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Direct or indirect action mechanisms of Naringin in maintaining bone homeostasis

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ABSTRACT

Disruption of bone homeostasis is the pathological basis of bone diseases. Multiple cells work together to maintain homeostasis and bone health. As a natural flavonoid compound, Naringin (NG) can positively affect the maintenance of bone homeostasis by acting on different types of cells. In this review, we discuss the direct and indirect osteoprotective effects of NG as well as the underlying mechanisms, and we provide a critical perspective on its clinical translation.

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Introduction

Bone is a composite and dynamic tissue that comprises minerals and organic material. Bone remodels continuously throughout life, and this remodeling process relies on the interaction and coordination of multiple cells, including osteocytes, osteoclasts, osteoblasts, vascular endothelial cells, and immune cells (1). In particular, the osteoblast–osteoclast balance assists in maintaining bone homeostasis (2). Osteoclasts originate from hematopoietic stem cells (HSCs), and osteoclast progenitors are recruited to the damaged bone surface by chemokines. Subsequently, osteoclast progenitors further differentiate from matured osteoclasts and resorb damaged bone under the function of macrophage colony-stimulating factor (M-CSF), monocyte chemoattractant protein-1 (MCP-1), and receptor activator of nuclear factor-κb ligand (RANKL) (3,4). Osteoblasts arise from multipotent mesenchymal precursors. Mature osteoblasts produce a new bone matrix that is mineralized and replaces the resorbed bone matrix, and this is how bone formation is completed (5). However, dysregulation of the dynamic equilibrium between bone formation and bone resorption results in various bone diseases, which are primarily attributed to the disruption of bone homeostasis. In recent years, bone diseases, such as osteoporosis, femoral head necrosis, bone defect, and bone nonunion, have become a major worldwide medical burden (6). Traditional bone disease treatments have poor clinical efficacy due to the limited bone tissue self-renewal (7). Therefore, bone grafts with embedded osteogenic growth factors are considered the "gold standard" clinical treatment for bone repair (8). However, its applicability and therapeutic effect are limited by high production costs and potential adverse effects (9). Currently, more and more studies have focused on natural products for bone repair. The use of traditional Chinese medicines (TCMs) has attracted great interest because of their widespread availability, cost-effectiveness, strong biological activity, and low toxicity (10). NG, the main active ingredient of the TCM Rhizoma Drynaria, also known as Gu-Sui-Bu, has been used in TCM formulas to cure bone diseases and promote osteogenesis differentiation of stem cells (11). Although numerous studies have demonstrated that NG has great potential in the treatment of orthopedic diseases (12,13), the underlying mechanism remains unclear. This article shows the basic properties of NG, summarizes the direct or indirect bone-protective effect of NG in maintaining bone homeostasis (Table 1), and itemizes its mechanism.

Basic properties of NG

NG is abundantly present in the peel and pulp of citrus fruits. It has a specific chemical composition ($C_{27}H_{32}O_{14}$, molecular weight: 580.55, Figure 1) and exists as a dihydroflavone compound (14). traditional isolation methods

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Table 1. Effects of NG on multiple cells in the skeletal system.

Target cells	Effects
Osteoblasts	• Increases osteoblasts proliferation by activating estrogen receptors • Increases Runx2, OCN, and ALP expression • Increases BMP-2 expression • Increases osteoblast autophagy • Increases osteoblast activity by blocking the oxidative stress • Decreases osteoblast apoptosis
Osteoclasts	• Promotes mitochondria-mediated apoptosis of osteoclasts • Reduces osteoclast differentiation
Vascular endothelial cells	• Stimulates angiogenesis and chemotaxis migration • Enhances neovascularization • Inhibits apoptosis
Mesenchymal stem cells	• Regulates the affinity between BMP and the receptor • Promotes proliferation • Enhances osteogenic differentiation • Enhances the migration ability • Stimulates chemokine synthesis and secretion • Facilitates antioxidation • Decreases inflammation-associated impairment

Runx2: Runt-related transcription factor 2; OCN: Osteocalcin; ALP: Alkaline phosphatase; BMP-2: Bone morphogenetic protein 2.

