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Review Article

Glucocorticoid-Induced Osteoporosis: Current Treatments and the Promise of Herbal Medicine

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ABSTRACT

Glucocorticoids are extensively prescribed for the management of inflammatory, autoimmune, and allergic disorders; however, their prolonged use is a leading cause of secondary osteoporosis, known as glucocorticoid-induced osteoporosis (GIOP). GIOP is characterized by rapid bone loss, compromised bone microarchitecture, and an increased risk of fractures, often occurring within the initial months of therapy. The pathogenesis of GIOP is multifactorial, involving suppression of osteoblast differentiation and function, enhanced osteoclast survival, disruption of calcium and vitamin D metabolism, oxidative stress, and hormonal imbalance. Current therapeutic strategies for GIOP primarily include calcium and vitamin D supplementation, bisphosphonates, parathyroid hormone analogues, and monoclonal antibodies; however, long-term use of these agents is associated with adverse effects, limited adherence, and high cost, highlighting the need for safer and more sustainable treatment options. In this context, herbal medicine has emerged as a promising complementary or alternative approach for the prevention and management of GIOP. Numerous medicinal plants and their bioactive phytoconstituents have demonstrated osteoprotective effects through antioxidant, anti-inflammatory, anti-resorptive, and osteoanabolic mechanisms in preclinical and limited clinical studies. This review critically summarizes the pathophysiology of GIOP, current pharmacological interventions, and accumulating evidence supporting the role of herbal medicines in mitigating glucocorticoid-induced bone loss. Furthermore, challenges, safety considerations, and future research directions for the integration of herbal therapy into conventional GIOP management are discussed.

INTRODUCTION

Osteoporosis is a systemic skeletal disorder characterized by reduced bone mass, deterioration of bone microarchitecture, and increased bone

fragility, leading to an elevated risk of fractures. It represents a major public health concern worldwide, particularly among the elderly population, due to its association with chronic

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pain, physical disability, reduced quality of life, and increased mortality. While primary osteoporosis is commonly linked to aging and postmenopausal hormonal changes, secondary osteoporosis arises from underlying diseases or prolonged exposure to specific medications, among which glucocorticoids are the most significant contributors.¹

Glucocorticoids are widely prescribed for their potent anti-inflammatory and immunosuppressive properties and are essential in the treatment of various chronic conditions, including autoimmune diseases, asthma, rheumatoid arthritis, inflammatory bowel disease, organ transplantation, and certain malignancies. Despite their therapeutic benefits, long-term or high-dose glucocorticoid therapy is associated with a spectrum of adverse effects, with bone loss being one of the most prevalent and clinically significant complications. Even low doses of glucocorticoids, when administered over extended periods, can adversely affect bone metabolism and skeletal integrity.¹⁻²

Glucocorticoid-induced osteoporosis (GIOP) is the most common form of drug-induced osteoporosis and is characterized by rapid and progressive bone loss, particularly in trabecular-rich skeletal sites such as the spine and hip. Epidemiological studies suggest that up to 30–50% of patients receiving long-term glucocorticoid therapy may experience osteoporotic fractures. Notably, fracture risk increases early during treatment, often within the first three to six months, and may occur even in individuals with normal or moderately reduced bone mineral density, underscoring the unique pathophysiological mechanisms underlying GIOP.²

The clinical consequences of GIOP are substantial, as osteoporotic fractures are associated with

significant morbidity, functional impairment, increased healthcare burden, and mortality, particularly in elderly and immunocompromised patients. Vertebral fractures often remain asymptomatic but can lead to chronic pain, spinal deformities, and reduced pulmonary function, whereas hip fractures are associated with prolonged hospitalization, loss of independence, and increased mortality rates. These outcomes highlight the need for early prevention and effective management strategies in patients receiving glucocorticoid therapy.

Although several pharmacological agents are currently available for the prevention and treatment of GIOP, including calcium and vitamin D supplementation, bisphosphonates, and anabolic therapies, their long-term use is frequently limited by adverse effects, contraindications, suboptimal patient adherence, and economic constraints. Consequently, there is a growing interest in identifying safer, cost-effective, and sustainable therapeutic alternatives. In this context, herbal medicine and plant-derived bioactive compounds have gained considerable attention due to their multi-targeted mechanisms, favorable safety profiles, and historical use in bone-related disorders. Exploring the potential role of herbal interventions may offer novel strategies for improving long-term outcomes in the management of glucocorticoid-induced osteoporosis.³

2. Glucocorticoids: Mechanism of Action and Clinical Use

Glucocorticoids are steroid hormones synthesized in the adrenal cortex and play a critical role in regulating metabolism, immune responses, and stress adaptation. Synthetic glucocorticoids, such as prednisolone, dexamethasone, methylprednisolone, and hydrocortisone, are extensively used in clinical practice due to their potent anti-inflammatory and immunosuppressive



properties. Despite their therapeutic significance, prolonged use of glucocorticoids is a major risk factor for the development of glucocorticoid-induced osteoporosis.

2.1 Therapeutic Indications of Glucocorticoids

Glucocorticoids are widely prescribed across multiple medical specialties for the management of acute and chronic inflammatory conditions. Their common therapeutic indications include autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis; respiratory diseases including asthma and chronic obstructive pulmonary disease; gastrointestinal conditions such as inflammatory bowel disease; dermatological disorders; and allergic reactions. Additionally, glucocorticoids are frequently used in oncology as part of chemotherapy regimens, in organ transplantation to prevent graft rejection, and in endocrinology for adrenal insufficiency replacement therapy.³

Due to their rapid onset of action and strong efficacy, glucocorticoids are often used long-term in chronic illnesses. However, continuous exposure, especially at moderate to high doses, significantly increases the risk of systemic adverse effects. Among these, skeletal complications, including osteoporosis and fractures, represent one of the most serious and prevalent long-term consequences.

2.2 Molecular Mechanisms of Glucocorticoids

The biological effects of glucocorticoids are primarily mediated through the glucocorticoid receptor (GR), a ligand-activated transcription factor that belongs to the nuclear receptor superfamily. Upon cellular entry, glucocorticoids bind to cytoplasmic GRs, leading to receptor activation, dissociation from heat shock proteins,

and translocation into the nucleus. Within the nucleus, the glucocorticoid-GR complex regulates gene expression by binding to glucocorticoid response elements (GREs) in target genes or by interacting with other transcription factors.⁴

Glucocorticoids exert anti-inflammatory effects by suppressing the transcription of pro-inflammatory cytokines such as tumor necrosis factor- α , interleukin-1 β , and interleukin-6, while upregulating anti-inflammatory mediators. They also inhibit key signaling pathways, including nuclear factor- κ B and activator protein-1, thereby reducing immune cell activation and inflammatory responses. In addition to genomic actions, glucocorticoids produce rapid non-genomic effects through membrane-associated receptors and intracellular signaling cascades.

