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Herba Epimedii extraction overcome Rosiglitazone induced bone loss in diabetic rats

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Abstract

Diabetes mellitus patients are more prone to suffer from bone fractures. *Herba Epimedii* has been demonstrated to be an osteoporosis reducer in the past. However, it is yet uncertain if *Herba Epimedii* may protect diabetic rats from bone loss when co-administered with rosiglitazone (RSG). This study examines the impact of *Herba Epimedii* on bone oxidative stress and turnover markers in diabetic rats co-treated with rosiglitazone (RSG). Streptozotocin (STZ) causes diabetics. Wistar albino rats were placed into five groups, each with six rats: control (vehicle therapy), Streptozotocin (diabetes) group, *Herba Epimedii* group, Rosiglitazone, and Rosiglitazone +*Herba Epimedii*.

Each medication was given by gastric gavage once a day for 35 days. Insulin, oxidative stress, and bone turnover markers were measured in the blood using ELISA assays. Insulin and osteocalcin levels were significantly higher in diabetic rats administered *Herba Epimedii* than in diabetic control rats. *Herba Epimedii* may be able to prevent diabetic osteoporosis in RSG-treated diabetic rats by enhancing osteogenesis and lowering bone oxidative stress. The utility of *Herba Epimedii* as an osteoporosis therapy in diabetic individuals is supported by these findings.

Keywords: *Herba Epimedii*, Diabetes, Osteoporosis, Rosiglitazone

Introduction

Diabetes has been related to a variety of orthopaedic illnesses and problems in the lower limbs, many of which negatively influence one's quality of life.[1] Diabetes causes bone loss, osteopenia, and osteoporosis by increasing osteoclast activity.[2] Reports of delayed bone healing[3,4] reduced growth plate thickness,[5] and higher cortical porosity indicate the existence of poor bone quality in diabetic patients.[6] As a result, understanding the processes behind diabetes-related changes in bone microstructure necessitates a concentrated effort. Bone formation and bone resorption oppose each other at remodelling sites. A disruption in the delicate balance between these two processes causes osteoarthritis and osteoporosis.[7,8]

Clinical and experimental studies show that an increase in osteoclast activity and a reduction in osteoblast activity lowers bone strength.[9] STZ-induced diabetes has been proposed as a suitable model for learning about the pathophysiological foundations of diabetes-related bone loss in several studies.[10] The specific toxicity of STZ was used to create diabetic osteoporosis mouse models.[11-14] STZ has been found to be dangerous not just to the insulin-producing beta cells in the pancreas, but also to the skeletal muscles.

It's worth mentioning that skeletal muscle can function as a bone quality mediator and predictor.[15] STZ has been shown in several studies to decrease bone growth and increase the number of active osteoclasts. According to oxidative[16] stress and hyperglycemia, STZ lowers BMD and promotes trabecular bone loss. Both glucose metabolism and bone mass are controlled by PPAR. Recent data shows that anti-diabetic thiazolidinediones (e.g., RSG) have undesirable bone effects when used to modulate PPAR activation.[17]*Herba Epimedii* and its extracts have garnered worldwide attention for its anti-osteoporosis properties. A review of the literature indicated that a number of research on the bone-strengthening action of *Herba Epimedii* and some of its active components, such as total flavonoids and icariin, have recently been published.

Only a few writers have evaluated the anti-osteoporosis characteristics of *Herba Epimedii* and its most abundant active component, icariin. Pharmacokinetic and toxicology studies have verified the effectiveness and safety of *Herba Epimedii* and its most abundant active component, icariin.[18]Although *Herba Epimedii* has demonstrated significant anti-osteoporotic effects in a model of osteoporosis, it is uncertain if it can prevent bone loss in diabetic rats when combined with RSG. We decided to study in STZ-treated rats because of the impact of *Herba Epimedii* therapy on bone oxidative stress and turnover markers.

Materials and Methods

Animals:

The experiment was conducted with male Sprague-Dawley rats weighing 100–120 g obtained from King Khalid University's Central Animal House in Abha, Saudi Arabia. The rats were maintained in a temperature-controlled facility (21 °C, 12 hour light/dark cycle) and fed standard rat chow with full access to water. The animal ethics committee at King Khalid University approved the experiment methods, which included diabetes induction and sacrifice, and they were carried out in compliance with the

US National Institute of Health's standards for the care and use of laboratory animals (NIH Publication No. 85-23,revised 1996).

Induction of diabetes:

A single intraperitoneal injection of 60 mg/kg STZ dissolved in 10 mM citrate buffer was used to chemically produce diabetes-like hyperglycemia in rats (pH 4.5). The rats were given 5% glucose water for two days after receiving STZ to avoid drug-induced hypoglycemia. After a week of injection, animals with fasting blood glucose levels more than 11 mmol/L were classified as diabetic.[19] The rats in the control group got the same amount of isotonic NaCl injection as the experimental animals.