for NG include organic solvent extraction, water boiling extraction, and alkali combined acid extraction. In recent years, ultrasonic extraction and microwave extraction have been reported to improve the extraction rate of NG with reduced costs and without causing pollution concerns (15-18). In cell experiments, NG, a colorless needle-like crystalline powder, is usually dissolved in dimethyl sulfoxide at a concentration not exceeding 0.1% (19). Studies have shown that its biological activities help lower blood lipid levels, regulate blood sugar, and relieve pain; furthermore, it possesses anti-oxidation, bacteriostasis, and spasmolysis properties (20). NG nourishes the kidney and benefits Yang in TCM (21). More importantly, NG, as one of the main ingredients of Rhizoma Drynaria (a famous Chinese herb for bone injury), also plays an important role in the treatment of bone diseases (22). Many kinds of drugs have been successfully applied for the clinical treatment of bone injuries, such as bone healing capsules and bone hyperplasia tablets, and NG is often the main active ingredient in these drugs (23). The significance of NG in repairing bone defects has predominantly been studied in animal and in *vitro* models (24,25); however, its potential mechanism and signal pathway are unclear.

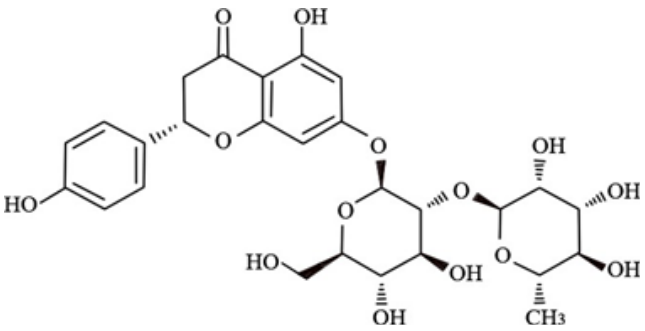

Figure 1. Chemical structure of NG (14).

Direct bone-protective effect of NG

Estrogen-like effects of NG promote bone formation

The bone-protective effect of NG may be attributed to its estrogen-like properties (26). Characteristically, estrogen decline in menopausal women is implicated in inducing osteoporosis (27). After NG treatment, the bone mineral density (BMD), bone volume relative to total tissue volume (BV/TV), and trabecular thickness (Tb. Th) were significantly increased in the ovariectomized (OVX) osteoporotic rat model (28). NG has also been demonstrated to inhibit bone loss and promote bone formation in the OVX osteoporotic mice model and the retinoic acid-induced osteoporosis rat model; its activity may be mediated through the activation of estrogen receptors (ER) in osteoblasts (29,30). Wu et al. found that NG induced ALP gene expression and osteoblast mineralization by enhancing the estrogen receptor alpha (ERα) transactivation activity and improving its translocation to the nuclei. However, these NG-induced effects were attenuated by methylpiperidinopyrazole (MPP), a specific inhibitor of Erα (31).

NG regulates the key osteogenic factor BMP-2

NG could be a good natural BMP regulator. BMP is a multifunctional growth factor that can regulate the expression of osteogenesis-related genes, such as Runx2, OCN, collagen I (Col I), and ALP. BMP-2 is among the most important signaling molecules in maintaining the sustained phenotype of mature osteoblasts (32,33).

Xu et al. demonstrated that the proliferation and differentiation of osteoblasts, Runx2 and OCN expression, and ALP activity were significantly higher when stimulated by 100μM NG combined with BMP-2 than when stimulated by NG or BMP-2 alone (34). BMP-2 seems to be a target protein for NG. Wu et al. reported that NG not only stimulates osteoblast proliferation, differentiation, and maturation but also upregulates BMP-2 expression in cultured os-

teoblasts via phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt), and c-Fos/c-Jun and activator protein-1 (AP-1)-dependent signaling pathways (35).

The anti-inflammatory and antioxidant activity of NG prevents bone loss

The maintenance of normal bone structure and function depends on the dynamic balance between bone formation and resorption, which can be disrupted by external factors, such as glucocorticoids (GCs) (36-38). GCs are a well-known risk factor for iatrogenic osteoporosis (39). They reduce bone formation by inhibiting osteoblast function and increasing the apoptosis of mature osteocytes, and moreover, they stimulate bone resorption to some extent (40).

