

## The Potential of Plant Extracts to Substitute for Nsaid Drugs that can Inhibit Post-Operative Bone Healing : A Literature Review

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### ABSTRACT

Bone fractures are a global public health concern. Fractures are a significant burden on individuals, families, societies, and healthcare systems, because they can cause work absences, decreased productivity, disabilities, reduced quality of life, health loss, and high healthcare expenses. Bone healing is a complex process that allows the repair of broken bones without scar tissue formation. NSAIDs have long been an essential part of our strategy for pain management in post-traumatic environments. The use of nonsteroidal anti-inflammatory drugs (NSAIDs), which are frequently used by patients as both anti-inflammatory and analgesic agents, is one of these causes. NSAIDs have been investigated for a long time, with conflicting results regarding their effects on bone repairs. Most plant parts have been used as extracts, and they may have anti-inflammatory and antioxidant properties related to these conditions. From the six studies that correlated, we found that the use of plant extracts promotes bone healing by enhancing osteogenesis, the rate of calcification, and the creation and mineralization of bone calli, thereby expediting the process of new bone formation at the fracture location. These benefits may be related to the antioxidant and anti-inflammatory properties of the extracts. From these results, it can be concluded that plant extracts can potentially substitute NSAIDs as anti-inflammatory agents in postoperative bone healing.

**KEYWORDS:** Plant Extract, Bone Fracture, NSAID, Bone Healing

### ARTICLE DETAILS

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### INTRODUCTION

Bone fractures are a public health issue around the world.<sup>1</sup> Fractures are a significant burden on individuals, families, societies, and healthcare systems, because they can cause work absences, decreased productivity, disability, reduced quality of life, health loss, and high health-care expenses.<sup>2</sup> From the results of a systematic analysis of the global burden of disease 2019, which took data from 204 countries and territories, it was found that from 1990 to 2019, the age-standardized global rates of fracture incidence, prevalence, and years lived with disability (YLDs) decreased slightly, while the absolute counts substantially increased. Globally, in 2019, there were 178 million new fractures (an increase of 33.4% since 1990), 455 million prevalent cases of acute or long-term symptoms of a fracture (an increase of 70.1% since 1990), and 25.8 million YLDs.<sup>3</sup> In the United States, the cost of treating fractures was roughly \$17.8 billion in 2015, and by 2025, costs are expected to reach \$25 billion annually.<sup>4</sup> Bone healing is a complex system of processes that allows broken bones to be repaired without the formation of scar

tissue. Multiple cell types must work together to complete this process while being signaled by a variety of cytokines and chemokines. Both direct bone healing (where no callus forms) and indirect bone healing (where callus forms) can cure fractures. Endochondral and intramembranous bone healing can be further differentiated based on mechanical stability at the fracture site. Good stability at the fracture site in intramembranous ossification allows mesenchymal stem cells (MSCs) to differentiate directly into osteoblasts. On the other hand, the formation of cartilage as a first step to improve stability at the fracture site before ossification is a component of endochondral bone formation.<sup>5</sup> Environmental circumstances, medications, and physiological changes are just a few of the many elements that might affect the healing process. NSAIDs have been an essential part of our strategy for pain management in the posttraumatic environment for a long time. The usage of Nonsteroidal anti-Inflammatory drugs (NSAIDs), which are frequently used by patients as both an anti-inflammatory and an analgesic, is one of these

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causes. NSAIDs have been investigated for a long time with conflicting results regarding their effects on bone repair.<sup>6</sup> Many studies have examined the advantages and disadvantages of NSAIDs in bone healing in both animal and human tissues in vitro and in vivo. Studies that have demonstrated that NSAIDs significantly influence bone healing are categorized according to NSAIDs' mechanisms of action. Numerous studies comparing the benefits and disadvantages of NSAIDs in bone healing in both animal and human tissues to clinical RCTs have been published. Six RCTs (609 patients) were included in this study. Patients who received NSAIDs after the fracture had an increased risk of non-union (OR 3.47). However, if the studies were divided according to the duration of NSAID administration, individuals who got the drugs for shorter periods (2 weeks) did not exhibit a significantly higher risk of nonunion than those who had them for a longer time (>4 weeks).<sup>6</sup>