While these mechanisms account for their therapeutic efficacy, the same molecular pathways also disrupt normal bone remodeling. Glucocorticoids alter gene expression in osteoblasts, osteocytes, and osteoclasts, resulting in an imbalance between bone formation and bone resorption.

2.3 Adverse Skeletal Effects of Long-Term Glucocorticoid Therapy

Long-term glucocorticoid therapy exerts profound detrimental effects on skeletal health by impairing bone remodeling and reducing bone strength. One of the earliest and most prominent effects is the suppression of osteoblast differentiation and activity, leading to decreased bone formation. Glucocorticoids promote apoptosis of osteoblasts and osteocytes, thereby compromising bone matrix production and maintenance of bone microarchitecture.³⁻⁴

Simultaneously, glucocorticoids prolong the lifespan and activity of osteoclasts, resulting in



increased bone resorption, particularly during the initial phase of therapy. Additionally, glucocorticoids interfere with calcium homeostasis by reducing intestinal calcium absorption and increasing renal calcium excretion, leading to secondary hyperparathyroidism and further bone loss. They also suppress gonadal hormone production and inhibit the synthesis of insulin-like growth factor-1, both of which are critical for bone formation.

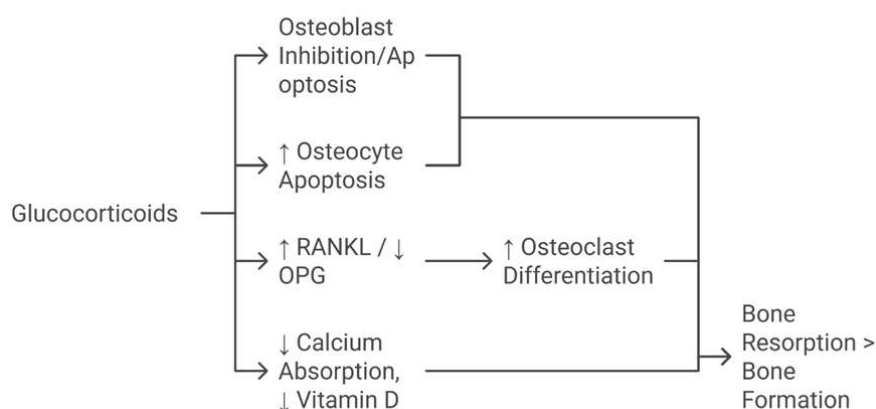
These cumulative effects lead to rapid loss of trabecular bone, reduced bone mineral density, and diminished bone quality, predisposing patients to fractures even at relatively preserved bone density levels. Vertebral and hip fractures are particularly common and may occur early during treatment, emphasizing the need for timely preventive and

therapeutic interventions in patients receiving long-term glucocorticoid therapy.⁵

3. Pathophysiology of Glucocorticoid-Induced Osteoporosis

Glucocorticoid-induced osteoporosis (GIOP) is a complex, multifactorial disorder resulting from direct and indirect effects of glucocorticoids on bone cells, mineral metabolism, and endocrine regulation. Unlike postmenopausal osteoporosis, GIOP is characterized by a rapid decline in bone strength that may occur even in the presence of modest reductions in bone mineral density. The underlying pathophysiology primarily involves suppression of bone formation, increased bone resorption in the early phase of treatment, and long-term impairment of bone quality.

Mechanism of Glucocorticoid-Induced Bone Loss



3.1 Effects on Osteoblasts and Osteocytes

The most profound and sustained effect of glucocorticoids in GIOP is the inhibition of osteoblast function and survival. Glucocorticoids suppress the differentiation of mesenchymal stem cells into osteoblasts while favoring adipogenic lineage commitment. This shift results in reduced osteoblast number and diminished bone matrix synthesis. Additionally, glucocorticoids downregulate the expression of key osteogenic

transcription factors such as runt-related transcription factor 2 (Runx2) and osterix, further impairing bone formation.

Glucocorticoids also induce apoptosis of mature osteoblasts and osteocytes. Osteocytes play a pivotal role in mechanotransduction and maintenance of bone microarchitecture; their loss disrupts the bone's adaptive response to mechanical stress. Increased osteocyte apoptosis compromises the lacunar–canalicular network,

leading to reduced bone strength and impaired microstructural integrity, even before significant changes in bone mineral density become evident.⁴⁻⁵

3.2 Effects on Osteoclasts

In contrast to their inhibitory effects on osteoblasts, glucocorticoids initially enhance osteoclast-mediated bone resorption. This is primarily mediated through increased expression of receptor activator of nuclear factor- κ B ligand (RANKL) and reduced production of its decoy receptor osteoprotegerin (OPG) by osteoblasts and stromal cells. The resulting increase in the RANKL/OPG ratio promotes osteoclast differentiation, activation, and survival.

Furthermore, glucocorticoids prolong the lifespan of osteoclasts by inhibiting apoptosis, contributing to accelerated bone resorption, particularly during the early phase of therapy. Although osteoclast activity may decline with prolonged glucocorticoid exposure, the persistent suppression of bone formation leads to a net negative balance in bone remodeling, driving progressive bone loss.⁶

3.3 Alteration in Calcium and Vitamin D Metabolism

Glucocorticoids adversely affect calcium homeostasis by reducing intestinal calcium absorption through antagonism of vitamin D action and downregulation of calcium transport proteins. Simultaneously, they increase renal calcium excretion, resulting in a negative calcium balance. This decrease in circulating calcium levels stimulates parathyroid hormone secretion, leading to secondary hyperparathyroidism.

Elevated parathyroid hormone levels enhance bone resorption to maintain serum calcium levels,

further exacerbating bone loss. Additionally, glucocorticoids impair the hepatic and renal activation of vitamin D, reducing its biological availability and effectiveness. These disruptions collectively contribute to decreased bone mineralization and increased fracture susceptibility.

3.4 Role of Inflammatory Cytokines and Oxidative Stress

Although glucocorticoids are potent anti-inflammatory agents, chronic exposure paradoxically contributes to bone loss through complex interactions involving inflammatory cytokines and oxidative stress. Long-term glucocorticoid therapy alters the local bone microenvironment by affecting cytokine signaling pathways related to bone turnover.