Huang et al. discovered that NG significantly protected against steroid-induced avascular necrosis of the femoral head (SANFH). Furthermore, they found that NG significantly increased mRNA levels of osteogenic genes by regulating peroxisome proliferator-activated receptor (PPAR) γ, neurogenic locus notch homolog protein (Notch), and phosphorylated-Akt (p-Akt) protein expression while inhibiting caspase-3 activity in the SANFH rabbit model (41). Similarly, Kuang et al. demonstrated that apoptotic proteins, such as caspase-3 and Bad, were inhibited by NG, and in the meanwhile, the effect of NG on the rescue of osteocyte apoptosis was mediated by p-Akt. They speculated that the Akt/Bad signaling pathway was a key target in NG-related function using bioinformatics analysis (42). Moreover, Ge et al. found that not only proliferation and differentiation but also autophagy of osteoblasts was promoted by NG. The expression of autophagosome and its related factors in glucocorticoid-induced osteoporosis (GIOP) rat tissues was increased after NG treatment, and NG treatment partially reversed the suppressive effects of PI3K/Akt/mTOR pathway inhibitor on autophagy (43). Notably, GCs-induced bone loss is also related to oxidative stress. Li et al. observed that the level of oxidative stress was increased in inflammatory bowel disease (IBD) rats treated with dexamethasone (DEX), leading to the inhibition of proliferation, differentiation, and activity of osteoblasts. However, the oxidative stress was reduced in NG-treated rats (44). Rivoria et al. concluded that NG prevented bone loss in patients with type 1 diabetes mellitus, at least partially, by blocking oxidative stress (45).

NG promotes angiogenesis

Adequate blood supply is an important factor in the process of bone regeneration (46,47). NG could stimulate the angiogenesis and chemotaxis migration of human umbilical vascular endothelial cells (HUVECs) through increased matrix metalloproteinase (MMP)-2 activity and augmentation of vascular endothelial growth factor (VEGF) ligand/receptor interaction (48), and NG affects promoting bone mass and treating osteoporosis by increasing the amounts of VEGF and vascular endothelial growth factor receptor (VEGFR)-2 (49). Shangguan et al. showed that NG inhibits apoptosis in vascular endothelial cells via mitochondrial- and ER stress-mediated apoptotic pathways and promotes angiogenesis, thereby exhibiting an anti-osteoporotic effect (50). Moreover, NG could promote endothelial progenitor cell (EPC) proliferation activity via the C-X-C motif chemokine ligand 12 (CXCL12)/C-X-C chemokine receptor type 4 (CXCR4) axis, which is mediated by the PI3K/Akt signaling pathway, thus resulting in EPCs which can replenish the injured endothelium and enhance neovascularization (51).

NG effectively inhibits bone resorption

NG stimulates osteoclast apoptosis and inhibits osteoclast resorption. Li et al. indicated that NG promotes the mitochondria-mediated apoptosis of osteoclasts. Specifically, NG can downregulate the expression of anti-apoptotic factors B-cell lymphoma-2 (BCL-2) and upregulate pro-apoptotic factors Bcl-2 associated X protein (BAX), thereby increasing the permeability of the mitochondrial membrane, and initiating the caspase-dependent apoptosis of osteoclasts (52). Notably, RANKL and osteoprotegerin (OPG) are important factors of osteoclast differentiation and maturation, and the balance of OPG and RANKL controls bone metabolic homeostasis. The inhibition of osteoclast resorption by NG may be associated with the RANKL/RANK/ OPG system (53,54). Xu et al. showed that NG could make osteoblasts secrete OPG by synergistically enhancing the metabolism of 1,25-dihydroxy vitamin D3, thereby reducing the number of osteoclasts and preventing bone loss (55). Yang et al. found that NG could enhance the mRNA and protein levels of OPG in fibroblasts by stimulating the Wnt/β-catenin signaling pathway but had no significant effects on RANKL expression and secretion (56), suggesting that NG alters the OPG/RANKL ratio to inhibit osteoclast resorption.

Taken together, NG promotes bone formation by exerting estrogen-like effects, regulating the BMP-2 status, and inhibiting oxidative stress. Furthermore, NG promotes osteoblast autophagy, enhances angiogenesis, and inhibits osteoclast resorption, indicating its potential as a natural drug to maintain bone homeostasis (Figure 2).

