ABSTRACT

Estrogens are key regulators of human reproductive physiology acting through estrogen receptors (ERs). In humans there are two major estrogen receptor subtypes, and they are estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). Xenoestrogens are non-endogenous compounds having pharmacophoric features similar to that of estrogen, can bind to cellular ERs and cause agonistic or antagonistic outcomes. Many of the xenoestrogens are useful as therapeutic agents for conditions such as hormone replacement therapy, menopausal symptoms, cancers of the breast, ovary and prostate, etc.

Isoflavones (IFs) and deoxybenzoins (DOBs) are related class of compounds, having some affinity for ERs and thereby exhibiting estrogenic effects in mammalian cells. Some of the IFs and DOBs are potentially therapeutic for conditions such as prostate cancer and breast cancer. This study was aimed at designing some novel IFs and derivatives DOBs and evaluating their estrogenic potential. Of particular interest was to investigate the ability of these novel compounds to modulate the proliferation of human prostate cancer cells and breast cancer cells.
The positions and the substitutions to the isoflavone and deoxybenzoin scaffolds were determined by exploring the interaction of several ligands with the ligand binding domain of the ERs. Eight substituted IFs and three DOBs were designed and were computationally assessed for their ability to bind with the estrogen receptors. It was found from these studies that, except for one of the IF, the other compounds were potential ligands for the estrogen receptors.

The designed compounds (eight IFs and three DOBs) were synthesized and evaluated for their effect on the growth of human prostate cancer cells (PC3) and human breast cancer cells (MCF7). It was found that the DOBs stimulated proliferation of MCF7 while in PC3 they induced apoptosis. Among the IFs, one (CMPD1) stimulated proliferation of MCF7 cells but showing no significant effect on PC3 cells. Another IF (CMPD7) induced significant apoptosis in PC3 cells while showing no apparent effect on MCF7 cells. The other IFs had weak or no effect on the growth of both PC3 and MCF7 cells. It was also found that these active compounds were less potent in their effect, when compared to effects caused by estradiol or genistein on MCF7 and PC3 cells respectively.

To test whether the active compounds mediated their cellular effects through the ERs, Hep2 cells (human laryngeal carcinoma cell line) were transfected with vectors carrying either ERα or ERβ gene along with an ER dependent luciferase reporter vector (3xERE-TATA-luc). These cells
were treated with the test compounds and the level of induced luciferase activity was determined, as a measure of the ER agonist action of the compounds. It was found that the active compounds (DOB, CMPD1 and CMPD7) were able to induce expression of luciferase reporter gene. The other compounds showed no significant transcriptional activation of the reporter gene. This study also showed that the agonist action of DOB were not ER subtype specific, CMPD1 was ERα specific and CMPD7 was ERβ specific.

Since the compounds appeared to work through the ERs, the estrogenic effects on the cells were studied by analyzing the expression of estrogen induced genes – TFF1 and CTSD. It was found that the active compounds (DOB, CMPD1 and CMPD7), were able to induce the upregulation of these two genes in MCF7 and PC3, further confirming the estrogenic effects of IFs and DOB. However, in response to the other DOB (CMPD2, CMPD4, CMPD5, CMPD8, CMPD10, CMPD11), there was negligible stimulation of these genes in both MCF7 and PC3.

Taken together, these results showed that the isoflavone and deoxybenzoin can be derivatized to produce molecules which can act as agonists of estrogens and thereby alter the proliferation of estrogen dependent cell types such as cells of prostate and breast. The therapeutic potential of these compounds have the potentiality for management of cancers of prostate and breast, needs to be explored further.