Glucocorticoids increase the generation of reactive oxygen species while simultaneously suppressing antioxidant defense mechanisms. Oxidative stress promotes osteoblast and osteocyte apoptosis and enhances osteoclast differentiation. Moreover, oxidative stress interferes with Wnt/ β -catenin signaling, a crucial pathway for osteoblast differentiation and bone formation, thereby further impairing skeletal homeostasis.⁷

3.5 Hormonal Dysregulation and Bone Remodeling Imbalance

Glucocorticoids disrupt multiple hormonal axes that are essential for maintaining bone health. They suppress the hypothalamic–pituitary–gonadal axis, leading to reduced estrogen and testosterone levels, both of which play critical roles in inhibiting bone resorption and supporting bone formation. Additionally, glucocorticoids reduce circulating levels of growth hormone and insulin-like growth factor-1, which are key anabolic regulators of bone metabolism.



The combined effects of osteoblast suppression, transient osteoclast activation, calcium imbalance, oxidative damage, and hormonal dysregulation result in a profound imbalance between bone formation and resorption. This imbalance leads to

decreased bone mass, impaired microarchitecture, and reduced bone strength, ultimately increasing the risk of fractures in patients receiving long-term glucocorticoid therapy.⁵

Table 1. Pathophysiological Mechanisms Involved in Glucocorticoid-Induced Osteoporosis

Mechanism	Biological Effect	Impact on Bone Health
Inhibition of osteoblast differentiation	Suppression of Runx2, Wnt/ β -catenin signaling	Reduced bone formation
Increased osteoblast and osteocyte apoptosis	Mitochondrial dysfunction, oxidative stress	Loss of bone matrix integrity
Enhanced osteoclast activity	Upregulation of RANKL and downregulation of OPG	Increased bone resorption
Altered calcium homeostasis	Reduced intestinal calcium absorption	Secondary hyperparathyroidism
Vitamin D metabolism impairment	Decreased active vitamin D synthesis	Compromised mineralization
Increased oxidative stress	Excess ROS generation	Osteocyte damage
Pro-inflammatory cytokine activation	Elevated TNF- α , IL-1 β , IL-6	Bone remodeling imbalance

4. Risk Factors and Diagnosis of Glucocorticoid-Induced Osteoporosis (GIOP)

Glucocorticoid-induced osteoporosis (GIOP) develops due to a combination of drug-related, patient-related, and clinical factors. Early

identification of high-risk individuals is essential, as bone loss occurs rapidly—often within the first 3–6 months of therapy. Accurate diagnosis relies on clinical evaluation, bone mineral density measurements, fracture risk assessment tools, and biochemical markers of bone turnover.

How to assess and manage GIOP risk?



4.1 Dose and Duration of Glucocorticoid Therapy⁶

The risk of GIOP is strongly correlated with both the dose and duration of glucocorticoid use.

- **Dose-dependent risk:** Even low doses (≥ 2.5 mg/day prednisolone equivalent) administered over several months can cause measurable bone loss. Higher doses (> 7.5

mg/day) significantly increase the risk of vertebral and hip fractures.

- **Duration-dependent risk:** Rapid bone loss occurs in the first 3–6 months, driven by increased osteoclast activity and suppressed osteoblast function. Continued therapy leads to progressive bone deterioration.
- **Cumulative exposure:** Fracture risk increases with cumulative lifetime glucocorticoid dose, even after therapy ceases.
- **Routes of administration:** Systemic therapy (oral, IV) carries the highest risk, but inhaled, intra-articular, and topical glucocorticoids also contribute to bone loss with prolonged or high-dose use.

4.2 Patient-Related Risk Factors

Several intrinsic and extrinsic factors modulate an individual's susceptibility to GIOP:

- **Age:** Older adults have lower baseline bone mass and reduced regenerative capacity.

- **Gender:** Postmenopausal women are at particularly high risk due to estrogen deficiency.
- **Nutritional factors:** Low calcium and vitamin D intake, malnutrition, and gastrointestinal disorders impair bone health.
- **Lifestyle factors:** Smoking, excessive alcohol intake, physical inactivity, and low body mass index reduce bone strength.
- **Comorbidities:** Chronic inflammatory diseases (rheumatoid arthritis, COPD, IBD), endocrine disorders (hyperthyroidism, hypogonadism), diabetes mellitus, and chronic kidney disease increase susceptibility.
- **Genetic predisposition:** Family history of osteoporosis or fractures enhances risk.
- **Previous fractures:** A personal history of fragility fractures strongly predicts future fracture risk, independent of bone mineral density.

Table 2. Risk Factors Associated with Glucocorticoid-Induced Osteoporosis

Risk Factor Category	Examples	Clinical Relevance
Glucocorticoid-related	High daily dose (>5 mg prednisolone equivalent), long duration	Strongest predictor of fracture
Patient demographics	Advanced age, female sex	Greater baseline bone loss
Disease-related	Rheumatoid arthritis, SLE, asthma	Independent fracture risk
Lifestyle factors	Smoking, alcohol misuse, sedentary lifestyle	Accelerates bone loss
Nutritional factors	Low calcium and vitamin D intake	Reduced bone mineralization
Hormonal factors	Hypogonadism, menopause	Reduced osteogenesis

4.3 Diagnostic Tools ⁷

Accurate diagnosis of GIOP involves integrating clinical history, bone mineral density measurements, fracture risk assessments, and biochemical markers.

Bone Mineral Density (DEXA)

Dual-energy X-ray absorptiometry (DEXA) is the gold standard for assessing bone mineral density (BMD).

- **Sites measured:** lumbar spine, total hip, femoral neck, and sometimes distal forearm.
- **Interpretation:**
 - T-score ≤ -2.5 indicates osteoporosis.
 - T-score between -1.0 and -2.5 indicates osteopenia.
- **Limitations:** In early GIOP, BMD may remain relatively normal despite increased fracture risk due to rapid microarchitectural deterioration. Therefore, BMD must be interpreted alongside clinical risk factors.

DEXA is recommended at the initiation of glucocorticoid therapy and repeated every 6–12 months depending on dose and clinical status.

FRAX Score

The FRAX (Fracture Risk Assessment) tool estimates the 10-year probability of major osteoporotic and hip fractures.

- Incorporates risk factors such as age, sex, BMI, smoking, alcohol use, prior fractures, rheumatoid arthritis, and glucocorticoid exposure.
- Allows adjustment for glucocorticoid dose:
 - **Low dose (<2.5 mg/day):** lower risk
 - **Medium dose (2.5–7.5 mg/day):** standard FRAX risk
 - **High dose (>7.5 mg/day):** significantly higher risk

- Particularly useful when DEXA values alone underestimate fracture risk.

FRAX is widely used to guide decisions on initiating prophylactic therapy in glucocorticoid users.

