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Angelica Sinensis Extract : A Potential Drug to Enhance Osseointegration of Dental Implants in Osteoporosis Patients

Fei Gao[1] and Shimao Yang[2]*

[1]*Department of Anesthesiology, PR China*

[2]*Department of Oral and Maxillofacial Surgery, PR China*

***Corresponding author:** Shimao Yang, Department of Oral and Maxillofacial Surgery, Jinan Stomatology Hospital, Jinan, PR China

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Keywords: Angelica Sinensis; Postmenopausal Osteoporosis; Oestrogen; Dental Implant; Osseointegration

ABSTRACT

Background: Postmenopausal osteoporosis is a common skeletal disorder disease because of estrogen deficiency, characterized by increased bone turnover and reductions in bone mineral density. This disorder is a potential risk factor for dental implant surgery because it could increase the risk of oral infectious disease and decrease osseointegration around implants.

Presentation of the Hypothesis: Angelica sinensis root is one of the herbs most commonly used in China. Angelica sinensis extract (AS extract) has been reported to possess neuroprotective, anti-oxidant, hepatoprotective, anti-osteoarthritis, anti-cancer effects. It has also been utilized as a valuable remedy for anemia, menstrual irregularities, and constipation. Recent studies reveal that the AS extract has anti-osteoporotic effects on ovariectomized rats and could promote the proliferation of human bone cells. We therefore hypothesize that systemically or locally used AS extract could improve osseointegration of dental implants in osteoporosis patients.

Implications of the Hypothesis: Our hypothesis could contribute to provide an option to enhance success ratio of dental implants in postmenopausal osteoporosis by the replenishment of AS extract.

Abbreviations: TCM: Traditional Chinese Medicine, AS: Angelica Sinensis, ALP: Alkalinephosphatase, VOAS: Volatile Oils of Angelica Sinensis

Introduction

Postmenopausal osteoporosis is a common skeletal disorder disease which has become one of the most important public health problems in our ageing society. It is mainly caused by estrogen deficiency, while the lack of estrogen after menopause is associated with increased osteoblast (bone-forming cell) apoptosis [1]. These factors can lead to the increase of both osteoclastogenesis and osteoclast activity, eventually causing decreased bone mass and increased risk for osteoporosis [2]. Furthermore, genetic and hereditary factors, hormonal status, dietary habits as well as lifestyle may also involve the development of postmenopausal osteoporosis [3-5]. Some reports had showed that osteoporosis could impact the osteointegration owing to the skeletal disorder and changes of the bone remodeling, which was associated within creased bone turnover and reductions in bone mineral density [6-8]. Recent study indicates that inflammation also plays a critical role in bone remodeling and in pathogenesis of osteoporosis [9,10].

It is well known that the immune and skeletal systems interact and affect each other [11-14]. Recent years, the most frequently studied topics concern osteoporosis is focus on the the immune system, pro-inflammatory cytokines with their receptors and immunological mechanisms regulating bone metabolism. Oestrogen plays an important role in the regulation of immune function, and its receptors have been identified on monocytes, T and B lymphocytes [15]. Oestrogen deficiency could result in a marked increase in pro-

inflammatory cytokines, whereas the level of bone-forming factors is decreased [15,16]. Therefore, oestrogen deficiency may provide a more susceptible environment for bacteria and lead to the increase the risk of oral infectious disease, which may have a relationship with the imbalanced bone status of osteoporosis [17]. These elements make osteoporosis patients prone to peri-implantitis, which could be a potential risk factor for implants in dental surgery because it could decrease bone formation around implants and then affect osseointegration of dental implants.

Many previous studies have proved that the rate of osseointegration around dental implants is significantly reduced under osteoporotic conditions compared to the normal conditions [18,19]. Therefore, how to avoid implant loss and enhance success ratio of dental implants in postmenopausal osteoporosis patients is always a clinical focus. Angelica Sinensis (AS) root is one of the herbs most widely used in China. AS extract has been reported to possess neuroprotective, anti-oxidant, hepatoprotective, anti-osteoarthritis, anti-cancer effects [20-24]. It has also been utilized in Traditional Chinese Medicine (TCM) as a valuable remedy for anemia, menstrual irregularities, and constipation [25-28]. The diverse biological activities of AS extract mainly depend on the active compounds of phthalides, organic acids, polysaccharides, and flavones [29]. Recently, it has been recognized that the AS extract has anti-osteoporotic effects on ovariectomized rats [30]. Moreover, it could promote the proliferation and differentiation of human bone cells [31]. It also has been suggested that AS extract could inhibit RANKL-mediated osteoclast differentiation in bone marrow macrophages in vitro, indicating that it may serve as a useful drug in the prevention of bone loss [32].

