APIGENIN AND ITS NANO-LIPOSOMAL FORMULATION FOR COLORECTAL CANCER AND BACTERIAL CHEMOTHERAPY

Abstract: Recent emergence of drug-resistant cancer and bacterial strains has raised the alarming prospect of increased mortality and morbidity of humans. Thus, an opportunity to evaluate new agents for potential chemotherapeutic applications and development of novel formulations to effectively deliver therapeutic molecules arises. In order to unearth new agents with attractive pharmaceutical and therapeutic potential, phytochemical screening efforts have been recently intensified. This has yielded numerous plant-based bioactive compounds with therapeutic and preventive activities against different diseases. Apigenin is a bioactive natural flavone which has been recently reported to possess attractive chemical and biological properties however, a detailed understanding of the mechanisms by which apigenin acts at molecular level is of critical importance, which has still not been explored and deciphered in details. Hence, the present study attempted to unravel the molecular mechanism of the bioactivity of apigenin and subsequently devise a strategy to enhance its therapeutic potential through the use of nanotechnology. The poor aqueous solubility of apigenin limits its direct application as a potential chemotherapeutic agent which was overcome through the use of lipid-based nanocarrier, which effectively encapsulated the molecule. Dual-drug loaded liposomes are the current 'workhorses' in second generation nanomedicines that aim to simultaneously co-deliver therapeutic agents to achieve significantly increased anticancer activity along with reduced associated side effects. Sub-optimal response of conventional antibiotics against drug-resistant strains and their poor cellular accumulation has led to concerted efforts to identify newer agents and delivery systems to circumvent these problems The present study has thus endeavored to i) probe the chemotherapeutic potential of apigenin and its nano-liposomal formulation in colorectal cancer chemotherapy ii) evaluate the pro-oxidative effects triggered by apigenin in human colorectal cancer cells iii) develop and characterize dual drug loaded liposomes bearing Apigenin and 5-Fluorouracil (5-FU) and evaluate its therapeutic potential in colorectal cancer treatment and iv) probe the potential of apigenin liposomes in enhancing bacterial membrane perturbation and integrity loss. Apigenin was observed to induce rapid free radical species generation. Persistent oxidative stress at growth suppressive doses over extended treatment time period resulted in senescence. Senescence phenotype inducted by apigenin was attributed to changes in key molecules involved in p16-Rb and p53 independent p21 signaling pathways. Apigenin-based liposomes demonstrating enhanced stability and cytocompatibility against normal cell lines, displayed excellent chemotherapeutic properties against colorectal cancer both *in vitro* and *in vivo* compared to free drug. Apigenin mediated DNA damage activated ataxia telangiectasia mutated (ATM), triggering p53-dependent G_2/M checkpoint arrest response, which led to the decrease in cyclin B1. Combinatorial index calculation yielded synergistic activity of apigenin with 5-FU, that facilitated the development of a single liposomal nanocarrier for a viable combinatorial drug therapeutic regimen to effectively combat colorectal cancer. The underlying mechanism for the enhanced anti-neoplastic activity of the dual-drug loaded liposome was unravelled and assigned to the reversal of Warburg effect. The broad spectrum antibacterial activity of apigenin was detected and further potentiated through the use of liposomes, which induced membrane perturbation through enhanced reactive oxygen species generation ultimately resulting in bacterial lysis. Thus, apigenin and its liposomal formulation provide a new paradigm for the next generation of pharmaceuticals, and offer a suitable platform for future development of flavonoid-based chemotherapeutic formulations.