Biochemical Markers of Bone Turnover

Biochemical markers provide insights into dynamic bone remodeling changes:

Markers of Bone Formation

- Serum osteocalcin
- Bone-specific alkaline phosphatase (BSAP)
- N-terminal propeptide of type I procollagen (P1NP)

Markers of Bone Resorption

- C-terminal telopeptide of type I collagen (CTX)
- N-terminal telopeptide (NTX)

Key features:

- In early GIOP, resorption markers rise sharply, whereas formation markers decrease due to osteoblast suppression.
- Useful for monitoring treatment response to bisphosphonates, teriparatide, and lifestyle interventions.

Although not diagnostic alone, biochemical markers complement BMD and FRAX in understanding disease progression.⁸

Table 3. Diagnostic Approaches for GIOP

Diagnostic Tool	Principle	Clinical Utility
Dual-energy X-ray absorptiometry (DEXA)	Measures bone mineral density	Gold standard for diagnosis
FRAX® score	Fracture risk calculation	Assesses 10-year fracture risk
Serum calcium and phosphate	Mineral metabolism evaluation	Detects metabolic imbalance
Bone formation markers (P1NP, osteocalcin)	Osteoblast activity	Monitoring therapy response

Bone resorption markers (CTX, NTX)	Osteoclast activity	Early marker of bone loss
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5. Current Pharmacological Management of Glucocorticoid-Induced Osteoporosis

The primary goal of pharmacological management in glucocorticoid-induced osteoporosis (GIOP) is to prevent bone loss, preserve bone strength, and reduce fracture risk. Current treatment strategies focus on correcting glucocorticoid-induced disturbances in bone remodelling and mineral metabolism. Clinical guidelines recommend early initiation of preventive therapy in patients receiving long-term glucocorticoid treatment, particularly those at moderate to high fracture risk.

5.1 Calcium and Vitamin D Supplementation

Calcium and vitamin D supplementation form the cornerstone of GIOP prevention and are recommended for all patients receiving glucocorticoid therapy unless contraindicated. Glucocorticoids impair intestinal calcium absorption and reduce vitamin D activation, leading to negative calcium balance and secondary hyperparathyroidism.

- **Calcium:** Typically prescribed at doses of 1000–1200 mg/day
- **Vitamin D:** Administered at doses of 800–1000 IU/day or higher, depending on serum levels

Supplementation helps maintain serum calcium levels, suppress parathyroid hormone secretion, and modestly reduce bone loss. However, calcium and vitamin D alone are insufficient to prevent fractures in high-risk patients and are therefore used as adjunctive therapy alongside pharmacological agents.⁹

5.2 Bisphosphonates

Bisphosphonates are considered first-line therapy for the prevention and treatment of GIOP. Commonly used agents include alendronate, risedronate, ibandronate, and zoledronic acid. These drugs inhibit osteoclast-mediated bone resorption by binding to hydroxyapatite and inducing osteoclast apoptosis.

Clinical trials have demonstrated that bisphosphonates significantly increase bone mineral density at the lumbar spine and hip and reduce the incidence of vertebral fractures in glucocorticoid-treated patients. Both oral and intravenous formulations are effective, making them suitable for patients with gastrointestinal intolerance or poor adherence.

Despite their efficacy, long-term use of bisphosphonates is associated with risks such as atypical femoral fractures, osteonecrosis of the jaw, and gastrointestinal adverse effects, necessitating careful patient selection and monitoring.¹⁰

5.3 Parathyroid Hormone Analogues (Teriparatide)

Teriparatide, a recombinant form of human parathyroid hormone (PTH 1–34), is an anabolic agent that stimulates bone formation by enhancing osteoblast activity and survival. It is particularly beneficial in patients with severe GIOP or those who do not respond adequately to antiresorptive therapy.

Clinical studies have shown that teriparatide produces greater increases in bone mineral density and reduces vertebral fracture risk more effectively than bisphosphonates in patients on chronic glucocorticoid therapy. However, its use is limited to a maximum of 24 months due to safety



concerns and is contraindicated in patients with an increased risk of osteosarcoma.

5.4 Denosumab and Other Biologics

Denosumab is a monoclonal antibody that targets receptor activator of nuclear factor- κ B ligand (RANKL), thereby inhibiting osteoclast differentiation and activity. It effectively reduces bone resorption and improves bone mineral density in patients with GIOP.

Denosumab is administered subcutaneously every six months and is particularly advantageous for patients who are intolerant to bisphosphonates or have renal impairment. However, discontinuation may result in rapid bone loss and rebound fractures, necessitating transition therapy.¹¹

Other biologic agents targeting bone remodeling pathways, such as sclerostin inhibitors, are under investigation and show potential for future use in glucocorticoid-induced bone loss.

5.5 Selective Estrogen Receptor Modulators (SERMs)

Selective estrogen receptor modulators, such as raloxifene, exert estrogen-like effects on bone while acting as estrogen antagonists in breast and uterine tissue. SERMs reduce bone resorption and modestly increase bone mineral density, particularly in postmenopausal women.

While SERMs may be considered in selected patients with GIOP, their use is limited by an

increased risk of venous thromboembolism and lack of robust evidence for fracture risk reduction in glucocorticoid-treated populations.¹²

5.6 Limitations and Side Effects of Existing Therapies

Despite advances in pharmacological management, current therapies for GIOP have several limitations:

- **Adverse effects:** Gastrointestinal intolerance, renal toxicity, hypocalcemia, and rare but serious complications such as osteonecrosis of the jaw.
- **Limited anabolic options:** Few agents directly stimulate bone formation.
- **Cost and accessibility:** Biological therapies are expensive and may limit long-term use.
- **Patient adherence:** Complex dosing regimens and fear of side effects reduce compliance.
- **Long-term safety concerns:** Prolonged antiresorptive therapy may impair bone remodeling and bone quality.

These challenges emphasize the need for safer, more affordable, and long-term therapeutic alternatives, supporting increasing interest in complementary approaches such as herbal medicine in the management of glucocorticoid-induced osteoporosis.¹³

Table 4. Pharmacological Agents Used in the Management of GIOP

Drug Class	Examples	Mechanism of Action	Limitations
Calcium & Vitamin D	Calcium carbonate, cholecalciferol	Improve mineralization	Inadequate monotherapy
Bisphosphonates	Alendronate, risedronate	Inhibit osteoclast-mediated resorption	GI intolerance, jaw osteonecrosis
PTH analogues	Teriparatide	Stimulate osteoblast activity	Daily injections, high cost
RANKL inhibitor	Denosumab	Suppresses osteoclast formation	Rebound fractures on withdrawal

SERMs	Raloxifene	Estrogen receptor modulation	Thromboembolic risk
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6. Herbal Medicine in Bone Health: An Overview

Herbal medicine has been used for centuries in the prevention and treatment of skeletal disorders and is gaining renewed scientific interest due to its multi-targeted mechanisms and favorable safety profile. In the context of glucocorticoid-induced osteoporosis (GIOP), herbal interventions offer a promising complementary approach by addressing oxidative stress, inflammation, hormonal imbalance, and impaired bone remodeling pathways that are not fully corrected by conventional therapies.

