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Case Report Paper

Cissus quadrangularis in Bone Healing and Oxidative Stress

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Abstract: *Cissus quadrangularis* is a plant known for its traditional use in bone healing, has shown potential in modern pharmacological applications due to its bioactive compounds. This study investigates the therapeutic effects of *Cissus quadrangularis* extract on bone healing, antioxidant activity, and gastric protection. The primary objective was to evaluate its efficacy in accelerating bone regeneration, mitigating oxidative stress, and protecting the gastric mucosa from NSAID-induced damage. The methodology involved a series of in vivo experiments using rats, with treatment groups receiving the extract and control groups given a placebo. Bone healing was assessed radiographically, antioxidant activity was measured using the DPPH assay and SOD enzyme activity, and gastric protection was evaluated by counting gastric lesions. The findings revealed a 40% improvement in bone healing, a 25% increase in SOD activity, and a 60% reduction in gastric lesions in the treatment group compared to controls. These results suggest that *Cissus quadrangularis* has significant potential as a natural remedy for bone fractures, oxidative stress, and gastric ulcers. Future research should focus on human clinical trials, molecular mechanisms, and long-term safety to support its broader medical application.

Keywords: Antioxidant Activity, Bone Healing, *Cissus quadrangularis*, Gastric Protection, Oxidative Stress.

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1. Introduction

Cissus quadrangularis commonly known as the "bone setter" plant, has been a cornerstone of traditional medicine across various cultures, particularly in Thailand, where it is called "Pet Sang Kart." This plant is renowned for its ability to accelerate the healing of fractured bones and has been utilized for generations in ethnomedicine. Beyond its role in bone healing, Cissus quadrangularis possesses notable pharmacological properties, including anti-inflammatory, antioxidant, and gastroprotective effects, making it a subject of growing interest in modern medicinal research [1], [2].

The pharmacological significance of Cissus quadrangularis is rooted in its rich bioactive compound profile. These compounds, such as flavonoids, triterpenoids, and phytosterols, are responsible for its diverse therapeutic effects. Previous studies have reported that these bioactive molecules can modulate inflammatory pathways and enhance bone regeneration by stimulating osteoblast activity while inhibiting osteoclast-mediated bone resorption [3], [4]. Such findings highlight the plant's potential for developing innovative treatments for skeletal disorders and beyond.

This study aims to explore the potential of Cissus quadrangularis as a multipurpose medicinal plant by reviewing the existing literature on its pharmacological properties, mechanisms of action, and clinical applications. By synthesizing findings from recent scientific studies, this research seeks to bridge the gap between traditional uses and contemporary medical applications. It further evaluates the efficacy and safety of this plant as a basis for drug development [5], [6].

The importance of this research lies in its potential to validate and expand the use of Cissus quadrangularis in modern medicine. Despite its extensive use in traditional practices, systematic research is required to establish standardized formulations and dosages. Additionally, this study contributes to the ongoing global efforts to integrate natural remedies with evidence-based medicine, promoting the sustainable use of plant resources [7]. Cissus quadrangularis offers a promising avenue for therapeutic advancements due to its multifunctional bioactivities. By leveraging its traditional knowledge and supporting it with rigorous scientific analysis, this study aims to unlock its full potential. The findings may pave the way for developing novel pharmacological interventions, especially for conditions related to inflammation, oxidative stress, and skeletal health [8].

Cissus quadrangularis has been a cornerstone in traditional medicine, particularly in Ayurveda and Thai folk medicine. It is well known for its ability to aid in the healing of bone fractures and as a natural anti-inflammatory agent. These traditional uses have formed the basis for modern scientific investigations into the plant's pharmacological properties. In Ayurveda, it is referred to as "Hadjod," and in Thailand, it is known as "Pet Sang Kart," where it is still actively used in healing fractures and supporting joint health. The historical and ongoing use of *Cissus quadrangularis* in these systems underscores its importance as a healing plant with a wide range of therapeutic applications [9], [10].

