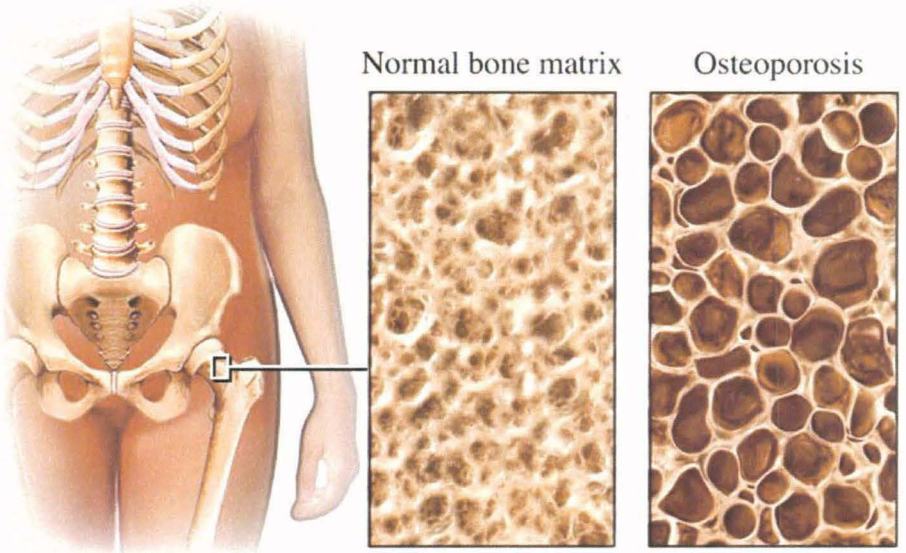
Chapter I: Introduction



Under current conditions, as more persons in the population live to elderly, the projected increase in longevity will inevitability be accompanied by an increase in a demographic shift in population towards a more aged society with the prevalence of osteoporosis and its associated complications. Osteoporosis is now a major public health threat, and its prevalence is expected to rise dramatically in the coming decades. The number of osteoporotic fracture worldwide by the year 2025 is expected to be ~2.78 million in women and ~1.16 millions in men [1]. According to estimates, there are about 50 million people with osteoporosis in India and the number will increase by 50% in coming 10 years [2].

The skeleton is a unique tissue providing support and mineral balance for the vertebrates. It is formed during growth and is maintained during adult life by continuous renewal of the matrix by the coupling of bone resorbing osteoclasts and new matrix synthesizing osteoblasts, a process called bone remodeling. During growth, bone formation exceeds bone resorption, resulting in bone expansion. In adults, a balance between bone resorption and bone formation maintains bone mass. With aging and/or after the menopause, an increased bone resorption relative to formation results in net bone loss. This may lead to osteoporosis, a common skeletal disease characterized by reduced bone mass, deterioration of bone microarchitecture, and increased susceptibility to fractures [3].

Given the fact that estrogen deficiency results in excessive bone resorption relative to bone formation, pharmacological interventions that decrease bone resorption are efficient at treating osteoporosis [4]. Estrogen replacement therapy (ERT) is undoubtedly the most effective in preventing post-menopausal bone loss. However, Many postmenopausal women are looking for alternatives to hormone replacement therapy, especially in light of the research findings in 2003 from the Women's Health Initiative showing several contraindications in women taking ERT

such as increased risk of breast and uterine cancers [5, 6]. Maintenance of calcium (Ca) and vitamin D levels in the body may not be an efficient prophylactic after menopause if the acquisition of peak bone mass is inadequate [7]. Selective estrogen receptor modulators (SERMs) such as raloxifene are effective only in reducing the risk of vertebral fracture. The other available antiresorptive agents such as calcitonin and bisphosphonates, too, are either not totally devoid of health hazards or are unacceptable due to their parenteral route of administration, high cost or both. Denosumab®, a fully human monoclonal antibody to RANKL that blocks its binding to the receptor activated nuclear factor-κB and hence osteoclast differentiation, was recently shown to reduce the risk of fractures in women with osteoporosis[8]. Although efficient at decreasing bone turnover rate, the long-term use of antiresorptives however results in compromised bone quality.

Since age-related bone loss is associated with insufficient bone formation relative to bone resorption, an alternate therapy is to promote bone formation. A major step forward in this field was the finding that, in contrast to continuous treatment, intermittent parathyroid hormone (PTH) increases bone formation in osteoporotic patients [9]. The increased bone formation induced by PTH (1-34) or (1-84) results in increased trabecular bone mass and cortical thickness, leading to a marked reduction in fracture risk in osteoporotic patients [9, 10]. This finding emphasizes the point that anabolic treatments may be more effective than antiresorptive drugs in the maintenance of bone quality and mass in osteoporosis. Although the development of intermittent PTH as an anabolic agent is a major advance in the treatment of osteoporosis, this treatment has some following limitations; (a) development of hypercalcemia and hypercalciuria, (b) risk of osteosarcoma and theoretical possibility of nonosseous cancer induction during PTH therapy [11], (c) high cost and (d) mode of administration (daily injections).

Thus, there is a need to develop efficient and safe drugs that are able to promote bone formation in osteoporosis. For more than a decade, there is a growing interest in assessing the role of plants and plant-derived compounds in the prevention and treatment of postmenopausal osteoporosis [12]. Many bioactive compounds have been discovered from plants which show anabolic properties with beneficial outcomes in postmenopausal osteoporosis [13]. India has a rich body of ethano-traditional knowledge that is used for medicinal purpose by the majority Indians [14].

Ulmus wallichiana is such a plant having ethno-medicinal use in the Kummaon and Garhwal regions of Western Himalayan part of India for rapid fracture healing [15][16], but has never been formally investigated. As healing of fracture involves new bone formation at the fracture site, we reasoned that the constituents of the plant extract might possess bone forming activity. The present study was designed for:

1. Evaluation of natural products for bone forming activity using osteoblast cell cultures derived from immature rat calvaria and bone marrow cells (BMCs).
2. Evaluation of anti-osteoporosis activity of natural product(s) showing promising bone forming activity *in vivo* following prolonged oral treatment using bilaterally overiectomized rat model. Various parameters such as bone mineral density, bone histomorphometry and biochemical markers of bone turnover will be evaluated.
3. *Ex vivo* evaluation of the production of osteoprogenitor cells in bone marrow of treated and control rats by determining the formation of mineralized nodules by BMCs.
4. Determination of estrogenicity and anti-estrogenicity profiles of promising agents *in vitro* and *in vivo*. In view of the reported contra-indications of estrogen replacement in postmenopausal women, only the agents showing no or negligible estrogenic activity in our test systems would be identified for detailed evaluation.
5. Study anabolic action of test agent(s) and natural products using gene expression markers of bone formation in osteoblast cells and define molecular basis for their actions.