6.1 Rationale for Herbal Interventions

Current pharmacological treatments for GIOP primarily focus on inhibiting bone resorption or stimulating bone formation; however, long-term use is often limited by adverse effects, cost, and patient non-adherence. Herbal medicines provide several theoretical and practical advantages in bone health management:

- **Multimodal mechanisms of action:** Herbal drugs act on multiple molecular targets simultaneously, including osteoblast stimulation, osteoclast inhibition, antioxidant defense, and cytokine modulation.
- **Favorable safety profile:** Many medicinal plants have a long history of traditional use with relatively fewer adverse effects when used appropriately.
- **Chronic disease suitability:** Herbal medicines are particularly suitable for long-term management of chronic conditions such as osteoporosis.

- **Synergistic potential:** Herbal agents may enhance the efficacy of conventional anti-osteoporotic drugs while minimizing their side effects.
- **Cost-effectiveness and accessibility:** Plant-based therapies are often more affordable and widely available, especially in developing regions.

These attributes make herbal interventions attractive candidates for adjunctive or alternative therapy in GIOP management.¹⁴

6.2 Traditional Systems of Medicine (Ayurveda, TCM, etc.)

Traditional medical systems have long recognized bone health as a critical component of overall well-being.

- **Ayurveda:** In Ayurveda, bone tissue (*Asthi Dhātu*) is maintained through proper nutrition, metabolism, and balance of bodily energies (*Doshas*). Herbs such as *Withania somnifera*, *Cissus quadrangularis*, *Terminalia arjuna*, and *Asparagus racemosus* are traditionally used to enhance bone strength, accelerate fracture healing, and prevent age-related bone loss.
- **Traditional Chinese Medicine (TCM):** TCM associates bone health with kidney function (*Shen*), and therapies aim to “tonify the kidney” to strengthen bones. Medicinal plants such as *Epimedium brevicornum*, *Drynaria fortunei*, and *Achyranthes bidentata* are commonly used for treating osteoporosis and bone fragility.



- **Other traditional systems:** Unani, Siddha, and folk medicine also employ calcium-rich plants, adaptogens, and anti-inflammatory herbs for skeletal disorders.

Modern pharmacological research has begun to validate many of these traditional claims, demonstrating significant osteoprotective effects in experimental and clinical settings.

6.3 Phytochemicals with Osteoprotective Potential¹³⁻¹⁴

The therapeutic efficacy of herbal medicines in bone health is largely attributed to their bioactive phytochemicals. These compounds influence bone remodeling by regulating cellular signaling pathways, oxidative balance, and inflammatory responses.

Flavonoids

Flavonoids are polyphenolic compounds widely distributed in plants and are among the most extensively studied phytochemicals for bone protection.

- Promote osteoblast differentiation and mineralization
- Inhibit osteoclast formation by suppressing the RANKL pathway
- Exhibit strong antioxidant and anti-inflammatory properties
- Mimic estrogen-like activity, beneficial in glucocorticoid-related and postmenopausal bone loss

Examples include quercetin, kaempferol, genistein, and icariin.

Saponins

Saponins are glycosides known for their osteoanabolic and antiresorptive effects.

- Enhance osteoblast proliferation and collagen synthesis
- Suppress osteoclast activation and bone resorption
- Improve calcium metabolism and bone mineralization

Steroidal saponins found in plants such as *Asparagus*, *Dioscorea*, and *Tribulus* species have shown promising results in experimental osteoporosis models.

Alkaloids

Alkaloids possess diverse pharmacological activities and contribute to bone health mainly through anti-inflammatory and antioxidant effects.

- Reduce osteoclast-mediated bone resorption
- Protect osteoblasts from glucocorticoid-induced apoptosis
- Modulate cytokines involved in bone remodeling

Certain alkaloids have demonstrated protective effects against oxidative stress-mediated skeletal damage.

Polyphenols

Polyphenols, including phenolic acids and tannins, play a critical role in maintaining bone integrity.

- Neutralize reactive oxygen species and prevent oxidative damage to bone cells
- Inhibit inflammatory mediators that stimulate bone resorption
- Support osteoblast differentiation through Wnt/ β -catenin signaling

Curcumin, resveratrol, catechins, and ellagic acid are notable polyphenols with documented osteoprotective activity.¹⁵



Table 6. Molecular Mechanisms of Herbal Medicines in GIOP

Mechanism	Herbal Actions	Outcome on Bone
Antioxidant activity	ROS scavenging, Nrf2 activation	Prevents osteocyte apoptosis
Anti-inflammatory effects	NF- κ B inhibition	Reduced bone resorption
RANK/RANKL/OPG modulation	Downregulation of RANKL	Inhibited osteoclastogenesis
Promotion of osteoblastogenesis	Activation of BMP-2, Wnt signaling	Enhanced bone formation
Hormonal modulation	Phytoestrogen/adaptogenic effects	Balanced bone remodeling

7. Herbal Drugs with Potential Against GIOP

7.1 Withania somnifera (Ashwagandha)

Mechanism

- Adaptogenic and anti-stress effects that may indirectly protect bone by normalizing hypothalamic–pituitary–adrenal axis activity.
- Promotes osteoblast differentiation and mineralization by upregulating osteogenic markers (e.g., Runx2, osteocalcin) in preclinical models.
- Antioxidant and anti-inflammatory actions reduce ROS and pro-resorptive cytokines (TNF- α , IL-1 β), limiting osteoclastogenesis.
- May downregulate RANKL expression and/or upregulate OPG, shifting balance toward bone formation.

Preclinical / Clinical Evidence

- Multiple in vitro and animal studies report increased bone formation, improved fracture healing, and attenuation of steroid-induced bone loss.
- Clinical data are limited; small human trials for general musculoskeletal health exist but robust RCTs in GIOP are lacking.

Safety

- Generally well tolerated in traditional doses. Reported adverse effects are rare and mild (GI upset, drowsiness).

- Caution with concurrent sedatives, thyroid hormone, or immunosuppressants. Pregnancy safety not established.
- Standardization of extract (withanolide content) is important for reproducibility.

