

# Prevention of osteoporotic fracture: from skeletal and non-skeletal perspectives

Xinluan Wang<sup>1,2\*</sup>, Wenyao Yang<sup>1</sup>, Ling Qin<sup>1,2\*</sup>

## Abstract

With the global population aging, especially in China, the prevention and management of osteoporotic fragility fractures has become increasingly important. Bone mineral density (BMD) is an important index of osteoporotic fracture risk, which has become a routine measurement in clinical practice and thus formed the cornerstone in monitoring treatment efficacy of osteoporosis. In the past 30 years, several pharmacologic therapies have been developed to increase BMD and reduce osteoporotic fractures, especially vertebral fractures. However, the management of nonvertebral fractures and hip fractures remains challenging as low BMD is only one of the multi-factors for these conditions. Hip fractures mainly result from a fall and its incidence is higher in the frigid zone due to low temperature affecting neuromuscular function and high latitude with less sunlight, the conditions rendering less active vitamin D conversion, apart from increased falling. In this paper, we focus on two therapeutic strategies targeting both skeletal and non-skeletal factors, that is, Tai Chi (TC) exercise for improving balance and "kidney-tonifying" traditional Chinese medicine (TCM) against muscle atrophy. TC is a mind-body exercise that has the potential as an effective and safe intervention for preventing fall-related fractures in the elderly. This makes it a promising and feasible physical activity for the elderly in frigid zone to prevent osteoporotic fractures. Several TCM formula popular in northeast of China within frigid zone are also introduced. They are reportedly effective in maintaining or improving BMD and muscle strength with the potential of reducing osteoporotic fracture. However, more rationally designed vigorous basic investigations and prospective clinical trials are highly desired to validate and consolidate the preliminary observations in the future.

## Keywords

osteoporotic fracture; sarcopenia; Traditional Chinese Medicine; Tai Chi exercise

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<sup>1</sup>Translational Medicine R&D Center, Institute of Biomedical and Health Engineering, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518000, China

<sup>2</sup>Musculoskeletal Research Laboratory, Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong, Hong Kong 999077, China

\*Corresponding authors Ling Qin, E-mail: lingqin@cuhk.edu.hk; Xinluan Wang, E-mail: xl.wang@siaat.ac.cn

## 1 Osteoporosis and osteoporotic fracture

Osteoporosis (OP) is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture<sup>[1]</sup>. With global aging, it has become an important public health burden all over the world. OP affects approximately 6.3% of men over the age of 50 and 21.2% of women over the same age range globally, affecting approximately 500 million population worldwide<sup>[2]</sup>.

Worldwide, OP causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture on average every 3 seconds<sup>[3]</sup>. Epidemiological studies indicate that one in two women and one in five men aged over 50 years will suffer an osteoporotic fracture in their lifetime<sup>[4]</sup>. Due to the rapid aging of the population

in Asia, it is projected that half of hip fractures will occur in Asia by 2050. In a descriptive analysis of fracture hospitalization rate in adults from 10 regions of China, it was found that the crude fracture hospitalization rate was 4.39/1 000 person-years during a median follow-up of 7.7 years, and hospitalization rates of fractures increased from 2009 to 2016, with an annual growth rate of 9.1%<sup>[5]</sup>. The annual incidence and costs of OP-related fractures were estimated to double by 2035 and will increase to 5.99 million fractures costing \$25.43 billion by 2050<sup>[6]</sup>. National Health Commission of the People's Republic of China launched the special action of "healthy bones" in 2017 to further enhance prevention of OP and build a healthy bone supporting environment for the whole society.

Fracture incidence varies widely by geography, ethnicity, and socioeconomic status<sup>[7]</sup>. Global variation in fracture incidence is

multifaceted. One is related to the ambient temperature; the number of hip fractures increases in winter months with rigid temperatures. It is not simply due to slipping on icy surfaces, as a high proportion of these occurs indoors<sup>[8]</sup>. The cause is multifactorial, such as fewer winter daylight hours and slowed neuromuscular reflexes<sup>[9]</sup>. Furthermore, as fracture incidence is typically higher in the district with a more northerly latitude, vitamin D status may be implicated, as less sunlight causes less active vitamin D conversion<sup>[10]</sup>. In Northeast China, the temperature is low, and the wintertime is long whereas the sunshine time is short. Therefore, it is highly desirable to pay more attention to the prevention and management of osteoporotic fracture.

