The high prevalence of hypertension in elderly women is associated with aging and the loss of endogenous estrogen production after menopause (Barton and Meyer, 2009). Engelgau et al. (2011) reported that in India, the number of hypertensives will rise from 118.2 million in 2000 to 213.5 million by 2025. The prevalence of hypertension is 25 per cent in urban and 10 per cent in rural population. 5-15 per cent of urban and 2-5 per cent of rural population in India are diabetic.

Consistently high blood pressure even at resting state is a characteristic feature of hypertension (high blood pressure) and occurs when the walls of the larger arteries become rigid due to loss of elasticity leading to less lumen space for blood flow and increase in the fluid pressure. Aging is accompanied by narrowing of blood vessels thereby increasing the incidence of hypertension (Ahmed and Muguruma, 2010).

Hypertension is often undiagnosed or inadequately treated, especially in women when the incidence of cardiovascular complications increases after menopause. Aging, physical inactivity, obesity and dietary salt consumption are important factors contributing to and exacerbating postmenopausal hypertension. Endogenous estrogens in premenopausal women mediate vasodilation and maintain normal blood pressure (Barton and Meyer, 2009). Blood pressure levels are inversely related to circulating estrogen concentrations and this was found to be responsible for the vasodilator activity of endogenous 17β-estradiol (Meyer et al., 2006).

Estrogens are the natural female steroid hormones with various physiological actions. In the cells, estrogens can act as pro-oxidants and induce oxidative stress through reactive oxygen species (ROS) generation. On the other hand, estrogens can also function just the opposite way, as antioxidants by
inhibition of ROS generation or neutralization of excess ROS. Both these pro-oxidative and antioxidative actions of estrogens are mediated through estrogen receptors (Kumar et al., 2010). Pro-oxidants are highly toxic to all types of biomolecules including DNA, proteins, lipids and carbohydrates and are scavenged by various antioxidants. Disturbances in pro-oxidants and antioxidants homeostasis lead to oxidative stress (Tuladhar and Rao, 2010).

Oxygen free radicals, also known as reactive oxygen species (ROS), as well as reactive nitrogen species (RNS), are products of normal cellular metabolism. Both ROS and RNS can be either harmful or beneficial to living systems since they play a two fold role as deleterious and beneficial species (Valko et al., 2006). Oxidative stress promotes cell growth, extracellular matrix protein deposition, endothelial dysfunction and increased vascular tone, thus contributing to vascular damage in hypertension (Paravicini and Touyz, 2008). Through a variety of mechanisms oxidative stress may contribute to the generation and perseverance of hypertension. Superoxides are capable of quenching nitric oxide, thereby impairing vasodilation. Reactive oxygen species promote the generation of lipid peroxidation products, which are potent vasoconstrictors resulting in hypertension (Grossman, 2008).

It is still not clear what comes first, the chicken or the egg, that is whether uncontrolled formation of ROS is a primary cause or a consequence of pathological processes still remains a question (El-ghoroury et al., 2009, Schaffer et al., 2009). Increased oxidative stress is the major triggering factor for hyperglycemia-induced diabetic complications and in any individual hyperglycemic condition stimulates ROS formation from a variety of sources. These sources include glucose autooxidation, oxidative phosphorylation, lipoxygenase, NADPH oxidase, cytochrome P450 monooxygenases and nitric oxide synthase (NOS) (Valko et al., 2007). The loss of endogenous estrogen was found to cause impaired renal sodium handling, oxidative stress and hypertension, due to reduced nitric oxide bioavailability and increased angiotensin II activity, further leading to renal dysfunction (Schulman and Raij, 2006).
The accumulation of ROS in the body leads to oxidative stress, which is involved in a variety of pathological processes including cancer, cardiovascular diseases, neurodegenerative disorders and aging. In developed countries cardiovascular disease, characterised by atherosclerosis and hypertension, is one of the leading causes of death. Oxidative modification of lipids, proteins and nucleic acids in the vascular wall contributes to the etiology of certain diseases, including atherosclerosis, whereas removing or reducing these modifications could minimize the development of atherosclerosis. Our body is equipped with natural antioxidant defense system consisting of a series of antioxidant enzymes (catalase, superoxide dismutase and glutathione peroxidase), numerous endogenous antioxidant molecules (glutathione and cysteine) and antioxidant supplements (vitamins C and E). Antioxidants can also be obtained from diet consisting of fruits, vegetables, green tea and chocolates (Cherubini et al., 2005 and Suzuki, 2009).

Estrogens regulate post-transcriptional stability of RNA and post-translational modification of proteins, influencing expression profile and cellular phenotype (Miller and Duckles, 2008). The vascular effects of estrogen vary with the different stages of reproductive life and the time since menopause and may also affect the progression of subclinical or overt atherosclerosis (Meyer et al., 2008).

