Ergosterol and Its Metabolites as Liver X Receptor Agonists: Exploring Their Anticancer Potential in Colorectal Cancer Through Experimental Models and Molecular Mechanisms.

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Colorectal cancer (CRC) is the third most diagnosed and second deadliest cancer globally. Aberrant cholesterol homeostasis drives metastasis and chemotherapeutic resistance, key causes of cancer-associated mortality. Liver X receptors (LXRs) are one of the key transcription factors that regulate cholesterol efflux. We investigated the potential of novel sterols: ergosterol (Erg), ergosta-7,22,24(28)-trien-3β-ol (Erg1), ergosta-5,22,25-trien-3-ol (Erg2), ergosta-5,7,22,24(28)-tetraen-3β-ol (Erg3), and ergosta-7,22-dien-3β-ol (Erg4) as LXR agonists. Molecular docking and dynamics studies revealed that these sterols exhibit higher binding affinity and stability with LXRs than its artificial agonists. Functional assays showed that Erg and Erg2 significantly activated LXRs, with EC50 values of 5.64 and 4.83μM respectively, ultimately enhancing the mRNA expression of NR1H2, ABCA1, ABCG1, and ApoE. Flow cytometry also confirmed ABCA1 accumulation upon Erg treatment, indicating the induction of cholesterol efflux. Given the critical role of cholesterol metabolism in CRC, we further explored the anticancer potential of Erg and Erg2. In HCT116 cells, they induced late-stage apoptosis by upregulating Bax and CD95 while downregulating Bcl-2. They also suppressed cell proliferation by reducing the protein expression of cyclin D1, Ras, and MEK1/2 and inhibiting PI3K phosphorylation. Additionally, they impaired metastasis by decreasing SW620 and HCT116 cell migration and downregulating MMP2 and MMP9 protein levels. The chemo-preventive potential of ergosterol was validated in a DMH+DSS-induced CRC model, where it significantly reduced tumor burden, Ki-67 expression, and cancer-like features in colonic mucosa. Ergosterol also induced apoptosis and suppressed β-catenin and PI3K/Akt signaling while promoting cholesterol efflux. Conclusively, these findings highlight ergosterol as a potent LXR agonist with selective anticancer activity, mediated through its pleiotropic mode of action.

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