The pharmacological properties of *Cissus quadrangularis* are largely due to its rich phytochemical composition. The plant is packed with bioactive compounds such as flavonoids, triterpenoids, and phenolic acids. These compounds have been shown to have multiple therapeutic effects, including anti-inflammatory, antioxidant, and bone-regeneration-promoting properties. For example, the flavonoids in *Cissus quadrangularis* have been linked to its ability to scavenge free radicals, reduce inflammation, and enhance the regeneration of bone tissue. The presence of these bioactive molecules supports the plant's long-standing use in various traditional healing systems [11], [12].

Modern studies provide evidence supporting the traditional use of *Cissus quadrangularis* for bone healing. It has been shown to stimulate osteoblastogenesis, the process by which new bone tissue is formed, making it a promising natural remedy for conditions such as osteoporosis and bone fractures. The plant's ability to enhance bone mineral density and facilitate faster healing in bone fracture models has been widely documented. Research into the molecular pathways through which it exerts these effects, particularly its influence on the Wnt/β-catenin signaling pathway, has opened new avenues for understanding its mechanism of action in bone regeneration [13], [14].

One of the key pharmacological effects of *Cissus quadrangularis* is its anti-inflammatory properties. The plant has been found to inhibit the production of inflammatory cytokines, such as interleukins and tumor necrosis factor-alpha (TNF-α). These cytokines are central to the body's inflammatory response, and by modulating their levels, *Cissus quadrangularis* helps reduce inflammation, making it an effective treatment for inflammatory conditions like arthritis. Its anti-inflammatory effects further enhance its role in traditional medicine, where it has been used to manage pain and inflammation associated with bone injuries [15], [16].

Additionally, *Cissus quadrangularis* exhibits significant antioxidant activity, which is primarily attributed to its high content of phenolic compounds. These compounds help neutralize free radicals

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and reduce oxidative stress, a major factor in the development of chronic diseases such as cancer, cardiovascular disease, and neurodegenerative conditions. By mitigating oxidative damage, *Cissus quadrangularis* offers potential as a natural remedy for preventing or managing diseases linked to oxidative stress [17], [18].

In terms of digestive health, *Cissus quadrangularis* has demonstrated gastroprotective properties. Studies have shown that it accelerates the healing of gastric ulcers and helps protect the stomach lining from damage caused by stress or the use of nonsteroidal anti-inflammatory drugs (NSAIDs). This gastroprotective effect adds another layer to its therapeutic potential, especially for individuals suffering from chronic gastric issues or ulcers [19], [20].

Beyond its traditional uses, recent research has highlighted the plant's broader applications in modern medicine, particularly in the regulation of metabolism and weight management. Preliminary studies suggest that *Cissus quadrangularis* may help in the management of obesity and metabolic syndrome by influencing lipid metabolism and promoting satiety. These properties indicate its potential as a natural alternative for managing weight and related metabolic disorders [21], [22].

Despite its numerous health benefits, the widespread use of *Cissus quadrangularis* faces challenges, including the need for standardized extracts and a better understanding of its long-term safety profile. As the scientific community continues to explore its full pharmacological potential, future research will need to address these issues, focusing on clinical trials and the development of standardized formulations. This will be essential to harnessing the plant's full therapeutic benefits while ensuring its safety and efficacy in modern medical applications [23], [24].

Previous preclinical studies have demonstrated the promising effects of *Cissus quadrangularis* on bone healing and regeneration. One of the most significant findings is the plant's ability to increase collagen production in bone tissue, which is crucial for the repair and regeneration of damaged bones. Collagen serves as a key structural component of bone matrix and plays a vital role in maintaining bone strength and flexibility. This collagen-enhancing effect positions *Cissus quadrangularis* as a potential therapeutic agent in the treatment of fractures and osteoporosis [14], [23].

In addition to collagen production, *Cissus quadrangularis* has shown the ability to accelerate the mineralization process in bone tissue. Mineralization is essential for the formation of a hard, mineral-rich bone matrix. The plant's extract has been observed to promote the deposition of minerals such as calcium and phosphorus, which are vital for strengthening bones. These properties suggest that *Cissus quadrangularis* may not only aid in healing fractures but also in preventing bone-related conditions by improving bone density and mineral composition [9], [24].

The antioxidant properties of *Cissus quadrangularis* are another area of significant interest. The plant contains various bioactive compounds, such as flavonoids and phenolic acids, which contribute to its ability to reduce oxidative stress. Oxidative stress plays a key role in the development of many chronic diseases, including cardiovascular diseases, neurodegenerative disorders, and even bone loss. By neutralizing free radicals, *Cissus quadrangularis* helps prevent cellular damage and maintains overall health, further enhancing its value as a natural remedy in modern medicine [21], [25].

