Executive Summary

Osteoporosis is a silent progressive skeletal disorder mainly characterized by low mineral density, microarchitectural deterioration and increased fracture risk. According to the World Health Organization (WHO), Osteoporosis has been considered as a major global public health problem secondary to coronary heart disease affecting millions of people worldwide, irrespective of race, ethnic group or age. It majorly affects postmenopausal women and elderly people. The prevalence of the disease was estimated to affect approximately 200 million people worldwide with attendant costs exceeding 10 billion dollars per annum. Hormone replacement therapy has been effectively utilized to treat postmenopausal osteoporosis. But, long term usage of HRT and other antiresorptive or anabolic agents are associated with serious side effects. Therefore, the usages of alternate medicines such as herbals are accentuated to minimize or substitute these drugs.

Lack of scientific data for potential use in bone loss and related adverse side effects of current antiosteoporotic drugs led us to investigate the effects of ethanol and aqueous extract of *Sesbania grandiflora* for osteoporosis in different experimental models. Usages of products from plant origin are now being the alternative approach for the prevention and treatment of osteoporosis. But, a secondary concern is uterine endometrial hyperplasia, or excessive cell growth in the uterus, which may occasionally lead to precancerous stage after long term treatment. Therefore osteoporosis study should be monitored for participants for endometrial hyperplasia.

*Sesbania grandiflora* is an Ayurvedic plant, traditionally employed to treat or prevent female related hormonal disorders and mitigating symptoms of menopausal conditions. Therefore, *S.grandiflora* leaf extracts were studied to determine the antiosteoporotic activity and the prenatal exposure of the extracts on the bone mass in adult offspring. Postmenopausal osteoporosis in ovariectomized female rats was mimicked as estrogen deficiency in humans leading to osteopenia, confirmed by heavy bone loss. Steroid induced osteoporotic model in both male and female showed similar clinical signs as in humans.

The ethanolic and aqueous extracts of *S. grandiflora* leaves were prepared by Soxhlet extraction method successively. Phytochemical analysis showed presence of flavonoids, phenols, saponins and tannins in both the extracts. The HPLC and HPTLC results of both extracts have shown the presence of flavonoids – quercetin, phenols, tannins and saponins.
which may be responsible for the RBC membrane stabilization against heat induced lysis. Both the extracts have shown no toxicity on brine shrimps. Both the extracts were assessed for \textit{in vitro} pharmacological actions such as antioxidant and reducing power. The free radical scavenging activities were significantly improved by EQSG and AQSG. Both the extracts suggested of being good scavengers of free radicals including hydroxyl radical, hydrogen peroxide radical, superoxide radicals and nitric oxide radicals generated during oxidative stress.

\textit{In vivo} antiosteoporotic study of different extracts was carried out in ovariectomized rat models. Ovariectomy resulted in significant increase in body weight, enhanced bone turnover and marrow cavity of femoral diaphysis, repressed BMD and osteodystrophy within several weeks, contributing to bone resorption. The results were further evident by significant increase of bone resorption biochemical markers. Treatment with EQSG and AQSG for 90 days significantly regulates the bone turnover by ameliorating the increase levels of bone resorption markers. The results were supported by increased femoral and vertebral compression strength and BMD; improved trabecular bone microarchitecture by Micro CT and histopathological data that proved the marked restoration of bone loss by enhanced ossification, mineralization and calcified cartilagenous deposits by EQSG and AQSG treatment in dose dependent manner.

The effect of Raloxifene, EQSG and AQSG at 250 and 500 mg/kg dose was evaluated for uterine endometrial hyperplasia. The treatments showed increased uterus weight without causing hypertrophy as depicted by microscopic examination of uterus cells with no cell proliferation or hyperplasia. Consequently, an increased ER expression was observed in the rat endometrium after administration of EQSG, AQSG and raloxifene. From the data, it may be proposed that both the extracts were safe (non-uterotrophic) for use in postmenopausal osteoporosis and possess a similar potential like raloxifene with lower risk of endometrial carcinoma.

Similar observations were also seen in steroid induced osteoporotic model. Treatment with EQSG and AQSG in prednisolone treated rats markedly improved the bone structure and biomechanical strength in both male and female. Treatment with EQSG and AQSG significantly decreased total cholesterol, TGL, LDL and VLDL levels and elevated HDL levels compared with the GC rats, similar effect with ALN.
The current work was an attempt to evaluate the effect of prenatal exposure of EQSG and AQSG on the bone mass in adult offspring. The data clearly demonstrated that parental treatment with EQSG and AQSG to pregnant rats during gestation significantly influence the bone growth and improved the bone mass and strength. As observed from the results, the increased bodyweight, femur weight and biomechanical strength of treated adult offspring. For the first time, this study reveals that daily administration of EQSG and AQSG in estrogen deficient rats for 12 weeks improved serum E2 levels, trabecular microarchitecture, preservation of bone mass and biomechanical quality. As EQSG and AQSG showed good efficacy and found to be safe with oral administration at the dose of 2000mg/kg. It can be prepared conveniently, easily available and cost effective suggesting it as a clinical advantage as an alternative medicine to oestrogen therapy for preventing postmenopausal osteoporosis. However, studies are required for the identification of the bioactive compounds associated with the bone-protective effects in vivo and delineate the molecular mechanism(s), underlying therapeutic approach of *Sesbania grandiflora*, as a candidate for preventing osteoporosis.