## BONE FRACTURE AND BONE HEALING

A fracture is a breach in the structural continuity of the bone cortex, with a degree of injury to the surrounding soft tissues.<sup>7</sup> One of the most intricate series of processes, bone healing

aims to restore broken bones without the development of scar tissue. Numerous cell types, signaling pathways, and changes in the metabolic composition of the immediate area are involved in this physiological process. Most fractures mend indirectly over the course of the multiple phases. Bone healing can be primary (direct) or secondary (indirect). The interruption of the local blood supply, hypoxia, and development of a hematoma signal the start of indirect fracture healing right away after the fracture occurs (Figure 1).<sup>5</sup>

Both locally and systemically released cytokines and growth factors exert mitogenic and osteogenic effects on osteoprogenitor cells. As more growth factors and prostaglandins are produced in conjunction with the development of new blood vessels, mesenchymal stem cells (MSCs) are encouraged to differentiate into chondrogenic or osteogenic lineages, resulting in the creation of hard calli and initially woven bone. The restoration of mechanical strength and stability occurs as a result of a protracted period of remodeling, which is characterized by bone resorption and new bone creation.<sup>5,8,9</sup>

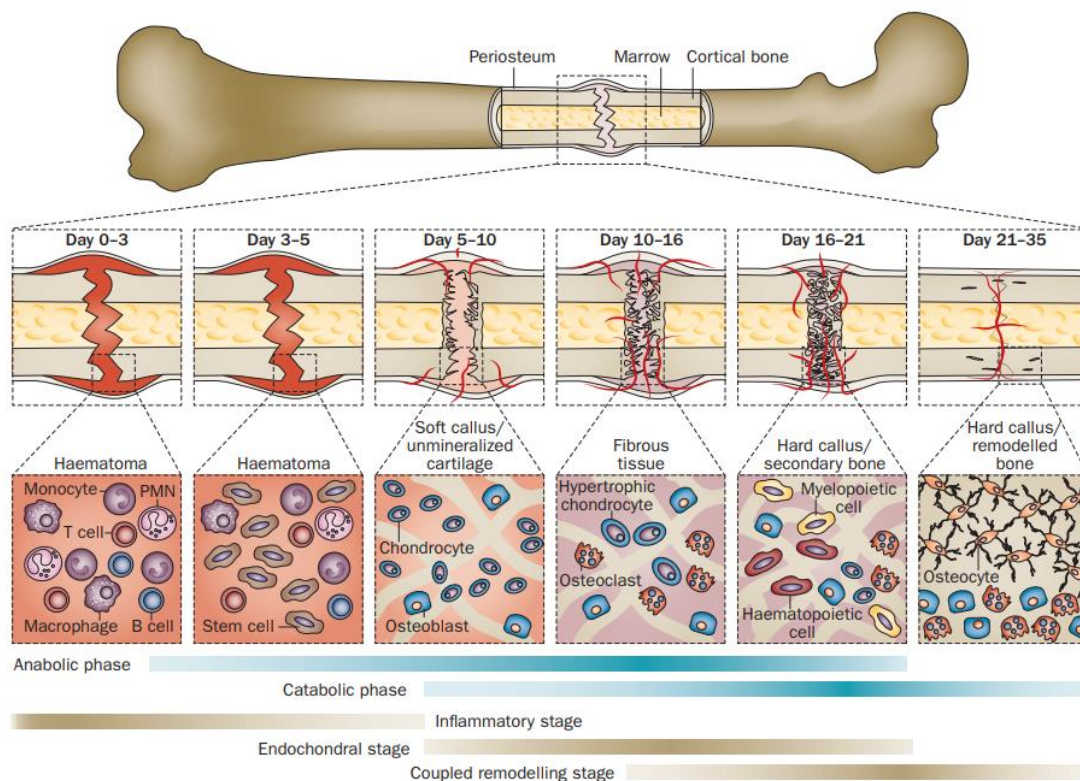


Figure 1 Femur Fracture Repair<sup>5</sup>

## NSAIDS AND BONE HEALING

Numerous local and systemic factors with varying degrees of affliction, such as fracture gap and comminution, blood flow disturbances, degree of soft tissue damage, insufficient mechanical stability, poor nutritional status, age, and smoking can influence the outcome of bone healing. The use

of various pharmacological drugs is a crucial component that may obstruct the body's capacity to repair a fracture. Some antibiotics, chemotherapeutic medications, and steroids have been shown to have adverse effects on bone repair. Additionally, it has been shown that NSAIDs, one of the most often given medications for pain relief and inflammation.<sup>6</sup>