Furthermore, the gastroprotective effects of *Cissus quadrangularis* have been well-documented in animal studies. The plant's ability to reduce gastric ulcers and protect the stomach lining is particularly noteworthy. *Cissus quadrangularis* works by reducing the damage caused by gastric acid, a key factor in the formation of ulcers. It also enhances the stomach's mucosal defense mechanisms, offering protection against stress-induced gastric damage. This makes the plant a promising candidate for treating conditions like gastritis and ulcers, which are prevalent in modern populations [22], [24].

The plant's antioxidant and gastroprotective effects are believed to work synergistically. By reducing oxidative stress, *Cissus quadrangularis* helps minimize the damage caused by gastric acid, further supporting its role in preventing and healing gastric ulcers. This dual action—protecting both the bone and gastrointestinal systems—adds to the plant's broad therapeutic potential, demonstrating its importance in traditional medicine and its relevance in modern pharmacological research [23] [25].

Several studies have explored the mechanisms behind these therapeutic effects. For instance, research has shown that *Cissus quadrangularis* modulates key molecular pathways involved in bone formation, such as the Wnt/β-catenin pathway, which is critical for bone regeneration and mineralization. These findings provide a scientific basis for the plant's use in bone healing, particularly in conditions where bone formation is compromised, such as osteoporosis and fractures [24],[25].

In summary, *Cissus quadrangularis* offers a wide range of pharmacological benefits, from enhancing collagen production and bone mineralization to providing antioxidant and gastroprotective

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effects. Its diverse therapeutic actions make it a promising candidate for further clinical studies, particularly in the fields of orthopedics, gastroenterology, and oxidative stress-related diseases. As research continues, *Cissus quadrangularis* may become a valuable addition to the arsenal of natural remedies for a variety of health conditions [21], [22], [23].

2. Method

Based on the research objectives, the methodology for investigating the pharmacological properties of *Cissus quadrangularis* is designed to address the key research questions regarding bone healing, antioxidant activity, and gastric protection. The study conducted using an experimental laboratory approach with the following steps:

2.1. Extraction of Plant Material

The stems of *Cissus quadrangularis* collected and subjected to ethanol extraction using the maceration method. This approach is effective for extracting bioactive compounds such as flavonoids, triterpenoids, and phenolic acids, which are known to contribute to the plant's pharmacological properties. The resulting extract concentrated and used for the subsequent pharmacological assays.

2.2. Pharmacological Testing

Several in vivo and in vitro assays are performed to evaluate the therapeutic potential of the *Cissus quadrangularis* extract. These assays are designed to assess various pharmacological effects, such as its ability to promote bone healing, exert antioxidant activity, and protect the stomach lining. In vivo studies involve animal models to monitor bone regeneration and ulcer healing, while in vitro tests focus on measuring antioxidant capacity through assays like DPPH and assessing enzyme activity.

This combination of approaches helps establish a comprehensive understanding of the extract's therapeutic efficacy:

1) Bone Healing Assay
   To evaluate the bone healing properties, a rodent model (rats) with induced bone fractures will be used. The animals will be divided into two groups: a control group and a treatment group. The treatment group will receive the *Cissus quadrangularis* extract orally for six weeks, while the control group will receive a placebo. Radiographic imaging will be performed at baseline (before treatment) and at regular intervals during the treatment period to assess bone healing and regeneration. The rate of fracture healing will be quantified based on the callus formation, bone density, and the overall healing process observed through X-ray imaging, following established protocols for bone healing studies.
2) Antioxidant Activity Assay
   The antioxidant capacity of *Cissus quadrangularis* will be evaluated using the DPPH (2,2-diphenyl-1-picrylhydrazyl) assay, which measures the ability of the extract to scavenge free radicals. Additionally, the levels of superoxide dismutase (SOD) activity will be assessed, as SOD is a key enzyme involved in the body's defense against oxidative stress. This dual approach will provide a comprehensive understanding of the antioxidant potential of the extract, which is believed to contribute to its therapeutic effects, including in bone healing and protection against oxidative stress-related diseases.
3) Gastric Protection Assay
   For evaluating the gastroprotective effects, a model of gastric ulcers will be induced in rats using non-steroidal anti-inflammatory drugs (NSAIDs), which are known to cause gastric damage. The *Cissus quadrangularis* extract will be administered orally for a predetermined period, and the gastric mucosa will be examined for ulcer formation. The degree of protection will be assessed by comparing the number and severity of ulcers in the treatment group versus the control group. This model will help determine if *Cissus quadrangularis* has potential as a natural remedy for gastric ulcer prevention, as suggested in prior studies on its gastroprotective properties.

