Life Sciences 147 (2016) 46–58

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Natural products for treatment of osteoporosis: The effects and mechanisms on promoting osteoblast-mediated bone formation

Jing An *, Hao Yang, Qian Zhang, Cuicui Liu, Jingjing Zhao, Lingling Zhang, Bo Chen

Translational Medicine Centre, Hong-Hui Hospital, Xi'an Jiaotong University College of Medicine, Xi'an 710054, China

ARTICLE INFO

Article history:
Received 31 August 2015
Received in revised form 4 January 2016
Accepted 13 January 2016
Available online 18 January 2016

Chemical compounds studied in this article:
Icariin (PubChem CID): 5,318,997
Naringin (PubChem CID): 442,428
Genistein (PubChem CID): 5,280,961
Puerarin (PubChem CID): 5,281,807
Psoralen (PubChem CID): 6199
Osthole (PubChem CID): 10,228
Costunolide (PubChem CID): 5,281,437
Kirenol (PubChem CID): 15,736,732
Vanillic acid (PubChem CID): 8468
Honokiol (PubChem CID): 72,303

Keywords:
Osteoporosis
Osteoblasts
Traditional Chinese medicines
Natural products
Molecular mechanism

ABSTRACT

Osteoporosis is a systemic metabolic bone disease characterized by a reduction in bone mass, bone quality, and microarchitectural deterioration. An imbalance in bone remodeling that is caused by more osteoclast-mediated bone resorption than osteoblast-mediated bone formation results in such pathologic bone disorder. Traditional Chinese medicines (TCM) have long been used to prevent and treat osteoporosis and have received extensive attentions and researches at home and abroad, because they have fewer adverse reactions and are more suitable for long-term use compared with chemically synthesized medicines. Here, we put the emphasis on osteoblasts, summarized the detailed research progress on the active compounds derived from TCM with potential anti-osteoporosis effects and their molecular mechanisms on promoting osteoblast-mediated bone formation. It could be concluded that TCM with kidney-tonifying, spleen-tonifying, and stasis-removing effects all have the potential effects on treating osteoporosis. The active ingredients derived from TCM that possess effects on promoting osteoblasts proliferation and differentiation include flavonoids, glycosides, coumarins, terpenoids (sesquiterpenoids, monoterpenoids, diterpenoids), phenolic acids, phenols and others (tetrameric stilbene, anthraquinones, diarylheptanoids). And it was confirmed that the bone formation effect induced by the above natural products was regulated by the expressions of bone specific matrix proteins (ALP, BSP, OCN, OPN, COL I), transcription factor (Runx2, Cbfa1, Osx), signal pathways (MAPK, BMP), local factors (ROS, NO), OPG/RANKL system of osteoblasts and estrogen-like biological activities. All the studies provided theoretical basis for clinical application, as well as new drug research and development on treating osteoporosis.

Contents

Abbreviations: ALP, alkaline phosphatase; OCN, osteocalcin (bone gamma-carboxyglutamic acid protein, BGLAP); OPN, osteopontin ("bone-bridging" protein, secreted phosphoprotein 1, SPP1); BSP, bone sialoprotein; COL I, collagen type I; COL1A1, collagen type I, alpha 1; Runx2, runt-related transcription factor 2; Cbfa1, core binding factor α1; Osx, osterix; OPG, osteoprotegerin; RANK, receptor activator of NF-κB; RANKL, receptor activator of NF-κB ligand; MSCs, mesenchymal stem cells; BMSCs, bone marrow stromal cells; BMMSCs, bone marrow mesenchymal stem cells; MAPKs, mitogen-activated protein kinases; ERK, extracellular signal-regulated kinase; JNK, c-Jun N terminal kinase; BMPs, bone morphogenetic proteins; PKC, protein kinase C; BMD, bone mineral density; ERs, estrogen receptors; EREs, estrogen response elements; ROS, reactive oxygen species; C/EBP-β, CCAAT-enhancer-binding protein-β; MDA, malondialdehyde; NO, nitric oxide; NOS, nitric oxide synthase; sGC, soluble guanylyl cyclase; cGMP, cyclic guanosine monophosphate; PKG, protein kinase-G; PI3K, phosphatidylinositol 3-kinase.

* Corresponding author.
E-mail address: anjing198812@126.com (J. An).

http://dx.doi.org/10.1016/j.lfs.2016.01.024
0024-3205/

1. Introduction

Bone, a highly mineralized connective tissue, is continuously broken-down and re-formed in a process of turnover known as bone remodeling, which occurs through the interaction and balance between bone forming cells, called osteoblasts, and bone resorbing cells, called osteoclasts [1]. Bone remodeling is regulated by several systemic hormones (e.g., parathyroid hormone, 1,25-dihydroxyvitamin D3, sex hormones and calcitonin) and local factors (e.g., nitric oxide, prostaglandins, growth factors and cytokines) [2,3] This remodeling is responsible for normal skeletal formation, skeletal functions and mineral homeostasis. Deregulation in one of these processes can lead to bone diseases such as osteoporosis.