Indirect bone-protective effect of NG

Mechanisms involved in NG-mediated stem cells proliferation and osteogenesis

The ability of NG to exert beneficial effects on bone health is highly related to its pro-osteogenic effects on osteoprogenitor cells and stem cells. Studies have shown that mesenchymal stem cells (MSCs) induced by NG exhibit osteoblastic properties of enrichment of ALP, synthesis of Col I and osteopontin (OPN), and formation of the calcified nodule and NG can also promote the secretion of BMP (57). Moreover, different types of BMP receptors (BMPR-1A and BMPR-1B) regulate the ultimate differentiation of MSCs by conducting different signals (58). NG induces osteogenic differentiation of MSCs by regulating the af-

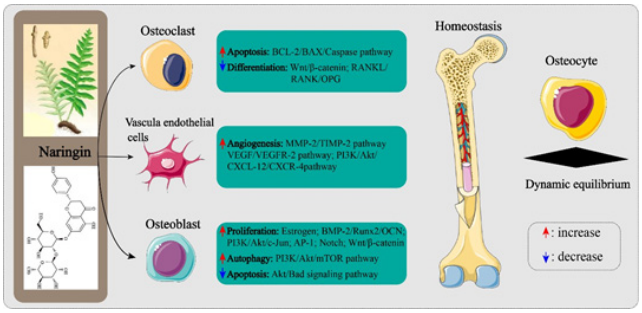

Figure 2. Signaling pathways involved in osteoclast, osteoblast, and angiogenesis of NG (29,30,34,35,41-43,48,49,51-54).

finity between BMP and its receptor. Dong et al. found that NG could block BMPR-1A signaling by inhibiting the binding of BMP-2 and BMPR-1A, thus enhancing BMPR-1B signaling, consequently resulting in osteogenesis (59). Runx2 is an important target gene in the BMP signaling pathway of osteogenic differentiation of MSCs (60-62). Liu et al. found that NG may promote the osteogenic differentiation of human amniotic fluid-derived stem cells (hAFSCs) through both BMP and Wnt/β-catenin signal transduction pathways and that Runx2 behaves as a cross-talking regulator between the BMP and Wnt/β-catenin signaling pathways (63). NG is widely recognized as an antioxidant agent and shows promising antioxidative function and anti-inflammatory activity in many studies in vitro and *in vivo* (64-66). Wang et al. demonstrated that NG increases the viability of human adipose-derived mesenchymal stem cells (hADMSCs) and protects hADMSCs from oxidative stress-induced inhibition of osteogenic differentiation via Wnt signaling. NG can upregulate the Wnt signaling pathway by increasing β-catenin and cyclin D1 protein and therefore reverse the negative effects of H_2O_2 on the Wnt signaling pathway in hADMSCs (67). Li et al. found that NG enhances mitochondrial homeostasis and prevents the apoptosis of nucleus pulposus-derived mesenchymal stem cells (NPMSCs) in vitro by activating the PI3K/Akt pathway to facilitate antioxidation (68). A study using a specific NF-κb inhibitor (BAY 11-7082) indicated that NF-κb inhibition rescued the impaired differentiation of MSCs in the inflammatory microenvironment (69). Similarly, Cao et al. suggested that tumor necrosis factor (TNF-α) activates the NF-κb signaling pathway, which is known to inhibit osteogenesis. NG prevented NF-κb signaling activation by inhibiting the phosphorylation of IκBα and nuclear translocation of p65 kinase (p65), indicating that NG potentially relieves the inflammation-associated impairment of MSC osteogenic differentiation (70).