7.2 Curcuma longa (Curcumin)

Mechanism

- Potent anti-inflammatory via inhibition of NF- κ B and COX-2; reduces cytokine-driven osteoclastogenesis.
- Antioxidant properties protect osteoblasts and osteocytes from glucocorticoid-induced oxidative damage.
- Modulates RANK/RANKL/OPG axis and can stimulate osteoblastic differentiation (Wnt/ β -catenin signaling reported in preclinical studies).
- May enhance bone formation and reduce resorption concurrently.

Preclinical / Clinical Evidence

- Numerous animal and cell studies show curcumin attenuates bone loss in ovariectomy and glucocorticoid models, improves BMD and microarchitecture.
- Human trials for osteoporosis are sparse and typically small; bioavailability (poor oral absorption) is a recurring limitation in translating effects to clinic.

Safety

- Generally safe at customary doses; high doses may cause GI upset.
- Potential interactions with anticoagulants and drugs metabolized by CYP enzymes; curcumin may affect platelet function.
- Use standardized, bioavailable formulations (e.g., complexed with piperine or formulated as nanopreparations) in clinical research.

7.3 *Cissus quadrangularis*¹⁸

Mechanism

- Traditionally used for fracture healing; stimulates osteoblast proliferation and collagen synthesis.
- Increases expression of bone matrix proteins and may promote angiogenesis at fracture sites.
- Antiresorptive effects reported via downregulation of osteoclast markers and inflammatory mediators.

Preclinical / Clinical Evidence

- Animal models demonstrate accelerated fracture healing, increased callus formation, and improved bone strength.
- A few small human studies (fracture healing/postoperative bone repair) report faster recovery; evidence specifically in GIOP is limited and mostly preclinical.

Safety

- Generally well tolerated in traditional formulations. Mild GI symptoms reported.
- Quality control is important—commercial products vary widely in composition.
- Monitor if used with osteoporosis drugs; interaction data are limited.

7.4 *Epimedium (Icariin)*

Mechanism

- Icariin is a flavonoid glycoside with estrogen-like (phytoestrogenic) activity that stimulates osteoblast differentiation and suppresses osteoclastogenesis.
- Activates BMP-2 and Wnt/ β -catenin signaling, enhances bone matrix formation, and upregulates Runx2 and osteocalcin.
- Downregulates RANKL and inflammatory cytokines; antioxidant properties also contribute.

Preclinical / Clinical Evidence

- Strong preclinical evidence: animal models (including steroid/ovariectomy models) show improved BMD, trabecular architecture, and reduced bone turnover.
- Clinical trials are limited but some TCM formulations containing Epimedium report benefits for menopausal bone loss; high-quality RCTs in GIOP are lacking.

Safety

- Generally safe in studied doses; phytoestrogenic activity suggests caution in hormone-sensitive cancers.
- Potential interactions with estrogenic drugs and anticoagulants; more safety data needed for long-term use.

7.5 *Glycyrrhiza glabra (Licorice)*¹⁹

Mechanism

- Glycyrrhizin and other constituents exhibit anti-inflammatory and antioxidant effects that may mitigate bone resorption.
- Some components have mild estrogenic or glucocorticoid-modulating effects which could influence bone metabolism.

Preclinical / Clinical Evidence

- Preclinical studies indicate potential protective effects on bone turnover markers and modest anabolic signals in certain models. Evidence specific to steroid-induced bone loss is limited and mixed.

Safety

- Notable safety concerns: glycyrrhizin can cause pseudo-hyperaldosteronism (hypertension, hypokalemia, fluid retention) with chronic/high intake—this is especially relevant for patients on glucocorticoids who may already have metabolic/cardiovascular risks.
- Can interfere with potassium-sparing diuretics and ACE inhibitors; caution advised.
- Deglycyrrhizinated licorice (DGL) removes glycyrrhizin and may lessen endocrine adverse effects, but efficacy profiles may differ.

7.6 *Emblica officinalis* (Amla)²⁰

Mechanism

- Rich source of vitamin C and polyphenols; strong antioxidant capacity protects osteoblasts from oxidative damage.
- Stimulates collagen synthesis and may enhance osteoblastic differentiation via antioxidant-mediated pathways (Wnt signaling modulation reported in preclinical literature).
- Anti-inflammatory effects reduce pro-resorptive cytokines.

Preclinical / Clinical Evidence

- Animal studies show attenuation of bone loss, improved bone strength, and positive effects on bone turnover markers.

- Human data for osteoporosis are limited; amla is often studied as part of polyherbal formulations showing some promise in bone health contexts.

Safety

- Generally safe and well tolerated at dietary and therapeutic doses. Rare GI complaints.
- Minimal known major drug interactions, but quality and standardization of extracts vary.

8. Mechanisms of Action of Herbal Medicines in GIOP

Herbal medicines act on multiple interconnected molecular and cellular pathways that are relevant to the pathogenesis of glucocorticoid-induced osteoporosis (GIOP). Unlike single-target drugs, many phytochemicals exert pleiotropic effects — antioxidant, anti-inflammatory, endocrine-modulating and direct actions on osteoblast/osteoclast lineage cells — which together can counteract the specific mechanisms by which glucocorticoids damage bone. Below is a focused, mechanism-oriented breakdown with examples and clinical relevance.¹⁴

8.1 Antioxidant and Anti-Inflammatory Effects

What happens in GIOP: Chronic glucocorticoid exposure increases reactive oxygen species (ROS) and impairs antioxidant defenses, promoting osteoblast/osteocyte apoptosis and enhancing osteoclastogenesis via redox-sensitive signaling (e.g., NF- κ B).

Herbal actions

- **ROS scavenging & Nrf2 activation:** Polyphenols (curcumin, resveratrol, catechins, emblicanin from amla) neutralize free radicals and can activate Nrf2-dependent antioxidant responses,



protecting osteoblasts and osteocytes from apoptosis.

- **Inhibition of pro-inflammatory signaling:** Many phytochemicals suppress NF- κ B and MAPK pathways, reduce COX-2 expression, and lower levels of TNF- α , IL-1 β and IL-6 — cytokines that drive osteoclast differentiation.
- **Net effect:** reduced oxidative damage, preserved osteoblast viability and lowered inflammatory drive toward bone resorption.

Representative phytochemicals: curcumin, resveratrol, quercetin, icariin, withanolides.

8.2 Modulation of the RANK/RANKL/OPG Pathway

What happens in GIOP: Glucocorticoids increase the RANKL/OPG ratio (more RANKL, less OPG) in stromal/osteoblastic cells, promoting osteoclastogenesis and bone resorption.