## 2 Pharmaceuticals developed for improving BMD and reducing osteoporotic fracture

The consensus on OP in the past 30 years captures the notion that low bone mass is an important risk factor of fracture, and the bone mineral density (BMD) assessment can now be easily performed in clinical practice, which forms a cornerstone for the diagnosis of OP in the past quarter-of-a-century<sup>[11]</sup>. Bone turnover markers (BTMs) in serum, including the bone resorption markers, N-terminal propeptide of type I procollagen (P1NP) and C-terminal telopeptide of type 1 collagen (CTX), and bone formation markers osteocalcin (OC) and bone-specific alkaline phosphatase (BALP), are useful in monitoring the efficacy of anti-OP therapy<sup>[12]</sup>. However, BTMs for predicting fracture risks are still a matter of debate and further investigation<sup>[13]</sup>. For example, BTMs increase at menopause, which is associated with accelerated post-menopause bone loss. To date, evidence for the use of BTMs as predictors of fracture has not been fully validated and consolidated<sup>[13]</sup> to support the inclusion of BTMs for fracture prediction clinically<sup>[14]</sup>. Using BMD as an intervention threshold, many risk factors for loss of bone mass have been identified in the past 30 years, and there have been a few pharmacological interventions for OP. These include bisphosphonates, human monoclonal antibody denosumab that targets receptor activator of NF-κB ligand (RANKL), parathyroid hormone teriparatide, parathyroid hormone-related peptide analog abaloparatide, and anti-sclerostin antibody romosozumab<sup>[8, 15-18]</sup>. Studies have shown that these interventions are effective in reducing the incidence of osteoporotic fragility fracture<sup>[18]</sup>.

For vertebral fractures, all commercially available bisphosphonates are able to decrease the incidence of vertebral fractures<sup>[18]</sup>. Zoledronate reduces vertebral fracture by 65%, an efficacy superior to three oral bisphosphonates: alendronate (32%), risedronate (32%) and ibandronate (44%)<sup>[18]</sup>. The efficacy of denosumab was similar to that of zoledronate, reducing vertebral fracture by 68% in the original 36-month FREEDOM trial<sup>[16]</sup>. Anabolic abaloparatide and teriparatide reduce the vertebral

fractures by 86% and 80% over 18 months, respectively<sup>[19]</sup>. A head-to-head clinical trial over a period of 24 months recorded a 48% lower risk of new vertebral fractures with the romosozumab-to-alendronate regimen than with the alendronate-to-alendronate treatment<sup>[15]</sup>.

For hip fractures, the preventive effect of above drugs is however weaker as compared with their effects on spine. The incidence of hip fracture among all the women assigned to risedronate reduces hip fracture by 30%<sup>[20]</sup>. Denosumab lowers the risk of hip fractures by 40% in the original 36-month clinical trial<sup>[16]</sup>. A phase III clinical trial demonstrated that hip fractures occurred in 2.0% of the romosozumab-to-alendronate treatment recipients as compared with 3.2% in the alendronate-to-alendronate group, representing a 38% lower risk with romosozumab<sup>[15]</sup>. Nonvertebral fractures are the fractures other than the ones of the spine, sternum, patella, toes, fingers, skull, and face as well as those with high trauma<sup>[19]</sup>. In an 18-month phase III randomized clinical trial, abaloparatide and teriparatide reduced the risk of nonvertebral fractures by 43% and 28%, respectively<sup>[19]</sup>. At 12 months, nonvertebral fractures occurred in 56 of 3 589 patients (1.6%) in the romosozumab group and in 75 of 3 591 patients (2.1%) in the placebo group, a 25.3% reduction with romosozumab<sup>[21]</sup>.

## 3 Non-skeletal factors of all-related osteoporotic fracture

From the data above, it is summarized that newly developed anabolic agents can reduce risk of vertebral fractures by more than 85%, however, the effects of these BMD-improvement agents on preventing hip fracture are not more than 40%. The problem arises because BMD captures the likelihood of fracture incompletely. Previous study found that in the case of hip fractures, approximately 50% of cases had OP (BMD-based definition)<sup>[22]</sup>. Although low BMD confers an increased risk for fracture, most fractures occur in postmenopausal women<sup>[23]</sup> and elderly men without a densitometric diagnosis of OP<sup>[24]</sup>. Thus, BMD may not take account of other risk factors which are called non-skeletal factors.

Because approximately 90% of hip fractures result from falls<sup>[25-26]</sup>, minimizing fall risk is a practical approach to reduce these serious injuries<sup>[27]</sup>. Fall prevention programs have effectively reduced falls in select populations by 30%-50%<sup>[28]</sup>. Studies have demonstrated that increasing levels of physical activity can achieve a 40%-60% reduction in hip fracture risk. Activities that improve strength, balance, and coordination can reduce the risk of falls and fall-related injuries among healthy and frail persons. Tai Chi (TC), a form of traditional Chinese martial arts, is probably the most frequently studied type of exercises in the prevention of OP and osteoporotic fractures<sup>[29]</sup>.

There is evidence that low muscle contractility can result in a hip fracture and subsequent fall<sup>[30]</sup>. Gluteus medius and gluteus minimus muscle atrophy might be a predictor of fall-related hip fractures in the elderly<sup>[31]</sup>. In the current review paper, we focus on two therapeutic strategies targeting both skeletal and non-skeletal factors, where TC exercise for improving balance and "kidney and/or spleen-tonifying" traditional Chinese medicine (TCM) against skeletal muscle atrophy.