The mitogen-activated protein kinase (MAPK), mainly p38 kinase(p38), extracellular signal-regulated kinase (ERK)1/2, and Jun amino-terminal kinases (JNK), signaling pathway regulates various physiological processes of cells, such as growth, proliferation, differentiation, and apoptosis (71); it is closely associated with osteogenic differentiation of MSCs (72-74). NG enhanced the osteogenic differentiation of MSCs by activating the ERK signaling pathway. Wang et al. found that NG significantly activated the phosphorylation of ERK1/2 and upregulated the expression of osteogenesis-related proteins, such as Runx2, in a dose-dependent manner in MSCs; however, the NG-induced relatively higher levels of Runx2 were reversed when ERK1/2 signaling pathway was blocked (75). Wei et al. investigated the role of the MAPK signaling pathway in the osteogenic differentiation of periodontal ligament stem cells (PDLSCs) induced by NG. The results showed that NG significantly increased the osteogenic markers and promoted the phosphorylation of ERK1/2 but did not affect the phosphorylation of P38 and JNK (76). Although studies have shown that different members of the MAPK family have different effects on osteogenesis (77-79), the MAPK signaling pathway is at least partially involved in NG-induced osteogenic differentiation of stem cells, and Runx2 is among the most important transcription factors during this process. NG-potentiated osteogenic differentiation of stem cells is related to the enhanced Notch signaling pathway. Yu et al. reported that although NG markedly increased the biological effects and osteogenesis-related genes of BMSCs, it inhibited PPARγ2 expression. Notch1 protein was activated under osteogenic induction, which was further enhanced by NG. Conversely, treatment with the DAPT (a Notch signaling inhibitor) caused a partial decrease in the NG-induced expression level of Notch1(80). Consistent with these findings, Fan et al. found that miR-20a has a regulatory effect on PPARγ in BMSCs and that NG can promote BMSC differentiation into osteoblasts via the upregulation of miR-20a and the downregulation of PPARγ (81). In addition, Wang et al. reported that NG promotes BMSC osteogenic proliferation and differentiation by inactivating Janus kinase 2/ signal transducer and activator of transcription 3 (JAK2/STAT3) signaling (82).

NG promotes stem cell migration

Although the effects of NG on MSCs are mostly focused on promoting proliferation and differentiation, the migration of endogenous or exogenous MSCs to target tissue is also essential (83). Guo et al. reported that NG promotes the migration and proliferation of human dental pulp stem cells (hDPSCs) by activating the Wnt/β-catenin signaling pathway (84). Lin et al. found that an appropriate concentration of NG not only enhances MSC migration directly but also further enhances MSC mobility by stimulating chemokine synthesis and secretion. Ras was markedly activated in the NG-treated groups, but MSC migration was significantly decreased upon treatment with a Ras inhibitor, suggesting that NG enhances the migration ability of MSCs by activating the Ras signaling pathway (85).

In summary, NG promotes proliferation and osteogenesis in stem cells by multiple signaling pathways, including the BMP/Runx2, Wnt/β-catenin, PIK3/Akt, NF-κb, MAPK/ERK/P38, Notch, and JAK2/STAT3 pathways. Furthermore, NG also promotes MSC migration via the Ras pathway (Figure 3).

Prospects

Various risk factors lead to the disruption of bone tissue homeostasis, which is often reflected in insufficient bone formation and increased bone resorption. NG protects osteocytes, promotes the proliferation and differentiation of osteoblasts, stimulates the apoptosis of osteoclasts, and thus directly maintains bone tissue homeostasis; furthermore, it also indirectly repairs bone damage by inducing osteogenic phenotypic differentiation of stem cells and promoting angiogenesis. These processes involve different mechanisms of action and signaling pathways, but the specific upstream and downstream relationships and

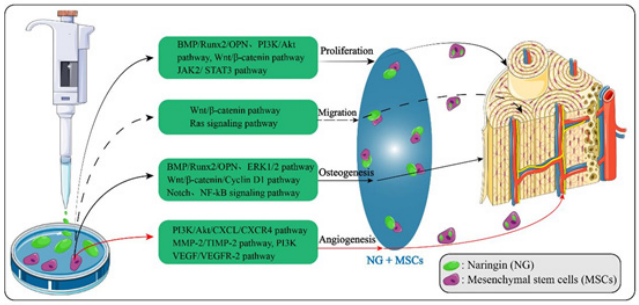

Figure 3. Signaling pathways involved in NG-mediated MSC proliferation, migration, osteogenesis, and angiogenesis(59,63,68,70,75,76,80-85).