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Owing to their strong analgesic and anti-inflammatory effects and fewer side effects than opioids, NSAIDs play an essential role in immediate pain following fracture or during the postoperative period after fracture repair.<sup>10,11</sup> However, research comparing NSAIDs and opiates has found that NSAIDs are at least as effective as opiates, and some research even suggests that NSAIDs might reduce pain ratings more effectively. NSAIDs have been recommended as the first line of treatment in pain management for acute pain, and opioids can only be introduced if NSAIDs alone are unable to sufficiently control pain. Furthermore, severe adverse effects such as respiratory depression, drowsiness, and cognitive impairments are avoided when NSAIDs are used instead of narcotic analgesics. This correlates to a shorter hospital stay for postoperative patients, enabling for early mobility and weight bearing.<sup>9,12</sup>

Depending on the physiological or pathological circumstances, prostaglandins (PGs) are autocrine and paracrine lipid mediators that are generated by a variety of cell types and are able to mediate either a stimulatory or resorptive action.<sup>13</sup> Prostaglandin administration has been demonstrated to increase cortical and trabecular mass and result in hyperostosis in newborns in animal models. Similarly, local treatment with PGs displayed stimulatory characteristics in rat long bones, suggesting a direct action on bone through the stimulation of osteogenesis. Osteoclasts are directly affected by PGs at the cellular level, increasing their functional activity and, as a result, boosting bone resorption through a mitogenic impact.<sup>14</sup> On the other hand, PGs can have an anabolic impact on the bone by promoting osteoblast differentiation and proliferation. One may assert that PGs maintain the proper balance between bone production and resorption.<sup>15</sup>

NSAIDs have roots in the extracts of plants that contain salicylate, which was first mentioned in ancient Roman and Greek literature. Willow tree extract is particularly well known for its antipyretic, analgesic, and anti-inflammatory properties. Arachidonic acid is transformed into prostaglandin endoperoxidases PGG<sub>2</sub> and PGH<sub>2</sub> during the production of prostaglandins by the cyclooxygenase (COX, also known as prostaglandin H synthase). Prostaglandins and thromboxanes, which are biologically active substances, are precursors of PGH<sub>2</sub>.<sup>16</sup>

Thromboxane A<sub>2</sub> (TXA<sub>2</sub>), prostacyclin (PGI<sub>2</sub>), PGD<sub>2</sub>, PGE<sub>2</sub>, and PGF<sub>2</sub> are produced by the isomerization of PGH<sub>2</sub>. However, COX-1 is constitutively expressed in most cells and is activated during physiological activities. Prostacyclin and PGE<sub>2</sub> reduce acid secretion, vasodilate the blood vessels of the gastric mucosa, and stimulate the synthesis of mucus, which serves as a protective barrier in the GI tract.<sup>17</sup> Prostaglandins is important for controlling blood flow and improving organ perfusion in the kidneys. Additionally expressed in fetuses and amniotic cells, the uterine epithelium during early pregnancy, and the central

nervous system, COX-1 is expected to have intricate integrative activity. In contrast, COX-2 is considered to be caused by inflammation as well as the presence of proinflammatory cytokines and mitogens. According to some studies, NSAIDs' ability to reduce inflammation is caused by their inhibition of COX-2, but COX-1 inhibition has been linked to negative consequences that interfere with the body's regulatory and protective processes. However, recent research has shown that COX-2 is also constitutively expressed in the brain, specifically in the hippocampus and cortical glutaminergic neurons as well as the kidneys, uterus, and prostate. Similar to COX-1, it has been demonstrated that it contributes to inflammation (such as lipopolysaccharide-induced inflammation) despite its constitutive expression.<sup>15,18</sup>