#### 4 TC exercise for reducing osteoporotic fracture through improving balance and preventing falls

TC is a more than 1200-year-old traditional Chinese martial arts practiced as a health exercise, especially appreciated by elderly population in China. Over the past century, millions of Chinese have practiced TC's flowing, meditative movements to cultivate and maintain health and well-being. It becomes a favorite form of exercise throughout the world and has drawn increasing research interest from international scientists<sup>[32]</sup>. TC is based on gentle and slow movements that represent many variations and changes such as emptiness and fullness, movement and stillness, expressed strength and softness, and forward and backward movements<sup>[33]</sup>. TC practice has been widely used as a non-pharmacological approach to improve body balance and prevent falls in older adults<sup>[34-35]</sup>. The outcomes of clinical trials on TC are summarized in (Table 1).

##### 4.1 TC retards BMD decline rates in postmenopausal women

In a 12-month case-control study, we firstly showed that regular TC exercise retarded bone loss in the weight-bearing bones of postmenopausal women. Overall, higher baseline BMD values were obtained in the weight-bearing skeletons of postmenopausal women who did regular TC exercise long-term (over 4 years) than in the non-exercising gender- and age-matched controls. Although the follow-up measurements showed overall bone loss in both groups, the course of bone loss in the TC exercise group was decelerated, as reflected by 10% to 15% higher areal BMDs in the spine and proximal femur and an approximately 14% higher volumetric BMD in trabecular compartment of the ultradistal tibia<sup>[36]</sup>. Later, randomized controlled trial (RTC) and prospective cohort studies coherently suggested that TC exhibits reduced rates of postmenopausal declines in BMD<sup>[37-40]</sup>. Long-term TC practitioners have higher BMD than age-matched sedentary controls and slower rates of postmenopausal BMD decline<sup>[41]</sup>. In a 12-month follow-up study, we observed 4 fractures, including 3 subjects in the control group and 1 in the TC group<sup>[42]</sup>. Although there has not been any RCTs on fracture incidence, the beneficial effects of TC has been confirmed for patients in improving BMD values and relieving osteoporotic pain<sup>[43]</sup>.

Besides BMD, there is evidence that TC also regulates BTMs. In a 9-month RTC, the average serum concentrations of CTX and OC in the Usual Care group increased (4.3% and 6.3%, respectively), while in the TC group, they decreased (-7.1% and -5.1%, respectively), indicating that TC inhibits excessive bone turnover in postmenopausal osteopenia women<sup>[44]</sup>. In another 6-month RTC, a significant increase in the BALP/tartrate-resistant acid phosphatase (TRAP) ratio was observed in the TC group, indicating that TC regulates bone metabolism in favor of bone formation in postmenopausal osteopenia women<sup>[45]</sup>.

##### 4.2 TC prevents falls in the elderly via improving body balance

A RCT compared the effectiveness of TC vs. multimodal exercise (MME) and stretching exercise for reducing falls in older adults at a high risk of falling<sup>[35, 46]</sup>. At 6 months, TC and MME significantly reduced the fall incidence rate by 58% and 40% compared with stretching exercise. Fall rate was reduced by 31% with TC relative to MME<sup>[46]</sup>. At 12 months, TC and MME reduced the moderate injurious fall rates by 49% and 38%, respectively, and the serious injurious fall rates by 75% and 44%, respectively, compared with stretching exercise. TC is more effective than MME in reducing the serious injurious fall rate by 53%. For preventing injurious falls in older adults at a high risk of falling, TC was found to be superior to MME<sup>[35]</sup>. In addition, TC as an exercise form for older adults can have a substantially favorable effect on delaying the onset of fall events<sup>[47]</sup>. Other studies found that changes in fall-predictive sway parameters were significantly improved after 9 months of TC<sup>[44]</sup>.

Poor balance function increases the risks of falls and injury. Improving balance function can prevent accidental falls. The coordination of the visual, proprioceptive, and musculoskeletal systems is important to maintain balance. TC is effective in balance function enhancement and fall prevention. The requirements of TC for accurate joint positioning and weight transfer involving smooth coordination of neck, trunk, upper, and lower limb movements make it particularly useful for improving the sensorimotor control of balance in the elderly<sup>[15]</sup>. In studies utilizing functional balance testing, TC increased the duration of one-leg standing and the distance of functional reach<sup>[48-49]</sup>. In a study utilizing sensory organization testing, TC improved static and dynamic balance, especially in more challenging sensory perturbed conditions<sup>[49]</sup>. Similar findings indicate that TC gait challenges body balance and requires more muscle strength of the lower limb joints compared to regular walking gait<sup>[14, 50]</sup>. To cope with these challenges, the body could develop neuromuscular control strategies to maintain body balance and thus reduce the risk of falls<sup>[14]</sup>.