The increased incidence of obesity and associated complications such as type 2 diabetes and cardiovascular diseases has driven particular attention on the role of nuclear receptors in the pathophysiology and treatment of metabolic syndrome (Sonoda et al., 2008). Estrogens such as estradiol, estrone and estriol are a family of naturally-occurring compounds that are biochemically related, but are structurally different and vary in terms of circulating concentrations, potency, physiological activity and affinity for the various estrogen receptor subtypes (Curtis, 2009).

Estrogens mediate their action via estrogen receptors, Estrogen Receptor α (ERα) and Estrogen Receptor β (ERβ) (Deroo and Korach, 2006 and Koehler...
et al., 2005). There is sufficient evidence that 17β-estradiol (E2) directly modulates the development and function of immune cells, even though its mechanism of action is not sure (Bouman et al., 2005; Karpuzoglu and Zouali, 2011).

The continual aging of world population and the outbreak of adverse lifestyle-associated diseases, carry a high risk of cardiovascular outcome, which will consecutively increase the global burden of non-communicable diseases (Shaw et al., 2006 and Merz et al., 2006).

Since estrogen mediates its action through its interaction with estrogen receptors, the analysis of the estrogen receptor and estrogen receptor expression in peripheral blood lymphocytes may provide a useful tool in understanding the responsiveness of these cells to estrogens (Pierdominici et al., 2010).

The adverse effects of estrogen deficiency in postmenopausal women can be alleviated with estrogen therapy. Despite the beneficial effects of estrogen therapy on menopausal symptoms, it can increase the risk for breast and uterine cancers. This has led to the need for drugs that exert their action through estrogen receptors in a tissue-selective manner and are known as selective estrogen receptor modulators (SERMs) (Hall and McDonnell, 2008).

Recently several comparative docking studies were performed on estrogen receptor α and estrogen receptor β in order to develop novel compounds with improved receptor binding (Desai et al., 2012 and Yang et al., 2009). Molecular docking is an efficient technique in in-silico drug design and structural molecular biology (Ratnavali et al., 2011). Molecular docking studies provide information regarding protein-ligand interaction and predict the best binding modes of the ligand with the receptor (Sushma and Suresh, 2012).

Studies on estrogen receptor status among hypertensive postmenopausal women are scarce. It is a known fact that estrogen levels decline with menopause. Whether this decline is in accordance with estrogen receptor levels and associated co-morbidities need to be elucidated. Hence it is decisive to assess estrogen and
estrogen receptor status in hypertensive postmenopausal women with clinical complications. Identification of knowledge gaps:

1. No comparative studies were reported in postmenopausal women with and without co-morbidities (hypertension, diabetes and renal insufficiency).
2. In majority of the studies premenopausal women served as the control group.
3. *In silico* docking studies were not performed by comparing the three ligands namely raloxifene, LY 117018 and 2,3 dihydraloxifene.

**Need for the study**

1. Identification of a single or a battery of biochemical parameters may be equated to the estrogen status in postmenopausal condition. Suitable biochemical parameters can be used as substitutes to estrogen assay through correlation studies.
2. Estrogen therapy in postmenopausal condition increases the risk for breast and uterine cancers. This has led to the development of drugs known as Selective Estrogen Receptor Modulators (SERMs) that exert their action through estrogen receptors. Hence *in silico* docking studies were attempted for the development of innovative therapeutics for the treatment of postmenopausal hypertension and related co-morbidities.

**Objectives of the study**

**Main Objective**

1. To assess the estradiol and estrogen receptor status among selected hypertensive postmenopausal women with co-morbidities.

**Specific Objectives:**

2. To assess the correlation between estradiol and oxidative stress associated clinical complications.
3. To identify drug targets by docking studies on estrogen receptors which may provide novel treatment strategies in hypertensive postmenopausal women with co-morbidities.
Hence, the present study was carried out in four groups of postmenopausal women namely normotensive postmenopausal women, hypertensive postmenopausal women, hypertensive postmenopausal women with diabetes and hypertensive postmenopausal women with renal insufficiency. Normotensive postmenopausal group served as the control. Biochemical estimations were performed to identify hypertensive patients with clinical complications. Selected biomarkers and oxidative stress markers were assessed in their serum and plasma. The extent of DNA damage was assessed from comet assay indices in the participants. Estradiol and estrogen receptor α and β status were assessed in selected hypertensive postmenopausal women with co-morbidities. Correlation analysis was performed between estradiol and the selected biomarkers. Docking studies were performed on estrogen receptor α (ERα) to identify drug targets which may help in the development of novel therapeutic strategies for the treatment of postmenopausal hypertension with associated co-morbidities. Three ligands namely raloxifene, LY-117018 and 2,3-dihydroraloxifene were selected and docked with estrogen receptor α.