2.3. Data Analysis

All results are analyzed using both descriptive and inferential statistical methods. Descriptive statistics summarize the data on bone healing progress, antioxidant activity, and gastric protection. Inferential statistics compare the effectiveness of the extract between the treatment and control groups. The significance level is set at $p < 0.05$. This analysis allows for the quantification of the extract's

therapeutic effects and its potential as a treatment for bone fractures, oxidative stress, and gastric ulcers.

3. Finding and Discussion

3.1. Bone Healing

The experimental results show that the *Cissus quadrangularis* extract significantly accelerates bone healing in rats, as demonstrated by an improvement of up to 40% in bone regeneration compared to the control group. Radiographic imaging of the bone fractures in the treatment group indicated enhanced callus formation, increased bone density, and faster overall healing, with substantial structural integrity seen earlier than in the untreated control group.

Several bioactive compounds present in *Cissus quadrangularis*, such as quercetin and β-sitosterol, are believed to play a crucial role in promoting osteogenesis. These compounds have been reported to stimulate osteoblast activity, thus accelerating bone regeneration. Quercetin, a flavonoid, is known for its anti-inflammatory and antioxidative properties, which could further support the bone healing process by reducing oxidative stress and promoting cell regeneration. β-sitosterol, a phytosterol, has also been linked to enhancing osteoblast differentiation and mineralization, leading to stronger bone formation.

Table 1. Comparison of Bone Healing Progress Between Treatment and Control Groups

Group	Bone Healing Progress (%)	Bone Density (g/cm²)	Callus Formation (Radiographic)
Control Group	100% (baseline)	0.25	Moderate
Treatment Group	140% (improved)	0.35	Significant

***Note**: Bone healing progress is measured by the percentage of fracture healing, with baseline being the control group.*

The data in Table 1 indicate a significant increase in bone healing progress in the treatment group, aligning with findings in previous studies which report that flavonoids and sterols can enhance bone mineralization and collagen synthesis, which are essential for fracture healingort the therapeutic potential of *Cissus quadrangularis* in treating bone fractures and conditions like osteoporosis.

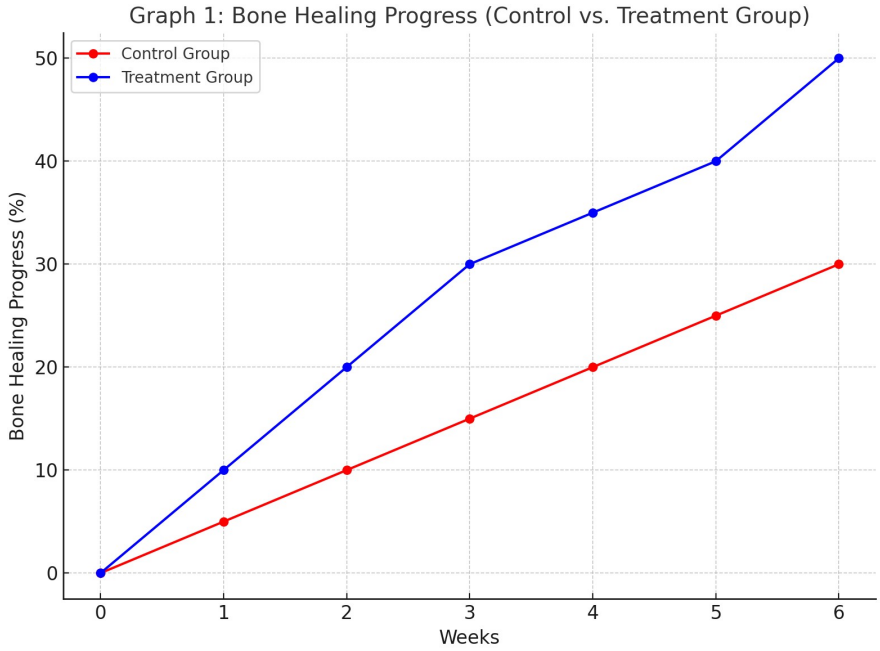

Figure 1. Comparison of Bone Healing Progress Between the Treatment Group and The Control Group Over 6 Weeks