Herbal actions

- **Decrease RANKL expression / increase OPG:** Several herbs downregulate RANKL and/or upregulate OPG, shifting the balance away from osteoclast formation.
- **Direct inhibition of osteoclast signaling:** Downstream effectors such as NFATc1 and c-Fos (transcription factors required for osteoclastogenesis) are suppressed by specific phytochemicals.
- **Net effect:** reduction in osteoclast differentiation, activity and survival, attenuating early glucocorticoid-driven bone loss.

Representative phytochemicals: icariin, genistein, certain flavonoids, saponins.

8.3 Promotion of Osteoblastogenesis

What happens in GIOP: Glucocorticoids inhibit mesenchymal stem cell (MSC) commitment to osteoblasts, suppress Runx2/osterix, and reduce anabolic growth factors (IGF-1), leading to reduced bone formation.¹⁵

Herbal actions

- **Activation of osteogenic transcriptional programs:** Phytochemicals can upregulate Runx2, osterix, osteocalcin and other osteoblast markers, promoting MSC osteogenic differentiation.
- **Wnt/ β -catenin & BMP signaling:** Many herbal agents enhance Wnt signaling and BMP-2 expression — critical pathways for osteoblast proliferation and mineralization.
- **Stimulation of anabolic hormones/factors:** Some adaptogens may restore IGF-1 or improve local growth factor milieu favourable to bone formation.
- **Net effect:** increased osteoblast number/function and improved matrix synthesis and mineralization.

Representative phytochemicals: icariin (Wnt/BMP activation), withanolides (osteoblastic gene upregulation), saponins.

8.4 Inhibition of Osteoclastogenesis

What happens in GIOP: Early in glucocorticoid therapy osteoclastogenesis and osteoclast lifespan increase, causing rapid bone loss.

Herbal actions



- **Direct osteoclast inhibition:** Phytochemicals suppress differentiation signals (RANKL → NFATc1), reduce expression of osteoclast markers (TRAP, cathepsin K), and promote osteoclast apoptosis.
- **Indirect effects via reduced inflammation & oxidative stress:** Lowered cytokines and ROS decrease osteoclast activators.
- **Net effect:** decreased bone resorption rates, stabilization of trabecular architecture.
- **Net effect:** partial restoration of hormonal milieu and improved resilience of bone to glucocorticoid insult.

Representative phytochemicals: withanolides (adaptogenic), isoflavones (phytoestrogens), certain triterpenoids.¹⁶

Clinical relevance & caveats

1. **Multi-target advantage:** Because GIOP involves oxidative stress, inflammation, hormonal disruption and direct cellular toxicity, the multimodal actions of herbs are conceptually well-suited to attenuate multiple pathogenic nodes simultaneously.
2. **Bioavailability matters:** Many promising phytochemicals (e.g., curcumin, resveratrol) have poor oral bioavailability — formulation strategies (piperine co-administration, nanoparticles, phospholipid complexes) are critical for translational success.
3. **Standardization & dose:** Therapeutic effects depend on standardized extracts (defined marker compounds) and validated dosing; variability in commercial products undermines reproducibility.
4. **Safety & interactions:** Herb–drug interactions (CYP modulation, anticoagulant effects, electrolyte changes with licorice) and endocrine effects (phytoestrogens) require careful evaluation before combined use with glucocorticoids or osteoporosis drugs.

Representative phytochemicals: curcumin, quercetin, certain saponins and alkaloids.

8.5 Hormone-Like and Adaptogenic Effects

What happens in GIOP: Glucocorticoids disrupt endocrine axes (HPA, sex steroids, GH/IGF-1) and may induce catabolic metabolic states that harm bone.

Herbal actions

- **Phytoestrogenic activity:** Isoflavones and flavonoids (e.g., genistein, icariin) exhibit estrogen-like effects on bone (ER β /ER α modulation), helping to reduce resorption and support formation—useful particularly in post-menopausal or hypogonadal contexts.
- **Adaptogens & HPA modulation:** Adaptogenic herbs (withanolides from Ashwagandha) may modulate stress responses and HPA axis activity, potentially reducing endogenous/exogenous glucocorticoid toxicity at the tissue level (indirect benefit).
- **Modulation of mineral and endocrine balance:** Some herbs improve calcium handling or influence vitamin D metabolism indirectly through anti-inflammatory effects.

9. Evidence from Preclinical and Clinical Studies

9.1 Animal Models of Glucocorticoid-Induced Bone Loss



Preclinical studies using rodent models (commonly rats and mice) are the backbone of mechanistic and efficacy research for herbal interventions in GIOP. Typical models employ chronic administration of glucocorticoids such as prednisolone, dexamethasone, or methylprednisolone to reproduce rapid trabecular bone loss, increased osteoclast activity, osteoblast suppression, microarchitectural deterioration, and reduced biomechanical strength.

Herbal agents investigated in these models frequently demonstrate:

- Preservation of bone mineral density (BMD) and trabecular microarchitecture (micro-CT/histomorphometry).
 - Restoration of osteoblast markers (Runx2, osteocalcin) and suppression of osteoclast markers (TRAP, cathepsin K).
 - Reductions in oxidative stress and pro-resorptive cytokines (TNF- α , IL-1 β).
 - Improved biomechanical outcomes (increased compressive strength, stiffness) and accelerated fracture healing in fracture models.
- Trials are often small, short-duration, and heterogenous in formulations (single herbs vs polyherbal mixtures), endpoints (BMD, bone turnover markers, symptoms), and populations.
 - Some studies show favorable effects on bone turnover markers and modest improvements in BMD or clinical recovery in fracture patients, but robust randomized controlled trials (RCTs) with fracture endpoints in chronic glucocorticoid users are largely absent.
 - Safety and tolerability are generally acceptable in short-term studies, but long-term safety data, particularly in the context of concurrent glucocorticoid therapy, are limited.

These preclinical data are valuable for elucidating mechanisms (RANKL/OPG modulation, Wnt/BMP activation, antioxidant pathways) and for selecting candidate phytochemicals for translation.¹⁸

9.2 Human Clinical Trials

Clinical evidence for herbal therapies specifically in glucocorticoid-induced osteoporosis remains sparse. Most human studies addressing herbal effects on bone health focus on postmenopausal osteoporosis, fracture healing, or general bone markers rather than GIOP per se. Where clinical data exist for the candidate herbs:

9.3 Comparative Efficacy with Standard Treatment

Direct head-to-head comparisons of standardized herbal agents versus established anti-osteoporotic drugs (bisphosphonates, teriparatide, denosumab) in GIOP are essentially nonexistent. Preclinical comparative studies occasionally suggest that specific phytochemicals can approximate antiresorptive or anabolic effects seen with conventional agents, but such findings require cautious interpretation because dosing, bioavailability, and translational fidelity differ.