Experimental design:

The rats were split into five groups: control (vehicle, Non-Diabetic control, n=6), diabetic control, Herba Epimedii(300 mg/kg/day, n=6), Rosiglitazone (4 mg/kg/day, n=6), and combination (Herba Epimedii 300 mg/kg/day + Rosiglitazone 4 mg/kg/day, n=6). Each medication was given by gastric gavage once a day for 35 days. Throughout the trial, the animals were examined daily for symptoms of illness. There were no animals that were really sick or died before the completion of the trial. The rats administered saline instead of streptozotocin in the control group (n=6) had normal blood glucose levels (120 mg/dl).

At the completion of the trial, all of the animals were fasted overnight and their blood glucose levels were tested. After that, the animals were administered anaesthesia with ketamine (80 mg/kg) and xylazine (8 mg/kg) before being killed at the end. The femur and tibia were separated by cutting near the stifle joint. The rats' blood (10–15 mL) was collected by heart puncture into a simple red-top tube containing no anticoagulants. The serum was stored in aliquots at 80 °C after centrifuging the blood samples at 4000 rpm for 15 minutes.

Determination of fasting blood glucose: After the rats had been fasted for 12–14 hours, blood samples were taken from their tail veins to test blood glucose levels using a glucometer. Blood will be taken with a 1-ml needle, put on a glucose strip, and quantified with a glucometer after the rats' tails have been washed with 70% (v/v) ethanol.

Measurements of bone oxidative stress and antioxidant activities:

The femur bone fragments were ground with a mortar and pestle. In a 10% (w/v) homogenising buffer, bone tissues were homogenised using a Teflon pestle (50 mM Tris-HCl, 1.15 percent KCl pH 7.4). The homogenates were spun at 9000 rpm for 10 minutes in a cooled centrifuge (4 °C) to remove nuclei and debris. The produced supernatant was tested using a TBARS assay kit for monitoring lipid peroxidation, a glutathione peroxidase (GPx) assay kit for GPX activity, and a superoxide dismutase (SOD) assay kit for SOD activity. The protein content was determined by the method[20], which utilised bovine serum albumin as a standard.

Marker of bone formation and bone resorption:

All bone formation and resorption indicators were measured using serum. A Rat-Mid Osteocalcin ELISA kit (IDS, UK) was used to assess the osteocalcin level, whereas a rat BALP ELISA kit was used to determine the BALP level (Qayee, Shanghai). Rat deoxypyridinoline (DPD) ELISA Kit (Qayee, Shanghai) was used to assess bone resorption DPD (Qayee, Shanghai). The optical density of all samples was measured at 450 nm using a microplate reader (Epoch Microplate Spectrophotometer, BioTek, USA).[21]

Statistical analysis:

All of the data was analysed using ANOVA. The significance was determined using Duncan's multiple comparison test. All of the analyses were carried out with a 95% level of confidence.

Results

Fasting blood glucose and serum insulin:

The DC rats exhibited higher fasting blood glucose and lower insulin levels than the NC animals (Table 1). Treatment with *Herba Epimedii* dramatically reduced fasting blood glucose levels while significantly raising serum insulin levels in diabetic *rat*.

Table 1. Effects of *Herba Epimedii* on fasting blood glucose level and serum insulin in STZ induced diabetic rats (data represent mean ± SD).

Groups	Fasting blood glucose (mmol/L)		Serum insulin (µIU/mL)
	Before	After	
NC	4.83 ± 0.33a	4.90 ± 0.12a	4.15 ± 3.14c
DC	19.00 ± 3.25b	30.12 ± 2.64b	1.54 ± 0.14a
Rosiglitazone	28.32 ± 3.61c	19.74 ± 3.73c	1.75 ± 0.25a
Herba Epimedii	26.86 ± 6.03c	22.26 ± 4.86c	2.38 ± 0.17b
Herba Epimedii+ Rosiglitazone	27.31 ± 3.80c	19.83 ± 3.44c	1.87 ± 0.29a

Values with different superscripts down the column indicate significant difference at ($p < 0.05$).

Oxidative stress marker and antioxidant enzymes in bone:

Table 2 summarises the effects of *Herba Epimedii* on bone lipid peroxidation and antioxidant enzyme activity. The DC rats had a considerable increase in MDA levels as compared to the NC rats, but no significant changes in GPx or SOD activity. A similar observation is reported in *Herba Epimedii* rats.

Table 2. Oxidative stress marker and antioxidant enzymes of various experimental groups (data represent mean ± SD).