Presentation of The Hypothesis

Our hypothesis is that systemically administration or locally used AS extract could enhance osseointegration of dental implants in postmenopausal osteoporosis patients. Then, it could provide an option to improve success ratio of dental implants in postmenopausal osteoporosis patients through the replenishment of AS extract. Angelica sinensis has been always used in traditional prescriptions for bone and tendon injuries. Hu XM reported that Angelica sinensis was one of the main ingredients in the Encyclopedia of Esoteric Prescriptions in TCM of fracture prescriptions [33]. It has shown that these prescriptions had significant effect in reducing the time needed for the injured bones to heal. AS extract was found to directly stimulate the proliferation of human bone cells, and improve the Alkalinephosphatase (ALP) activity, type I collagen synthesis of OPC-1 at dose-dependent manner [31]. It is possible that the extract of Angelica sinensis promoted mineralization of the organicmatrix, and then speeding up bone formation.

Results of the recent research showed that AS extract could prevent OVX-induced bone loss with efficacy comparable to that of estrogen. It significantly decreased the bone (femur) mineral density (BMD) loss, and the levels of bone turnover markers including serum ALP, Osteocalcin (OC), and Collagen type I C-telopeptide (CTx) compared to the OVX control group without influencing estrogen level were reduced markly [30]. Moreover, the preliminary study performed by our team recently in vitro indicated that AS extract could promote the mineralization as well as ALP activity of MC3T3 in a dose-dependent (Figure1). These results indicate that AS extract could be an effective natural alternative for the treatment of postmenopausal osteoporosis (Figures 1 & 2).

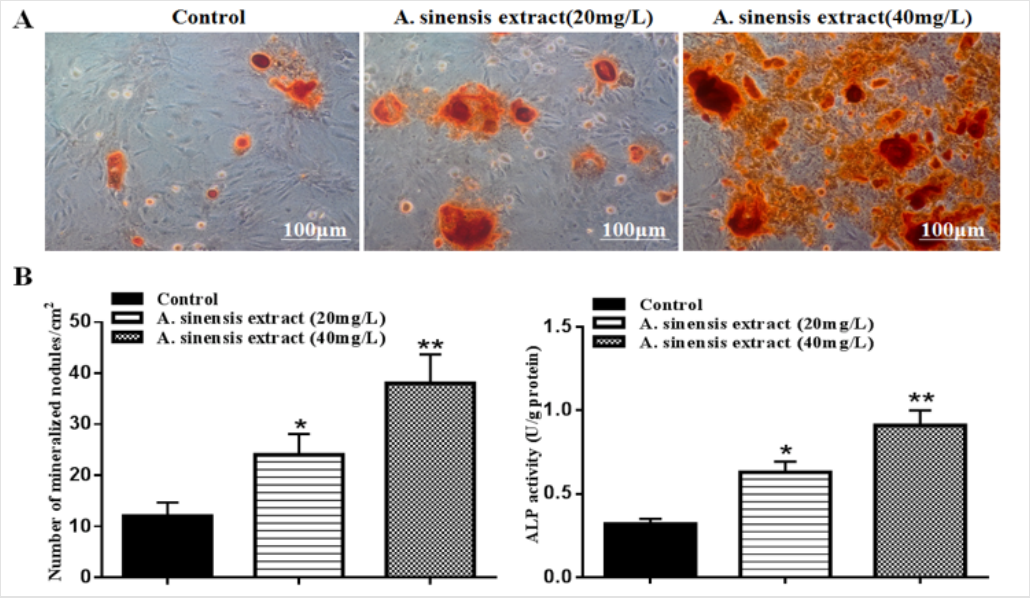

Figure 1: Alizarin red staining of MC3T3 cells. A: Microscopy observation of alizarin red-positive nodule stained MC3T3 cells inosteogenic medium with or without ASextract (20 or 40mg/L) for 2 weeks. B: Quantitation of the density of alizarin red-positive nodules formed and ALP assay of cells in different groups. Data from 3 cultures with triplicates were expressed as mean ± SD, error bars in the figure were indicated for SD; *p< 0.05 and **p < 0.01 vs. control.