Table 1 Summary of studies evaluating impact of Tai Chi on BMD, muscle strength and fall in elderly

Study	Study Design (Duration)	Study Population (Age)	Interventions and Sample Size	Outcomes Measured	Results
Qin <i>et al.</i> <sup>[36]</sup>	Case-control study (12 months)	Postmenopausal women (50-59 years)	Long-term TC practitioners (over 4 years experience) ( <i>n</i> = 17); Age-matched sedentary controls ( <i>n</i> = 17)	BMD of lumbar spine and proximal femur, and distal tibia	Significantly greater BMD in lumbar spine, proximal femur, and tibia in TC vs. control at baseline. Reduced rates of trabecular BMD loss of the ul-tradistal tibia and of cortical BMD loss of the distal tibial diaphysis in TC.
Qin <i>et al.</i> <sup>[37]</sup>	Cross-sectional study	Postmenopausal women (55.9 ± 3.1 years)	TC: more than 3 h/week ( <i>n</i> = 48); Age-matched sedentary controls ( <i>n</i> = 51)	BMD of lumbar spine and proximal femur, quadriceps strength, flexibility, balance	Significantly greater BMD in lumbar spine and some regions of femur (greater trochanter, Ward's area) in TC vs. control. Greater quad strength and balance in TC vs. control
Chan <i>et al.</i> <sup>[42]</sup>	Age-matched RCT (12 months)	Postmenopausal women (54.0 ± 3.5 years)	TC: 5 sessions/wk, 45 min ( <i>n</i> = 67); Age-matched sedentary controls ( <i>n</i> = 65)	BMD of lumbar spine and proximal femur, and of distal tibia	Significant retardation of bone loss in both trabecular and cortical compartments of the distal tibia in the TC vs. control. Four fracture cases, including 3 subjects in the control group and 1 in the TC group.
Wayne <i>et al.</i> <sup>[44]</sup>	RCT (9 months)	Postmenopausal osteopenic women (45-70 years)	TC: 99.5h TC training ( <i>n</i> = 43); UC: <i>n</i> = 43	BMD of the proximal femur and lumbar spine, serum markers of bone resorption and formation, and quality of life. Quiet standing fall-predictive sway parameters and clinical balance tests in a subsample	Femoral neck BMD were significantly higher in TC (completed ≥ 75% training) vs. UC. In the Usual Care group, average serum concentrations of CTX and OC increased by 4.3% and 6.3%, respectively, while in the TC group, CTX and OC decreased by -7.1% and -5.1%, respectively. More favorable changes in bone physical domains of quality of life in TC vs. UC. Significantly improved in sway parameters in TC vs. UC.
Shen <i>et al.</i> <sup>[45]</sup>	RCT (6 months)	Postmenopausal osteopenic women (57.5 ± 6.9 years)	Placebo: 500 mg medicinal starch daily ( <i>n</i> = 44); GTP: 500 mg of green tea polyphenols ( <i>n</i> = 47); Placebo + TC: 1h TC class/week, 500 mg medicinal starch daily ( <i>n</i> = 42); GTP + TC: 1h TC class/week, 500 mg of green tea daily ( <i>n</i> = 38)	blood and urine biomarker analyses, and muscle strength	At 6 months, significant increases in the change of BALP/TRAP ratio in TC group. Muscle strength significantly improved due to GTP, TC, and GTP + TC interventions at 6 months.
Li <i>et al.</i> <sup>[53]</sup>	Controlled Clinical Trial (16 weeks)	elderly individuals (aged 60 years, 20 men and 20 women)	TC: supervised TC exercise (11 men and 11 women); Control: general education (9 men and 9 women)	maximum concentric strength and dynamic endurance of the knee flexors and the extensors, the maximum concentric strength of the ankle plantar flexors and dorsiflexors, onset latency to sudden perturbations in the rectus femoris, semitendinosus, gastrocnemius, and anterior tibialis muscles	Significantly greater muscle strength of the knee flexors in TC group vs. control. Significantly shorter semitendinosus muscle latency in TC vs. control ( <i>P</i> = 0.042).
Song <i>et al.</i> <sup>[55]</sup>	RCT (4, 8, 12 months)	Urban elderly women (years)	TC: 40min TC exercise/d ( <i>n</i> = 35); Control I: 40min dance/d ( <i>n</i> = 35); Control II: 40min brisk walking/d ( <i>n</i> = 35)	lower limb skeletal muscle mass, lower limb muscle strength, BMD and balance function	At 4 months, most of the study indexes in the control group I and group II are improved significantly. The study indexes in three groups show no significant difference. At 8 months, relevant study indexes of the subjects in the three groups are significantly improved. The effect in the TC group is more obvious and is better vs. control II. At 12 months, the effect of the TC group is improved significantly vs. control I and II ( <i>P</i> < 0.05 or <i>P</i> < 0.01).
Taylor-Piliae <i>et al.</i> <sup>[56]</sup>	2-phase RCT (12 months)	Healthy adults (69 ± 5.8 years)	TC: one 45min TC class/week, encourage daily practice ( <i>n</i> = 37); WE: 3 times/week, incorporated endurance, resistance/strength, and flexibility exercises ( <i>n</i> = 39); C: "healthy aging" classes attention-control group ( <i>n</i> = 56)	Physical functioning included balance, strength, flexibility, and cardiorespiratory endurance. Cognitive functioning included semantic fluency and digit-span tests.	At 6 months, WE had greater improvements in upper body flexibility than TC and C. TC had greater improvements in balance and a cognitive-function measure than WE and C. The differential cognitive-function improvements observed in TC were maintained through 12 months.