	Oxidative stress marker	Antioxidant enzyme	
Groups	TBARS (nmol MDA/mg protein)	GPx (U/mg protein)	SOD (mU/mg protein)
NC	28.62 ± 0.60a	44.50 ± 0.68ab	0.51 ± 0.02
DC	61.60 ± 0.69b	43.43 ± 0.70bc	0.34± 0.03
Rosiglitazone	72.53 ± 8.30c	43.04 ± 0.88b	0.42 ± 0.05
Herba Epimedii	76.77 ± 0.04c	4.40 ± 0.44bc	0.57 ± 0.17
Herba Epimedii+ Rosiglitazone	75.18 ± 0.17c	44.20 ± 0.42bc	0.53 ± 0.15

Different superscripts ^{a,b,c} in a column differed significantly at ($p < 0.05$).

Bone turnover markers:

Although the STZ injection reduced blood osteocalcin, serum DPD was significantly higher in the STZ group than in the NC group (Table 3). Despite the fact that BALP values did not differ significantly between the groups, serum osteocalcin levels increased while DPD levels decreased after *Herba Epimedii* therapy.

Table 3. Changes in serum osteocalcin, BALP and DPD of various experimental groups (data represent mean ± SD).

Groups	Bone formation markers		Bone resorption marker
	Osteocalcin (ng/ml)	**BALP (ng/ml)**	**DPD (ng/ml)**
NC	135.77 ± 6.8c	101.48 ± 7.58b	166.07 ± 5.14b
DC	14.35 ± 0.77a	65.05 ± 4.62a	163.12 ± 0.14c
Rosiglitazone	55.42 ± 8.24b	82.39 ± 0.45a	152.17 ± 4.38ab
Herba Epimedii	154.64 ± 4.10d	75.30 ± 8.31a	144.53 ± 0.41a
Herba Epimedii+ Rosiglitazone	153.67 ± 4.10d	77.32 ± 8.31a	143.54 ± 0.32a

Discussion

Osteoarthritis is caused by changes in articular cartilage, which is responsible for lubricating the ends of bones.[22] STZ injection has also been related to a drop in femoral articular cartilage thickness, a reduction in chondrocyte numbers, and an increase in tidemark roughness. Together, these findings suggest that diabetic rats acquire osteoarthritis-like illness. Osteoarthritis-like symptoms have been observed in both T1DM and T2DM animals.[23-25] The activation of oxidative stress is thought to be a contributing factor in these changes.

It has been hypothesised that *Herba Epimedii* therapy slows the pathogenetic progression of osteoarthritis in diabetic rats. In both clinical and preclinical studies, oxidative stress has been demonstrated to affect the pathogenesis of osteopenia, osteoporosis, and osteoarthritis.[14,26,27] As a result, more study into the connection between oxidative stress and bone quality is necessary. We observed that DC rats exhibited greater levels of oxidative damage markers in our investigation. A significant increase in MDA level was also found in all treated animals in animal tests, which enhanced susceptibility to STZ-induced bone issues.[28]By influencing the activity of osteoclasts and osteoblasts, oxidative stress and hyperglycemia have been demonstrated to alter bone metabolism and architecture.

This was important since the *Herba Epimedii* rats had some of the highest MDA levels, despite having a lot of chondrocyte hypertrophy. Furthermore, higher plasma MDA levels have been related to osteoarthritis in its early stages.[27] People agree that *Herba Epimedii* can help to halt the progression of the condition. Measurement of bone turnover indicators makes sense since oxidative stress might alter the balance between osteoblast and osteoclast activities.[29] According to the findings of this study, blood DPD levels rose in DC rats, whereas serum osteocalcin and BALP activity decreased. This finding is in line with the findings of Zhukouskaya et al. (2015), who discovered that bone turnover suppression is a major characteristic of T1DM-related bone disease.

Our findings are supported by previous observations of increased serum DPD in rats with osteoarthritis and osteopenia.[30,31] Another noteworthy finding from this study is that blood osteocalcin levels rose following *Herba Epimedii* therapy while DPD levels decreased (Table 3).A variety of herbs with osteoprotective

characteristics have yielded similar results.[32] Despite the fact that osteocalcin is a specific osteoblast marker that closely correlates with histological alterations,[33] blood OC levels tended to change with meal consumption.[32] According to prior studies, osteocalcin does not appear to be as sensitive a marker as BALP.[34]

Indeed, BALP activity in *Herba Epimedii* rats is still low, indicating that mineral metabolism is still affected. BALP is a bone-specific alkaline phosphatase isoform that is generated by osteoblasts for bone remodelling but also reflects mineral metabolism.[35]The ratio of osteocalcin to DPD was nearly similar in the *Herba Epimedii* and NC groups, suggesting that an equilibrium between bone formation and bone resorption was almost achieved with *Herba Epimedii* treatment.

Conclusion

Our findings show that *Herba Epimedii*can help prevent bone loss in STZ-treated rats. *Herba Epimedii* treatment lowered fasting blood glucose levels, enhanced DPD activity, and enhanced insulin production.

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Conflicts of Interest:

“The authors state that they have no competing interests. The funders had no involvement in the study's design, data collection, analysis, or interpretation, manuscript preparation, or the decision to publish the findings.”

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