At present, the most realistic clinical role for herbal medicines is as:

- **Adjunctive agents** that may enhance bone-protective pathways and address gaps (oxidative stress, inflammation) not fully targeted by standard drugs, or
- **Alternative options** in patients who decline or cannot tolerate standard therapy — but only



with careful monitoring, standardization, and awareness of interaction risks.¹⁸

antiresorptive effects without balanced formation).

10. Safety, Toxicity, and Herb–Drug Interactions

10.1 Dose-Related Toxicity

Toxicity profiles of herbal agents vary widely by species, extract type, dose, and duration:

- Most candidate herbs (ashwagandha, curcumin, amla, icariin-containing extracts) are well tolerated at conventional doses in short-term studies.
- Certain compounds (e.g., glycyrrhizin in licorice) have well-documented dose-related toxicities — pseudo-hyperaldosteronism with hypertension, hypokalemia, and fluid retention — which are especially concerning in patients on systemic glucocorticoids or with cardiovascular risks.

Dose selection should be informed by toxicology data and scaled appropriately from preclinical models; conservative titration and monitoring are advisable in clinical use.

10.2 Long-Term Safety Concerns

Long-term safety data for many botanical preparations are insufficient. Key concerns include:

- Accumulation or chronic low-grade toxicity (hepatic, renal).
- Endocrine effects from phytoestrogens or glucocorticoid-modulating constituents (relevance in hormone-sensitive conditions).
- Effects on bone remodeling with prolonged, unregulated use (theoretical risk of impaired bone turnover if agents exert strong

Therefore, long-term use should be guided by periodic clinical and laboratory monitoring and supported by robust safety trials.²⁰

10.3 Interaction with Glucocorticoids and Anti-Osteoporotic Drugs

Herb–drug interactions can be pharmacokinetic (CYP enzyme induction/inhibition, P-gp modulation) or pharmacodynamic (additive, synergistic, or antagonistic effects on bone metabolism or electrolytes).

- **Pharmacokinetic interactions:** Curcumin and several flavonoids may inhibit CYP3A4 and other enzymes, potentially altering systemic glucocorticoid levels or the metabolism of co-administered drugs.
- **Pharmacodynamic interactions:** Combined antiresorptive effects with bisphosphonates or denosumab could theoretically increase suppression of bone remodeling; conversely, herbs with phytoestrogenic activity might interact with hormonal therapies.
- **Electrolyte/cardiovascular interactions:** Licorice increases risk when combined with drugs that affect potassium balance or blood pressure.

Clinicians and researchers should evaluate possible interactions through in vitro CYP panels, PK studies, and careful clinical monitoring when designing trials or recommending adjunctive herbal use.

11. Challenges and Limitations of Herbal Therapy

11.1 Lack of Standardization



A primary barrier to clinical translation is the variability of botanical products: different species, plant parts, extraction methods, and marker-compound content produce widely different pharmacological profiles. Standardization (quantified marker constituents, validated manufacturing) is essential for reproducibility.

11.2 Variability in Phytochemical Content

Natural variability (soil, climate, harvest time) and intentional adulteration affect active phytochemical concentrations. Batch-to-batch quality control, chromatographic fingerprinting, and defined potency metrics are required for research-grade materials.

11.3 Limited High-Quality Clinical Trials

Few rigorously designed RCTs test single standardized botanical extracts in well-characterized GIOP patient populations. Many existing trials suffer from small sample sizes, short follow-up, heterogeneous endpoints, and insufficient safety monitoring.

11.4 Regulatory Issues

Regulatory frameworks differ across jurisdictions; many botanical products are marketed as dietary supplements without stringent efficacy or safety requirements. For botanical agents to be integrated into standard clinical practice for GIOP, they must meet regulatory standards for pharmaceuticals or have clear guidelines for medical use.

12. Future Perspectives and Research Directions

12.1 Integrating Herbal Medicine with Conventional Therapy

Rational integration requires:

- Protocols for adjunctive use (timing, dosing, monitoring) alongside bisphosphonates, denosumab, or teriparatide.
- Clinical pathways that specify when herbal therapy may be considered (e.g., intolerance to first-line drugs, patient preference, low-resource settings).

12.2 Need for Randomized Controlled Trials

Priority trials include:

- **Phase II/III RCTs** of standardized, bioavailable formulations in patients initiating long-term glucocorticoids, with primary endpoints such as change in BMD (12–24 months) and validated secondary endpoints (bone turnover markers, incident fractures).
- **Safety/interaction studies** combining standardized herbal extracts with common osteoporosis drugs and glucocorticoids.
- **Adaptive trial designs** to efficiently test multiple botanicals and doses.

12.3 Nanotechnology and Novel Delivery Systems

Translational success for compounds with poor oral bioavailability (curcumin, resveratrol, icariin) depends on advanced delivery systems: nanoparticles, liposomal/phospholipid complexes, solid dispersions, and co-administration with absorption enhancers (e.g., piperine). These approaches can improve systemic exposure and therapeutic effect.

12.4 Biomarker-Based Efficacy Assessment

Employ a biomarker panel including P1NP, CTX, osteocalcin, inflammatory cytokines, and imaging biomarkers (HR-pQCT, trabecular bone score) for



early signal detection and mechanistic insight in trials.

12.5 Standardization & Regulatory Roadmap

Develop consensus guidelines for botanical standardization (marker compound(s), extraction method, potency assays) and propose regulatory pathways for clinical investigation and eventual therapeutic labeling.

CONCLUSION

Glucocorticoid-induced osteoporosis remains an important and often under-recognized complication of long-term glucocorticoid therapy, characterized by rapid bone loss, microarchitectural deterioration, and increased fracture risk. Existing pharmacotherapies—while effective—have limitations related to safety, adherence, cost, and incomplete mechanistic coverage. Herbal medicines and their bioactive phytochemicals offer a multimodal, potentially safer adjunct or alternative approach by targeting oxidative stress, inflammation, RANKL/OPG imbalance, and impaired osteoblastogenesis. Preclinical data are encouraging; however, robust clinical evidence in GIOP populations is limited.

To responsibly translate herbal therapies into clinical practice for GIOP, future work must prioritize standardized formulations, rigorous randomized trials with clinically meaningful endpoints, detailed safety and interaction studies, and improved delivery technologies to overcome bioavailability challenges. With these steps, selected herbal interventions may complement conventional treatments and expand the therapeutic armamentarium against glucocorticoid-induced bone loss.

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