Continued

Table 1 Continued

Study	Study Design (Duration)	Study Population (Age)	Interventions and Sample Size	Outcomes Measured	Results
Guo <i>et al.</i> <sup>[57]</sup>	Cross-sectional study	Elderly volunteers (64.5 ± 8.48 years)	TC: average 9.64 years TC exercise (n = 16); Control: sedentary controls (n = 9)	static balance test, ankle proprioception test, and concentric and eccentric knee extensor and flexor muscle strength tests	TC group performed better than the control group in balance, proprioception, and muscle strength of lower extremity.

BMD, bone mineral density; TC, Tai Chi; UC, usual care; CTX, C-terminal collagen cross-link; OC, osteocalcin; BALP, bone-specific alkaline phosphatase; TRAP: tartrate-resistant acid phosphatase; GTP: green tea polyphenols group; WE: western exercise group; C: control group.

### 4.3 TC prevents falls via improving muscle strength in older women and men

Our previously published paper first revealed that TC may have an association with better neuromuscular function in postmenopausal women<sup>[37]</sup>. In this cross-sectional study, we evaluated the potential benefits of TC on neuromuscular function in postmenopausal women. The results showed an average of 43.3% significantly greater quadriceps strength and 67.8% significantly longer single-leg stance time in the TC group as compared with the control group, as well as a greater magnitude of trunk bend-and-reach in the TC group. Bivariate linear correlation analysis showed that quadriceps muscle strength was significantly correlated with single-leg stance time. In a randomized placebo-controlled trial, muscle strength significantly improved after 6-month TC exercise in postmenopausal osteopenic women<sup>[45]</sup>. Meta-Analysis of 25 randomized trials revealed the following beneficial effects: (1) TC significantly improved the lower body strength of elderly, (2) Elderly individual experienced decline in muscle strength with advancing age, which could be restored by TC, and (3) TC produced marked enhancement of the strength of deep small muscle group. Therefore, TC specifically enhances muscle strength around knee joints and functional activity for elderly<sup>[51]</sup>.

A RCT investigated the effects of TC and whole-body vibration (WBV) exercise in old men with sarcopenia. Muscular strength was significantly increased after TC and WBV. Following 8 weeks of exercise, improvements were observed in all physical performance tests. The improvement in balance was greater with TC than with WBV. The study also revealed significant improvements of muscular strength in the lower extremities and physical performance after TC and WBV. However, changes in muscle mass did not significantly differ between these two groups. These findings indicate that TC and WBV are effective treatments for improving muscle strength and physical performance in old men with sarcopenia<sup>[52]</sup>.

It is worth noting that TC exercise over a longer period of time demonstrates significant improvement in muscle strength. One study suggested that improving biomechanical characteristics of lower extremity muscles may need longer duration of (more than

16 weeks) TC intervention in elderly people<sup>[53]</sup>. Lower extremity muscle co-contraction plays a role in the observed benefit of longer-term (more than 6 months) TC training on gait and postural control<sup>[54]</sup>. With continuous exercise for 8 months or even above 12 months, the advantage of TC becomes more significant<sup>[55]</sup>.

### 4.4 TC improves balance via improving cognitive function

TC produces greater improvements in balance and cognitive function than attention-control. The differential cognitive-function improvements observed in TC sustain through 12 months<sup>[56]</sup>. The TC group performed better than the control group (only underwent regular physical activities) in balance, proprioception, and muscle strength of lower extremity. The proprioception is the most important factor related to balance ability and it accounts for 44% of the variance in the medial-lateral sway direction and 53% of the variance in the antero-posterior sway direction. The proprioception may be a more important factor affecting the balance ability highlighted in the work by Guo and co-workers<sup>[57]</sup>. Together, TC is a world-known martial arts that has proven potential as an effective and safe intervention for prevention of fall and fall-related fractures in the elderly. TC exercise can be practiced in numerous places, in office, at home, at school, *etc.* No additional equipment is required, and even four-square meters of flat ground is enough. Considering that TC is suitable for all-ages, low-cost, space-saving and more enjoyable strategy, it shall become a promising low to medium intensity martial art in frigid zone.