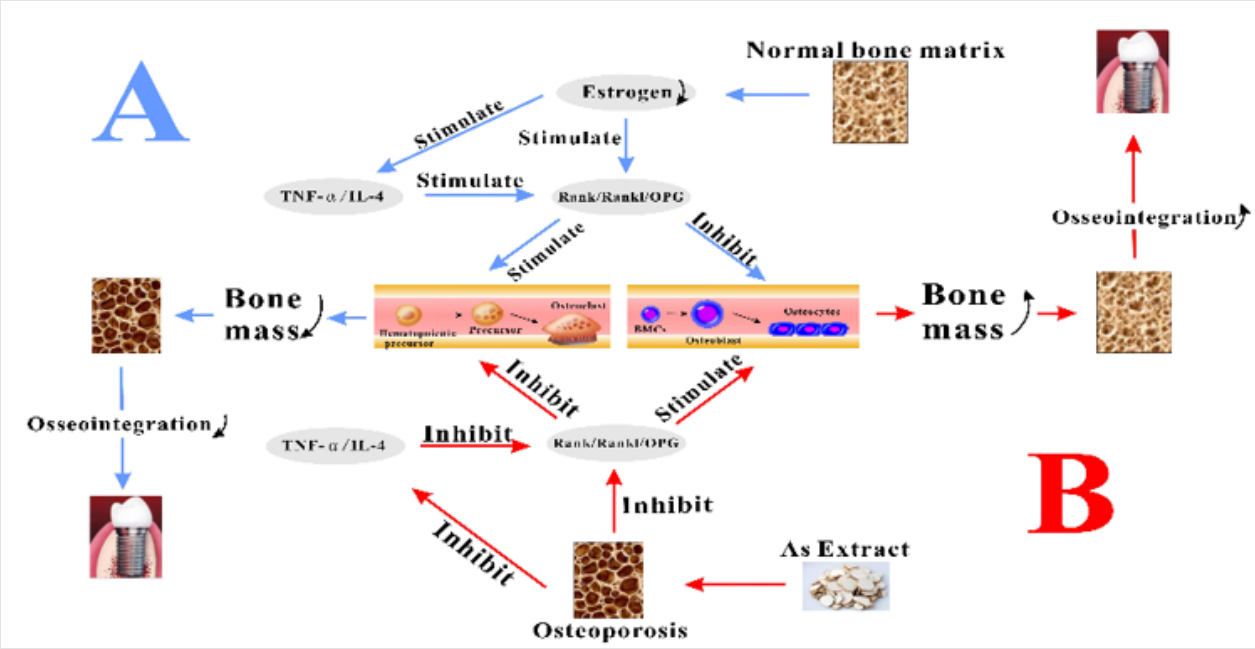

Figure 2: Effect of estrogen and AS Extract on bone mass A: Indicated by the blue rows show the possible mechanisms of estrogen causing bone loss. B: Indicated by the red rows show the possible mechanisms of As Extract increasing bone mass.

AS extract has been demonstrated the inhibitory effects on RANKL-mediated osteoclast differentiation from macrophages and bone resorption in vitro, and it also reduced the RANKL-induced expression of osteoclastic marker genes. Furthermore, AS extract weakened the activation of RANKL-induced signaling pathway including ERK, p38, JNK, NF-κB, AP-1and NFATc1 [32]. This observation suggests that AS extract may as a potential drug in the therapy for disorders associated with bone loss. Angelica sinensis has been used alone, or in combination with other traditional Chinese herbs, to treat various inflammatory diseases [34-36]. AS extract was found to have anti-inflammatory effects and activates the Nrf2 pathway, which protects against oxidative stress [37]. The aqueous extract of Angelica sinensis can inhibit wear debris particles-induced osteolysis through its ability of inhibiting TNF-α and IL-1β release by macrophages, providing a new possible way to prevent and treat aseptic loosening after total joint replacement [38].

In addition, Zhang WQ et al showed that the other form of Angelica sinensis, Volatile Oils of Angelica Sinensis (VOAS), could intervened in the metabolic process of inflammation by altering histidine metabolism, tryptophan metabolism, arachidonic acid metabolism, steroid hormone biosynthesis, fatty acid metabolism and energy metabolism. Metabonomics was used to reflect an organism's physiological and metabolic state comprehensively, and the VOAS was regarded as a potentially powerful tool that reveals anti-acute-inflammatory mechanism [39]. Therefore, the anti-inflammatory properties of AS extract may be a major component of its beneficial effects on promotion of osseointegration of dental implants in postmenopausal osteoporosis.

Implications of The Hypothesis

Postmenopausal osteoporosis poses a significant threat to millions of postmenopausal women. The lack of estrogen after menopause could activate Rank/Rankl/OPG signaling or TNF-α/IL-1 signaling which directly or indirectly stimulates osteocalst differentiation while inhibit osteoblast differentiation, and then resulting in bone loss as well as microarchitectural deterioration including bone fragility and an increased risk of fracture. Recent investigation has demonstrated that AS extract could prevent bone loss in OVX rats [30].AS extract could directly inhibit Rank/Rankl/OPG signaling and further prevent osteoclast differentiation [32]. Furthermore, AS extract also could decrease the OVX-induced serum TNF-α and IL-1 levels and indirectly inhibit Rank/Rankl/OPG signaling, then leading to osteoclast differentiation reduced while osteoblast differentiation increased (Figure 2). Accordingly, to provide an option to improve success ratio of dental implants in osteoporosis patients, we hypothesize that systemically or locally used AS extract could enhance osseointegration of dental implants in postmenopausal osteoporosis patients.

Conclusion

This hypothesis may contribute to provide an approach to decrease the failure ratio of dental implants in postmenopausal osteoporosis. However, further studies must be performed to prove our hypothesis.

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Authors' Contributions

Shimao Yang conceived the idea and formulated the main lines of the theory. Fei Gao performed data collection wrote the paper. All authors read and approved the final manuscript.

Competing Interests

The author declares that they have no competing interests.

Consent for Publication

Not applicable. Ethics approval and consent to participate.

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