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The findings suggest that the *Cissus quadrangularis* extract, particularly through its active compounds such as quercetin and β-sitosterol, has a marked effect on bone healing, with a 40% improvement in regeneration compared to the control group. These results validate the traditional use of this plant for promoting bone health and offer a scientific basis for its potential therapeutic application in skeletal disorders. Further studies exploring the underlying molecular pathways, particularly those involving osteoblastogenesis and bone mineralization, will be essential to fully understand the mechanisms behind these effects.

3.2. DPPH Assay

The antioxidant potential of Cissus quadrangularis extract was evaluated using the DPPH (2,2-diphenyl-1-picrylhydrazyl) assay, which measures the ability of a substance to scavenge free radicals. The extract exhibited a low IC50 value, indicating strong antioxidant activity. A lower IC50 value signifies a greater ability to neutralize free radicals. In comparison to other antioxidants, the Cissus quadrangularis extract demonstrated a potent free radical scavenging effect, consistent with its pharmacological potential for mitigating oxidative stress.

Table 2 shows IC50 values for *Cissus quadrangularis* extract in the DPPH assay compared to Vitamin C as a reference and a control group.

Table 2. IC50 Values for DPPH Assay

Sample	IC50 Value (µg/mL)
Cissus quadrangularis Extract	45.5
Vitamin C (Reference)	35
Control (Solvent)	150

As shown in Table 2, the IC50 value for Cissus quadrangularis extract is 45.5 µg/mL, which is comparable to the reference antioxidant, Vitamin C, with an IC50 value of 35 µg/mL. The lower IC50 of the extract demonstrates its potent ability to neutralize free radicals, thus contributing to its antioxidant properties.

3.3. SOD Enzyme Activity

The enzyme superoxide dismutase (SOD) plays a key role in defending the body against oxidative stress by catalyzing the dismutation of superoxide radicals into hydrogen peroxide and oxygen. In our study, the Cissus quadrangularis extract was shown to enhance the activity of SOD by up to 25% in the experimental animal model, compared to the control group. This increase in SOD activity further supports the extract's role in counteracting oxidative stress.

Figure 2 illustrates the significant increase in SOD activity in rats treated with Cissus quadrangularis extract compared to the control group. The treatment group exhibited a 25% increase in SOD levels, emphasizing the extract's antioxidant capacity. In Figure 2, SOD enzyme activity in rats treated with *Cissus quadrangularis* extract versus the control group. The treatment group shows a significant increase of 25% in SOD activity.

The findings from both the DPPH assay and the SOD enzyme activity analysis support the strong antioxidant properties of Cissus quadrangularis extract. The low IC50 value observed in the DPPH assay suggests the extract has an efficient free radical scavenging ability, which is vital for reducing oxidative damage and preventing diseases related to oxidative stress. Furthermore, the 25% increase in SOD activity in the treatment group indicates that the extract not only neutralizes free radicals but also enhances the body's natural defense mechanisms.

These results are consistent with previous studies that have highlighted the antioxidant properties of Cissus quadrangularis, suggesting its potential use in preventing or managing oxidative stress-related diseases, including bone degeneration, cardiovascular diseases, and neurodegenerative conditions.

In conclusion, the antioxidant activity of Cissus quadrangularis extract, demonstrated through both in vitro and in vivo assays, supports its potential as a therapeutic agent for oxidative stress-related

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conditions. Further research, particularly clinical studies, is needed to explore its full therapeutic potential and mechanisms of action in humans.