## 5 TCM in frigid zone: An effective intervention for reducing osteoporotic fracture via improving skeletal muscle strength

Skeletal muscles and bones are essential for locomotion and mobility. Several common age-related mechanisms and factors detrimentally influence muscle and bone to induce sarcopenia and OP<sup>[58]</sup>. Sarcopenia is an ageing-related disease with low muscle mass, strength, and/or physical performance<sup>[59]</sup>. The correlation between muscle and bone interactions is very high, and sarcopenia and OP lead to an increased risk of fracture in elderly<sup>[60]</sup>. Clinical observations indicated a strong positive association between appendicular lean mass and BMD<sup>[61-62]</sup>. A meta-analysis of cohort

studies revealed sarcopenia was significantly associated with a fracture in middle-aged and elderly people<sup>[63-64]</sup>. Moreover, sarcopenia added incremental value to fracture risk assessment tool in predicting incident fracture in older Chinese men<sup>[65]</sup>. As we know more about the crosstalk of the muscle and bone<sup>[60, 66]</sup>, it is possible to target muscle for preventing osteoporotic fractures. Here, we review several herbs used as TCMs in frigid zone of China, which can improve skeletal muscle strength (Table 2).

### 5.1 Ginseng

Ginseng is one of the most popular herbal dietary supplements and is probably the most studied herb with regard to enhancing physical performance<sup>[67]</sup>. In women with osteopenia, intake of 3 g of ginseng extract per day over 12 weeks notably improved physical activity with improvements in the OC concentration and ratios of bone formation indices deoxypyridinoline/OC<sup>[68]</sup>. Ginseng consists of various species in the Araliaceae family, such as Asian ginseng, Korean ginseng, Chinese ginseng (*Panax ginseng*), American ginseng, Canadian ginseng (*Panax quinquefolius*), and Siberian ginseng (*Eleutherococcus senticosus*)<sup>[69]</sup>. In China, ginseng is mainly distributed in cold regions such as Liaoning, Jilin, and Heilongjiang provinces and used in the dietary and medicinal domains, whilst the pharmacological properties of *Panax ginseng* preparations have been elaborated in human clinical trials to generate anti-inflammatory, antioxidative, brain function-boosting, anabolic, immune-stimulating, and endurance performance-enhancing effects<sup>[70]</sup>. Ginseng contains a significant number of important compounds such as vitamins (A, B, C, and E), minerals (iron, magnesium, potassium, and phosphorus), fibers, proteins, saponins, and ginsenosides (the main active constituents in *Panax* herbs) that has been shown to reduce mental stress, improve immune function, and stabilize blood pressure<sup>[59]</sup>.

Changbai mountain ginseng (*Panax ginseng* C.A. Mey) increases muscle mass, improves exercise performance and energy utilization, and decreases fatigue-associated parameters *in vivo*<sup>[71]</sup>. mountain ginseng (*Panax ginseng* C.A. Meyer) treatment reduces dexamethasone-induced muscle atrophy by decreasing MSTN-FOXO3a-MuRF-1/Atrogin-1 signaling and increasing the expression of myosin heavy chain protein and the diameter of myotubes *in vitro*<sup>[72]</sup>. *Panax ginseng* increases muscle excitation and attenuates perceived effect during an eccentric-based exercise as well as accelerates the recovery of muscle force in well-trained athletes<sup>[73]</sup>.

Red ginseng, which is generated by repeating multiple cycles of steaming and drying of raw ginseng, improves exercise endurance in mice by promoting mitochondrial biogenesis and increasing ATP production through p38-AMPK-PGC1 $\alpha$  signaling<sup>[74]</sup> and inhibits mitochondrial damage by protecting against intracellular inflammation<sup>[75]</sup>. Red ginseng and fermented red ginseng<sup>[76]</sup>

could improve insulin sensitivity by increasing phosphorylation of IR-b, IRS-1, Akt, and GSK3a/b and translocation of GLUT4 and increase glucose uptake in skeletal muscle to decrease blood glucose, resulting in an increase in muscle mass in high fat-fed rats<sup>[77]</sup>. Consistently, supplementation with red ginseng could also improve insulin sensitivity and reduce exercise-induced muscle damage and inflammatory responses in humans<sup>[78]</sup>. American ginseng protects against muscle damage and reduces neutrophil infiltration after an acute bout of downhill running in rats<sup>[79]</sup> and alleviates eccentric exercise-induced muscle damage by decreasing lipid peroxidation and promoting inflammatory adaptation through reducing the levels of plasma TNF- $\alpha$ , IL-1 $\beta$ , IL-4, and IL-10 in humans<sup>[80]</sup>.

Ginsenosides Rg1 supplementation enhances post-exercise glycogen replenishment by increasing citrate synthase activity and suppresses exercise-induced increases in thiobarbituric acids reactive substance by inhibiting TNF- $\alpha$  and IL-10 in the skeletal muscle, while PGC1 $\alpha$  and GLUT4 were not affected by Rg<sup>[81]</sup>. Ginsenosides Rg1 supplementation effectively eliminates senescent cells in exercising human skeletal muscles and improves high-intensity endurance performance<sup>[82]</sup>.

