INTRODUCTION
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Hormone imbalance associated diseases can originate purely as a disorder of a gland or as a consequence of changing hormonal status of an organ due to factors such as age and environmental influences (Prajapati et al., 2013). In this study, the focus was on benign prostate hyperplasia (BPH) and prostate cancer (PC). The etiology of both pathologies is not well defined; however it is irrefutable that variations in the hormonal status of the prostate are involved (Miah and Catto, 2014). Both of these diseases are extremely common in aging males; almost 90% of the men develop either BPH or PC between their fourth and ninth decades of life (Madersbacher, 2001). Despite their high prevalence, current medical care is unable to eradicate or completely cure BPH and PC, at least for a subset of patients. With the unprecedented ageing population, there is a demand for more novel forms of treatment strategy or perhaps a shift to preventive medicine. Plants are and hopefully will remain an essential source of therapeutic agents (Chughtai and Te, 2013). They are being used to isolate bioactive compounds for direct use as drugs (e.g. diterpenes, digoxin, morphine, taxol) and for producing bioactive compounds of novel or known structures as lead compounds (e.g. metformin and verapamil are based on natural compounds galegine and khellin respectively). Furthermore, since phytotherapy is becoming more popular amongst patients, plant-based medicine may have better patient acquiescence compared to synthetic drugs.

In aging men, decline in testicular function coincides with an increase in aromatization of adrenal androgens to estrogens in peripheral adipose tissues, resulting in a significant increase in estrogen to androgen ratio. This endocrine disorder associated with ‘andropause’ in males almost exponentially increases the risk of benign prostatic hyperplasia (BPH) and prostate cancer (Hafez and Hafez, 2004). Estrogenic stimulation with decreasing androgenic support contributes significantly to the genesis of BPH, prostate dysplasia, and prostate cancer (Steiner and Raghow, 2003). Approximately half of the human male population aged >50
Investigation of novel synthetic molecules and natural products for prostatic hyperplasia

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Introduction

years present histological evidences of BPH, while prostate cancer is amongst the most common male cancers (Wang et al., 2008; Mukherji et al., 2013) (Montie and Pienta, 1994). Prostatic enlargement associated with bladder obstruction is generally the end result of dysfunctional growth regulatory mechanisms within the gland that can result in the development of a benign stromal adenoma. Histological studies have shown that hyperplasia results from an increase of the epithelial and stromal components of the prostate (Rohr and Bartsch, 1980; Shapiro et al., 1992). Prostatic Cancer (PCa) is a leading cause of cancer-deaths in men (Stewart et al., 2005; MacRae et al., 2006). With an increase in the average life span of human beings, the number of patients with prostatic diseases has increased considerably over the years. However, existing methods of management are either highly invasive, e.g. surgical prostectomy (Carbone and Hodges, 2003) and/or partially effective with undesirable side effects, e.g. medical therapy with 5α-reductase inhibitors or α-adrenergic receptor blockers (Hirsch et al., 1993), and therefore new treatment strategies are required to be discovered that are more effective and safer. There is a growing body of evidence to suggest that estrogen signaling plays a significant role in normal and abnormal growth of the prostate gland (Ho, 2004; Risbridger et al., 2007; Singh et al., 2008). Estrogen executes signaling via binding with estrogen receptor (ERs), which are members of a nuclear receptor superfamily of ligand-activated transcription factors (Hobisch et al., 1997). Estrogen signaling mediated by the estrogen receptor beta (ER-β) has potential implications in normal and abnormal prostatic growth. The continuous expression of the receptor protein at significant levels in untreated primary and metastatic adenocarcinoma indicates that these tumors can use estrogens through ER-mediated pathways. The partial loss of the ER-β in recurrent tumors after androgen-deprivation may reflect the androgen dependence of ER-β gene expression in human prostate cancer (Fixemer et al., 2003). Signaling pathways involving ER-β, which govern whether prostate carcinoma cells maintain an epithelial phenotype or undergo epithelial-
mesenchymal transition, suggest that ER-β can have prognostic or therapeutic significance (Loda and Kaelin, 2010).

Thus, future strategy should include agents that could simultaneously target multiple pathways involved in the pathogenesis of prostatic hyperplasia and prostate cancer. Novel therapeutic agents specifically targeting the inhibition of ER as well as growth factor receptors and events within the signal transduction pathways constitute an ideal approach for the treatment of prostatic hyperplasia and prostate cancer in patients. In an endeavor to discover better therapeutic agents, we targeted the androgen receptor (AR); the estrogen receptor (ER); and Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling using novel designed and synthesized molecules as well as natural compounds isolated from plants, as drug candidates. To that end, we screened a series of isolated natural compounds and rationally designed novel compounds against prostatic hyperplasia and prostate cancer cells, evaluated the efficacy of the lead molecules and finally validated their molecular targets. The study has been divided into three chapters:

- Labda-8(17),12,14-trien-19-oic acid contained in fruits of Cupressus sempervirens suppresses benign prostatic hyperplasia in rat and in vitro human models through inhibition of androgen and STAT-3 signaling.
- Designed modulation of androgen and estrogen signaling inhibits telomerase activity and proliferation of human prostate cancer cells
- Anti-BPH effects of synthetic, multi sex-steroid receptor modulator DIMA in the rat model