TNBC cells. We also discuss the potential contributions of EGFR and HGF to the promotion of TNBC's MDR phenotype (multiple drug resistance). We have discovered a number of signalling pathways that might cooperate to cause treatment resistance in TNBC.

## Conflict of Interest

None

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None

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