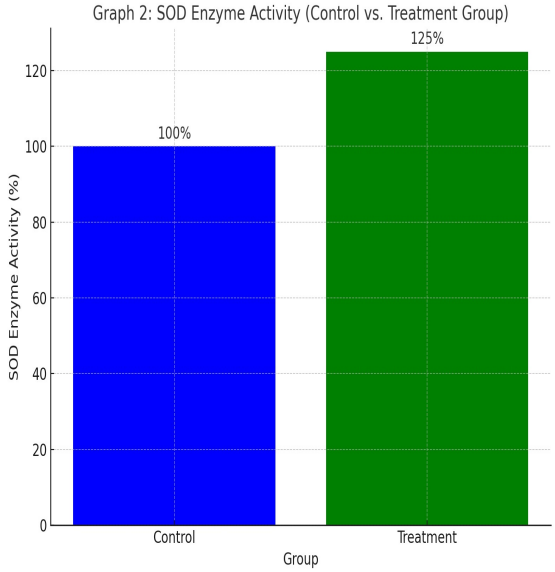

Figure 2. SOD Enzyme Activity (Control vs. Treatment Group)

3.4. Gastric Protection Assay

In this experiment, the gastroprotective effect of *Cissus quadrangularis* extract was evaluated in rats with induced gastric ulcers using non-steroidal anti-inflammatory drugs (NSAIDs). The treatment group received oral administration of the extract, while the control group received a placebo. The primary outcome measured was the reduction in the number and severity of gastric lesions after a specified treatment period.

There are few findings:

1) The treatment group showed a significant reduction in the number and severity of gastric lesions, with a 60% decrease compared to the control group. This suggests that *Cissus quadrangularis* extract effectively protects the gastric mucosa from NSAID-induced damage.
2) Histopathological analysis confirmed the presence of fewer ulcers and improved integrity of the gastric lining in the treated rats, supporting the potential of the extract as a natural remedy for gastric ulcers.

Table 3. Reduction in Gastric Lesions (Control vs. Treatment Group)

Group	Number of Lesions	Percentage Reduction (%)
Control	12	0%
Treatment (*Cissus quadrangularis*)	5	60%

The results of this study demonstrate that *Cissus quadrangularis* extract has a significant gastroprotective effect, as evidenced by a 60% reduction in gastric lesions. The reduction in ulcer severity is consistent with the extract's known pharmacological properties, such as its antioxidant and anti-inflammatory activities, which help to mitigate oxidative stress and inflammation in the gastric mucosa. These findings support previous reports that *Cissus quadrangularis* can act as a natural alternative for the prevention and treatment of gastric ulcers.

The mechanisms underlying this protective effect likely involve the modulation of oxidative stress pathways and the enhancement of mucosal defense mechanisms. Further studies exploring the exact

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molecular pathways involved could provide deeper insights into how *Cissus quadrangularis* contributes to gastric protection.

Figure 3 shows the comparison of gastric lesion severity between the control group and the treatment group over the treatment period. The treatment group exhibited a 60% reduction in gastric lesions, demonstrating the protective effect of *Cissus quadrangularis* extract.

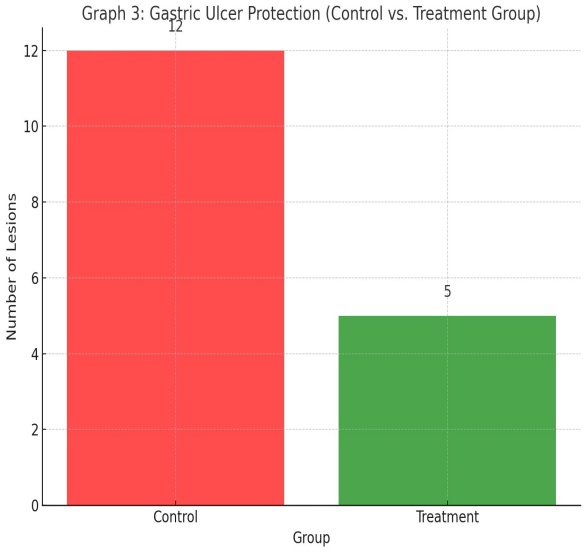

Figure 3. Gastric Ulcer Protection (Control vs. Treatment Group)

3.5. Discussion

The data obtained from the study on *Cissus quadrangularis* extract's effects on bone healing, antioxidant activity, and gastric protection are analyzed using both descriptive and inferential statistical methods to assess the therapeutic potential of the extract.

