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Biodegradable nanoparticulate co-delivery of flavonoid and doxorubicin: Mechanistic exploration and evaluation of anticancer effect *in vitro* and *in vivo*

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ABSTRACT

The proposed study involves delivering drug/bioactive using a single nanoplatform based on poly lactic-co-glycolic acid (PLGA) for better efficacy, synergistic effect, and reduced toxicity. PLGA was conjugated to doxorubicin (D1), and this conjugate was used for encapsulation of naringenin (D2) to develop naringenin loaded PLGA-doxorubicin nanoparticles (PDNG). The PDNG NPs were 165.4 ± 4.27 nm in size, having 0.112 ± 0.035 PDI, with -10.1 ± 2.74 zeta potential. The surface morphology was confirmed through transmission electron microscopy (TEM) and atomic force microscopy (AFM). The *in vitro* studies revealed that PDNG NPs exhibited selective anticancer potential in breast cancer cells, and induced apoptosis with S-phase inhibition *via* an increase in intrinsic reactive oxygen species (ROS) and altering the mitochondrial potential. The results also signified the efficient uptake of nanoparticles encapsulated drugs by cells besides elevating the caspase level suggesting programmed cell death induction upon treatment. *In vivo* studies results revealed better half-life (27.35 ± 1.58 and 11.98 ± 1.21 h for doxorubicin and naringenin) with higher plasma drug concentration. *In vivo* biodistribution study was also in accordance with the *in vitro* studies and in line with the *in vivo* pharmacokinetic. *In vivo* tumor regression assay portrayed that the formulation PDNG halts the tumor growth and lessen the tumor volume with the stable bodyweight of the mice. Conclusively, the dual delivery approach was beneficial and highly effective against tumor-induced mice.

1. Introduction

Breast cancer is one of the dreadful forms of cancers among women worldwide. The occurrence of this dangerous disease is increasing day by day, which is an alarming sign [1]. There are various factors which are engaged in the expansion of breast cancer. The reason behind the development of breast cancer is abnormalities in genetics and epigenetics. The most common factors related to the causes of breast cancer are the origin of cells, different molecular alterations, and diversity of patient background, including day to day routine. The overexpression of HER2 receptor causes the majority of breast cancer (20 to 30%) [2]. There are numerous types of traditional treatment protocols for breast cancer, including surgery, chemotherapy, and radiotherapy [3]. The various chemotherapies are approved for the management of breast cancer such as doxorubicin, cyclophosphamide, paclitaxel, docetaxel, tamoxifen etc. [4]. However, chemotherapy is associated with many side effects as well as drug resistance issues, which is a significant hurdle for the beneficial treatment regimen [5]. Combination therapy have many advantages such as enhanced synergistic effects and reducing drug resistance, compared to monotherapy.

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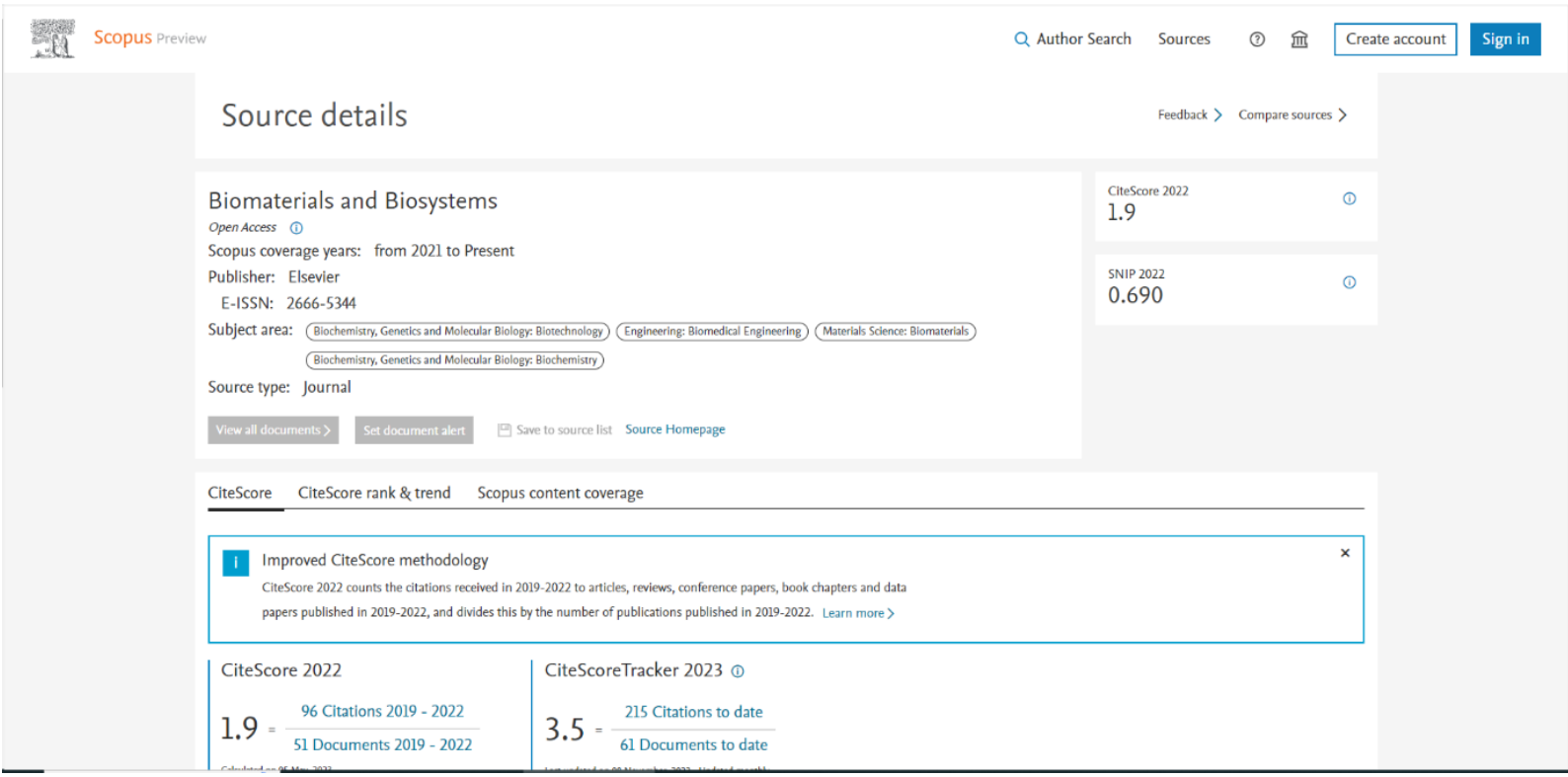
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