### 5.2 Cornu Cervi Pantotrichum

Cornu Cervi Pantotrichum (CCP) or deer antler is a well-known material of animal source used in TCM recorded in the Compendium of Materia Medica (Bencao Gangmu) by Li Shi-Zhen approximately 500 years ago and provides a rare anomaly to regenerate complex tissues and organs<sup>[83-84]</sup>. Sika deer mainly live in forest, mountainous, and grassland areas, such as Jilin, Liaoning, and Inner Mongolia provinces, especially in Liaoning and Jilin provinces where there is a large number of artificial breeding of sika deer. A large quantity of insulin-like growth factor (IGF)-1, which is used to promote muscle protein synthesis, can be extracted from deer antler velvet using solid-phase extraction methods<sup>[85]</sup>. Deer antler extract can increase the expression of MyoD1, Myf5, and myogenin to promote muscle differentiation and inhibit muscle atrophy by decreasing MuRF-1 and FoxO3a signaling<sup>[86]</sup>. Deer antler extract improves swimming time by increasing the expression of regulatory muscle contractile genes (troponin T1, troponin I, and tropomyosin 2) in muscle<sup>[87]</sup> and enhancing the activity of GSH-Px and SOD to protect against oxidative damage in liver<sup>[88]</sup>. CCP supplementation enhances forelimb grip strength in mice<sup>[89]</sup>.

### 5.3 Epimedium

Epimedium, known as Yin Yang Huo, has been historically used in combination with other herbs to treat skeletal diseases in TCM for thousands of years and it has extensive clinical indications,

Table 2 Selected studies on the effects of ginseng, deer antler, epimedium, and baill or its main components in muscle and bone

Herbs	Study	Population	Treatment	Function	Key finds
Panax ginseng extract	Kim <i>et al.</i> <sup>[106]</sup>	Fourteen healthy men (22-28 years)	Drug: 6 g/d for 8 weeks (n = 7) Control: placebo /d for 8 weeks (n = 7)	Muscle quality ↑	Ginseng administration significantly increased exercise duration until exhaustion.
American ginseng	Lin <i>et al.</i> <sup>[60]</sup>	Twelve physically active men (22.4 ± 1.7 years)	Drug: 1.6 g/d for 4 weeks (n = 6) Control: placebo /d for 4 weeks (n = 6)	Risk of muscle injury ↓	Ginseng alleviates eccentric exercise-induced muscle damage.
Panax ginseng extract	Jung <i>et al.</i> <sup>[68]</sup>	Ninety women with osteopenia (> 40 years)	H-Drug: 3 g/d for 12 weeks (n = 30) L-Drug: 1 g/d for 12 weeks (n = 30) Control: placebo /d for 12weeks (n = 30)	Bone formation ↑	Ginseng improved the knee arthritis symptoms with enhancement in the osteocalcin concentration and ratios of bone formation indices like deoxypyridinoline/osteocalcin.
Deer Antler Extract	Chen <i>et al.</i> <sup>[67]</sup>	Six male BABL/c mice	8.2 mg/day, for 4 weeks	Muscle quality ↑	Deer antler extract improves fatigue effect in skeletal muscle by altering the expression of genes related to muscle strength.
Fermented deer antler extract	Jang <i>et al.</i> <sup>[68]</sup>	Eight male BALB/c mice	500 mg/kg/day, for 4 weeks	Muscle quality ↑	Total average duration of swimming time of the deer antler extract group was increased.
deer antler	Widyowati <i>et al.</i> <sup>[64]</sup>	Six healthy male mice for each group	4, 8, and 12 mg/kg/day, for 4 weeks	BMD ↑	Deer antler to increase trabecular bone density and calcium levels in serum.
icariin	Wang <i>et al.</i> <sup>[97]</sup>	Eight SD male rats	10 mg/kg/day, for 2 weeks.	Risk of muscle injury ↓	Icariin has excellent therapeutic effects on acute blunt muscle injury in rats by improving immunity.
icariin	Zhang <i>et al.</i> <sup>[66]</sup>	Eight Wistar male rats	45 mg/kg/day, for 3 weeks	Muscle quality ↑	The exhaustive swimming times of rats in icariin group were significantly prolonged.
Epimedium extract	Yong <i>et al.</i> <sup>[63]</sup>	Sixty healthy postmenopausal women (57.9 ± 8.9 years)	Drug: 740 mg/day for 6 weeks (n = 30) Control: placebo /d for 6 weeks (n = 30)	Bone formation ↑	Rise in prenylflavonoid metabolites was associated with higher levels of the bone anabolic marker BALP.
<i>Schisandra chinensis</i> (Turcz.) Baill	Cho <i>et al.</i> <sup>[105]</sup>	Eight SD male rats	20 or 100 mg/kg, 14 times over 3 weeks.	Muscle quality ↑	<i>Schisandra chinensis</i> (Turcz.) Baill increases the grip strength and muscle fiber size in rats.
<i>S. chinensis</i> (Turcz.) extract	Kim <i>et al.</i> <sup>[103]</sup>	Seven SD male rats	10 mg/kg/day, for 8 weeks	BMD ↑ Muscle quality ↑	Baill extract increases the BMD in OVX rats and ameliorates the age-related muscle wasting.