the existence of interactions among NG-mediated multiple signaling pathways have not been clarified. Although studies have reported no significant cytotoxicity or systemic or local toxicity of NG (31,86,87), it is still important to specify a safe and effective dose and mode of administration. In vitro studies, NG has a dose-dependent (1–100 μg/mL) on the proliferative and osteogenic activity of MSCs (53,67), while others reported that a dose of 100 μg/mL was effective in decreasing MSC proliferation (88). Besides, the intervention concentrations of NG differed greatly between the two studies wherein NG inhibited osteoclast absorption (55,89). In vivo studies, NG has mostly been administered orally in OVX mice models, with different studies using NG interventions in animal models at doses ranging from 40–1500 mg/kg, and 300 mg appears to be the optimal concentration for the prevention of devitalized osteoporosis (30,49,88,90); however, lower doses (5mg/kg) of NG have also been reported to increase bone mass in OVX mice (91). Of course, there are different doses and delivery methods for different animal models (13,29). Different cell types and disease models differ in their sensitivity to NG and identifying how to develop different dosing criteria for different types of bone diseases deserves our attention. The low oral bioavailability of NG and its easy degradation in circulating blood and intestine are the main reasons limiting its therapeutic effect and clinical application (92), and therefore, it is particularly important to optimize the NG treatment regimen. Biomaterials loaded with NG can well control the release of NG and improve osteogenesis in vivo. NG combined with other therapeutic modalities (90), growth factors (34), or biomaterials (93-95) rather than monotherapy provides new ideas for maintaining bone homeostasis and for the application of natural derivatives in bone tissue engineering and regenerative medicine. In addition to NG, there are many other natural flavonoids that have biological and therapeutic effects (96-104).

In conclusion, NG has the advantages of ubiquity, cost-effectiveness, multi-biological activity, and multiple therapeutic targets. It has great potential for use in the treatment of various bone diseases in the future.

Abbreviations

NG: Naringin; HSCs: Hematopoietic stem cells; M-CSF: Macrophage colony-stimulating factor; MCP-1: Monocyte chemoattractant protein-1; RANKL: Receptor activator of nuclear factor-κb ligand; TCMs: Traditional Chinese medicines; Runx2: Runt-related transcription factor 2; OCN: Osteocalcin; ALP: Alkaline phosphatase; BMP-2: Bone morphogenetic protein 2; BMD: Bone mineral density; BV/TV: Bone volume relative to total tissue volume; Tb. Th: Trabecular thickness; OVX: Ovariectomized; ERα: Estrogen receptor alpha; MPP: Methylpiperidinopyrazole; Col I:Collagen I; PI3K: Phosphatidylinositol 3-kinase; Akt: Protein kinase B; AP-1: Activator protein-1; GCs: Glucocorticoids; SANFH: Steroid-induced avascular necrosis of the femoral head; PPAR: Peroxisome proliferator-activated receptor; Notch: Notch homolog protein; p-Akt: Phosphorylated-Akt; GIOP: Glucocorticoid-induced osteoporosis; IBD: Inflammatory bowel disease; DEX: Dexamethasone; HUVECs: Human umbilical vascular endothelial cells; MMP: Matrix metalloproteinase; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; EPC: Endothelial progenitor cell; CXCL12: C-X-C motif chemokine ligand 12; CXCR4: C-X-C chemokine receptor type 4; BCL-2: B-cell lymphoma-2; BAX: Bcl-2 associated X protein; OPG: Osteoprotegerin; MSCs: Mesenchymal stem cells; OPN: Osteopontin; hAFSCs: Human amniotic fluid-derived stem cells; hADMSCs: Human adipose-derived mesenchymal stem cells; NPMSCs: Nucleus pulposus-derived mesenchymal stem cells; TNF-α: Tumor necrosis factor; p65: p65 kinase; MAPK: Mitogen-activated protein kinase; p38: p38 kinase; ERK: Extracellular signal-regulated kinase; JNK: Jun amino-terminal kinases; PDLSCs: Periodontal ligament stem cells; JAK2/STAT3: Janus kinase 2/ signal transducer and activator of transcription 3; hDPSCs: Human dental pulp stem cells

Conflicts of interest

The authors declare that there are no competing interests associated with the manuscript.

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Author contribution

Xianghu Zhao and Jing Hu wrote the main manuscript text. Jie Liu, Yi Meng and Xiangzhong Liu collated the data and carried out the figure analyses of AI. Yu Ning and Haijia Xu participated in the discussions. Zhanghua Li designed the study and helped revise the manuscript. All authors have read and approved the final submitted manuscript.

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