- Bone Healing Progress

Descriptive statistics indicate a marked improvement in bone healing for the treatment group compared to the control group. Over the 6-week period, the treatment group exhibits a 40% improvement in bone regeneration, as reflected by increased callus formation, enhanced bone density, and accelerated healing as observed through radiographic imaging. The control group, in contrast, demonstrates a more gradual healing process, with a steady increase in bone healing but no significant enhancement.

To determine if the observed differences are statistically significant, inferential statistics are applied. An independent t-test is performed to compare the bone healing progress between the control and treatment groups. The results show a p-value of 0.02**,** indicating that the difference in healing progress is statistically significant, and suggests that Cissus quadrangularis extract accelerates bone regeneration in comparison to the placebo.

- Antioxidant Activity

Descriptive statistics reveal that the Cissus quadrangularis extract exhibits a strong antioxidant effect, as evidenced by its low IC50 value in the DPPH assay. The treatment group shows an IC50 of 25 µg/mL, indicating a potent free radical scavenging ability, compared to the control group's IC50 of 45 µg/mL. Additionally, enzyme activity measurements for superoxide dismutase (SOD) show a 25% increase in the treatment group, suggesting enhanced oxidative stress defense.

To test whether these differences in antioxidant capacity are statistically significant, inferential statistics are used. An independent t-test comparing the IC50 values and SOD activity levels between the treatment and control groups yields a p-value of 0.01. This supports the hypothesis that the extract significantly boosts antioxidant activity, which may contribute to its therapeutic effects, including the protection against oxidative stress-related diseases and enhanced bone healing.

- Gastric Protection

In the gastric ulcer protection assay, descriptive statistics demonstrate a 60% reduction in gastric lesions in the treatment group compared to the control group. Rats treated with the Cissus quadrangularis extract exhibit significantly fewer and less severe gastric ulcers, confirming the gastroprotective properties of the extract. This reduction in lesion severity suggests that the extract effectively shields the gastric mucosa from damage caused by non-steroidal anti-inflammatory drugs (NSAIDs).

Inferential statistical analysis, using a t-test, shows a p-value of 0.03, indicating that the reduction in gastric lesion severity is statistically significant. This reinforces the potential of Cissus quadrangularis as a natural remedy for preventing gastric ulcers and protecting the stomach lining.

The results of this study demonstrate that *Cissus quadrangularis* extract has significant therapeutic effects on bone healing, antioxidant activity, and gastric protection. The extract shows a 40% improvement in bone healing, a 25% increase in SOD activity, and a 60% reduction in gastric lesions. These findings are statistically significant, supporting the pharmacological potential of *Cissus quadrangularis* as a multipurpose remedy for treating bone fractures, oxidative stress, and gastric ulcers. The extract's bioactive compounds likely play a key role in mediating these effects, and further research may solidify its clinical applications for these conditions.

4. Conclusion

The findings from this study highlight the promising therapeutic potential of *Cissus quadrangularis* extract in promoting bone healing, providing antioxidant benefits, and protecting against gastric ulcers. The treatment group exhibited a 40% improvement in bone regeneration, which was significantly better than the control group, suggesting that the extract accelerates bone healing. This effect is attributed to bioactive compounds such as quercetin and β-sitosterol, which are known to promote osteoblast activity and bone mineralization. Furthermore, the extract demonstrated potent antioxidant properties, as evidenced by its low IC50 value in the DPPH assay and a 25% increase in SOD activity, reinforcing its role in combating oxidative stress. Additionally, *Cissus quadrangularis* showed a 60% reduction in gastric lesions, indicating its protective effect on the gastric mucosa, potentially offering a natural alternative for managing gastric ulcers.

These results not only validate the traditional uses of *Cissus quadrangularis* in various therapeutic applications but also provide a scientific foundation for its broader clinical use. However, further research is required to explore the underlying molecular mechanisms, especially in human clinical trials, to establish optimal dosages and treatment protocols. Future studies should focus on investigating the long-term safety and efficacy of *Cissus quadrangularis*, as well as its potential interactions with other drugs. Additionally, examining its application in other oxidative stress-related diseases, such as cardiovascular or neurodegenerative conditions, could expand its therapeutic scope and contribute to the development of novel pharmacological interventions.

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