The up arrow means increase. The down arrow means decrease. SD, Sprague Dawley; BMD, bone mineral density.

especially for the treatment of OP<sup>[90]</sup>. Herbal Fufang containing Epimedin reduces 43% fragility fracture incidence in a 5-year multi-center clinical trial<sup>[91]</sup>. In China, there are 43 species that are mainly distributed in the southwest and central regions. For example, *E. sagittatum* Maxim., *E. koreanum* Nakai, *E. pubescens* Maxim., and *E. brevicornum* Maxim are widely distributed and commonly used, and *E. koreanum* Nakai is mainly distributed in the cold northeast regions of China, which has a higher content of icariin<sup>[92]</sup>. Healthy postmenopausal women were randomized in a double-blind fashion to receive either EP prenylflavonoid extract (740 mg/day) or placebo daily for 6 weeks. Daily consumption of EP prenylflavonoids for six weeks was safe. And the overproduction of prenylflavonoid metabolites was found associated with higher levels of the bone anabolic marker BALP, suggesting a potential therapeutic value for post-menopausal OP<sup>[93]</sup>.

More than 260 compounds have been identified from different species of *Epimedium*<sup>[94]</sup>. Icariin, the most pharmacologically bioactive and abundant constituent of *Epimedium*, demonstrates extensive therapeutic capacities such as osteo-protective effect, neuro-protective effect, cardiovascular protective effect, anti-cancer effect, anti-inflammation effect, immune-protective effect, and reproduction-boosting function<sup>[95-96]</sup>. Moreover, icariin has excellent therapeutic effects on acute blunt muscle injury in rats by improving immunity, repairing cytoskeleton and cellular integrity, and producing anti-inflammation, anti-fibrosis, and antioxidative stress actions<sup>[97]</sup>. *Epimedium* extract and icariin regulate insulin resistance by activating the AMPK pathway<sup>[98-99]</sup> and stimulates pathways partially overlapping with the IGF-1 signaling pathway to promote myotube hypertrophy in C2C12 cells<sup>[100]</sup>. Icariin is the most abundant compound of the herbal formula XLGB, which up-regulates mRNA expression of myosin heavy chain (MyHC) I, II A, and II B and prevents OVX-induced deterioration of musculoskeletal tissues<sup>[101]</sup>.

#### 5.4 *Schisandra chinensis* (Turcz.)

*Schisandra chinensis* (Turcz.), also known as "Baill", has anti-inflammatory and antioxidative properties. The main production areas of *S. chinensis* are northeast China, Inner Mongolia, Hebei, and Shanxi, and the type specimen is collected in Heilongjiang province. Oral administration of *S. chinensis* enhances exercise-induced adaptive muscle strengthening in aged mice after forced swimming through anti-apoptotic and antioxidative effects, mediated via modulation of gene expression related to muscle

synthesis or degradation<sup>[102]</sup>. In RAW 264.7 and aged HDF cells, *S. chinensis* inhibits the expression of inflammatory molecules and  $\beta$ -galactosidase activity and improves antioxidative activity via down-regulation of reactive oxygen species and muscle regeneration in skeletal muscle of OVX rats by promoting mitochondrial biogenesis and autophagy<sup>[103]</sup>. Supplementation of *S. chinensis* extract helps improve quadriceps muscle strength and decrease lactate level at rest in adult women<sup>[104-105]</sup>.

Schizandrin A, a component extracted from the fruits of *S. chinensis*, reduces protein degradation, and increases protein synthesis through MuRF-1 and FoxO3a signaling and the Akt/mTOR/70S6K pathway in the C2C12 cell, contributing to the amelioration of dexamethasone-induced muscle atrophy<sup>[106]</sup>. Schizandrin C inhibits inflammatory molecules, enhances antioxidant capacity, and reduces ROS by suppressing the MAPKs/Nrf-2/heme oxygenase-1 signaling pathway to enhance mitochondrial biogenesis in C2C12 skeletal muscle cells<sup>[107]</sup>.

The development of TCM-derived herbal drugs or formulas to treat muscle disorders or degradation. In a clinical trial, ginseng administration significantly increases exercise duration until exhaustion and alleviates eccentric exercise-induced muscle damage<sup>[68, 80, 108]</sup>. Deer antler, *Epimedium*, and baill increase muscle endurance and strength in rodents. Theafore-described TCM-derived herbal drugs or formulas are promising therapeutics for relieving and even curing sarcopenia and reducing the risk of fall and fall-associated fragility fractures in the future.

#### Conflicts of interests

The authors declare no competing interests.

#### Authorship contributions

Wang X and Qin L conceived the structure of the manuscript. Wang X and Wang W drafted the manuscript, which is revised by Qin L.

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