Osteoporosis (OP) is a systemic metabolic bone disease that is characterized by microarchitectural deterioration, low bone mass, and increased risk of fractures, which is a prevalent disease that results from an increase in bone breakdown relative to bone formation. The clinical complications include fractures, disability and chronic pain. The causes of osteoporosis are very complicated, and the disease itself is closely related to aging, endocrine disorders, calcium malabsorption, and limb disuse, as well as immune, nutritional, and genetic factors [4]. Osteoporosis falls into two categories: Postmenopausal osteoporosis (Type 1 osteoporosis) is the most common disease in women after menopause, which is linked to an estrogen deficiency. Senile osteoporosis (Type 2 osteoporosis) is related to aging (>75 years) and results from a deficiency in dietary calcium, Vitamin D decline, or increased activity of the parathyroid glands [5].

Osteoporosis is a major global public health problem that is considered by the World Health Organization (WHO) to be an important health issue secondary to coronary heart disease. It can occur at any age and in any racial or ethnic group, affecting millions of people all over the world, especially the aging population [6]. In America, it threats an estimated 44 million people, or 55% of the people of 50 years of age and older [7]. In Europe, osteoporosis related fractures account for more disability-adjusted life years (DALYs) lost than common cancers except for lung cancer [8]. In China, it is estimated that over 90 million people are suffering from osteoporosis [9]. In addition, about 18% of women and 6% of men worldwide will experience hip fragility fractures resulting from osteoporosis [10]. Most cases of osteoporosis occur in postmenopausal women due to the dramatic estrogen levels decline associated with menopause. About 40% of postmenopausal women are affected by osteoporosis, and with an aging population, this number is expected to steadily increase in the near future [11]. The economic burden of osteoporosis is markedly increased with the expansion of aging world population [12].

The ideal strategy for treating osteoporosis is to inhibit bone resorption by osteoclasts and/or increase bone formation by osteoblasts. However, most of the current therapies for treating osteoporosis focus on inhibiting bone resorption, and there are only few agents available that promote bone formation. Major treatments currently used for osteoporosis include hormone-replacement therapy (HRT) [13], bisphosphonates [14], calcitonin, selective estrogen receptor modulators (SERMs) like raloxifene and droloxifen [15], recombinant human parathyroid hormone (rhPTH), Vitamin D analogs, and ipriflavone [16,17]. The effect of these drugs in increasing bone mass or recovering bone loss is relatively minor, probably no more than 2% per year [18]. However, conventional drug therapies have both pros and cons. For example, while estrogen replacement has produced positive results with respect to improved bone mineral density (BMD) and reduced fracture incidence in early menopause, its prolonged use is restricted because of potential complications such as breast cancer, uterine bleeding, and cardiovascular events. One concern related to the usage of bisphosphates is the complications of osteonecrosis of the jaw (ONJ). The incidence of ONJ disease seems relatively low in patients receiving oral bisphosphates for osteoporosis or Paget's disease and considerably higher in patients with malignancy receiving high doses of intravenous bisphosphates [19]. Despite an excellent safety profile for parathyroid hormone (PTH), concerns do arise from its persistence after discontinuation without sequential use of antiresorptive drugs [20]. In addition, PTH is contraindicated for patients at risk for osteosarcoma. The belief that combined use of both types of drugs may have a synergistic effect on BMD is not fully supported by some observational studies [21,22]. To date, most of the effective osteoporosis therapies reduce bone loss but do not restore lost bone mass and strength. It is desirable, therefore, to have satisfactory bone building (anabolic) agents that stimulate new bone formation and correct the imbalance of trabecular microarchitecture characteristic of established osteoporosis, which would create a new alternative for treating osteoporosis [23].

In recent years, there is a growing interest in the treatment of osteoporosis with plant-based therapies including traditional Chinese medicines (TCM), for which extensive experience has been accumulated over thousands of years [24]. TCM have been widely used in clinical practice to prevent and treat bone diseases in many countries of the world, because they have fewer adverse reactions and are more suitable for long-term use compared with chemically synthesized medicines. TCM contain numerous chemical constituents, which usually exert their therapeutic effects through multi-pathways and multi-targets, these properties are in correspondence with the multi-factorial pathogenesis of osteoporosis [25]. Natural products that derived from TCM have been shown to be excellent and reliable sources for the