Despite the advantages of NSAIDs, several studies have found negative effects of NSAIDs. Pountos et al. found that NSAIDs appear to affect the stage of mesenchymal stem cells, leading to the development of functional chondrocytes. Endogenous generation of PGE-2 did not bear this impact. The process appears to be the downregulation of the expression of important molecules like TGF-β.<sup>19</sup> The meta analysis by Pountos et al. reported that the study found no evidence of associations between various NSAIDs or even selectivity toward the enzyme COX-1 or COX-2 to explain the inhibition of bone healing.<sup>19</sup> According to Kellinsalmi et al., indomethacin, parecoxib, and NS398 inhibited human MSCs from differentiating into osteoblasts and led to a large rise in adipocytes, which suggests that osteogenesis was diverted to make adipocytes instead of bones.<sup>20</sup> NSAIDs' impact on fracture healing has even been equated by some writers to that of other pharmacological drugs like steroids. According to Hgevoid et al., short-term methylprednisolone treatment did not impair fracture healing but short-term indomethacin administration did.<sup>21</sup> According to Park et al., patients on ketorolac had a significantly greater frequency of nonunion or partial union, and their relative risk was around six times higher than that of the control group.<sup>22</sup> In a more recent investigation, Lumawig et al. found that diclofenac sodium inhibited spinal fusion in a dose-dependent manner, particularly when taken in the early postoperative period. Additionally, it was shown that patients who used NSAIDs for longer than three months after surgery had considerably decreased success and fusion rates.<sup>23</sup>

## THE POTENTIAL OF PLANT EXTRACTS IN THE BONE HEALING

Numerous plants have been used for therapeutic purposes since ancient times. Most plant parts have been used as extracts, and they may have anti-inflammatory and antioxidant properties that are related to conditions such as diabetes, atherosclerosis, neurodegenerative disease, and cancer. Additionally, the anti-inflammatory properties of plant extracts allow them to control the composition of gut

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microbiota. Many of the phytochemicals found in fruits and vegetables, including polyphenols, carotenoids, phytosterols, and polysaccharides, are compound phytochemicals that give them their therapeutic benefits. To determine the mode of action of the numerous natural chemicals found in plant extracts, phytochemical and ethnobotanical studies are currently being conducted. By inhibiting pro-inflammatory cytokines such as COX and lowering the translocation of NF- $\kappa$ B to the nucleus, plants can protect against several diseases whose genesis involves immunological dysfunction or chronic inflammation. The antioxidant properties of the cell enzymes and the oxidative stress brought on by an imbalance in the generation of reactive oxygen species (ROS) can both be controlled by the bioactive components of plants.<sup>24</sup> Although there are obvious advantages to using NSAIDs as painkillers after fractures, their widespread use has been questioned because of their alleged adverse effects on the mechanisms involved in bone repair. The favorable effects of plant substances on cellular activity and the development of the bone matrix have been investigated in clinical and preclinical research.<sup>9</sup> In order to explain the potential of plant extracts to substitute for NSAID drugs that can inhibit postoperative bone healing, Combining data from many research is crucial. We carefully examined the preclinical evidence in vivo to evaluate if the use of vegetal products in bone regeneration was appropriate in this situation.

## METHOD

This literature review uses a narrative or literature review method. The population in this literature review scientific articles on the potential of plant extracts as anti-inflammatory

agents for bone fracture healing. The sample used in this literature review is not less than 2013 english articles, and matched with the material discussed in this literature review. Meanwhile, the exclusion criteria are articles irrelevant to the topic published before 2013 were excluded. The PubMed/MEDLINE, Scopus, and Web of Science were used. We used the following keywords: "Plant extracts", "Bone Healing", "Animal model", and "Bone fracture". The exclusion criteria were based on the following: it is not bone, it is not a plant extract, not by oral or injection administration, laminectomy, absence of bone defects, peptides and fractions obtained from plants, compounds obtained from animals, in vitro, secondary studies (literature reviews, letters to the editor, case studies, comments, and editorials), marketed products, associated treatment (treatment with plant extracts associated with other plants and other compounds such as collagen matrix, laser, physical activity, and commercial drugs), and bone marrow. Articles that met the criteria were collected, along with a journal summary consisting of the author and year, plant parts, solvents used in the extraction, animal model, and outcome. This article was grouped into a table using the narrative review method to answer the research objectives. The data grouping must follow the order of author and year, plant parts, solvents used in the extraction, animal model, and outcome. Then, the grouped data are analyzed and searched for the most data. Subsequently, most of the data were analyzed using supporting journals to answer the research objectives. The data is presented in a table containing the author and year, plant parts, solvents used in the extraction, animal model, outcome (Table 1).

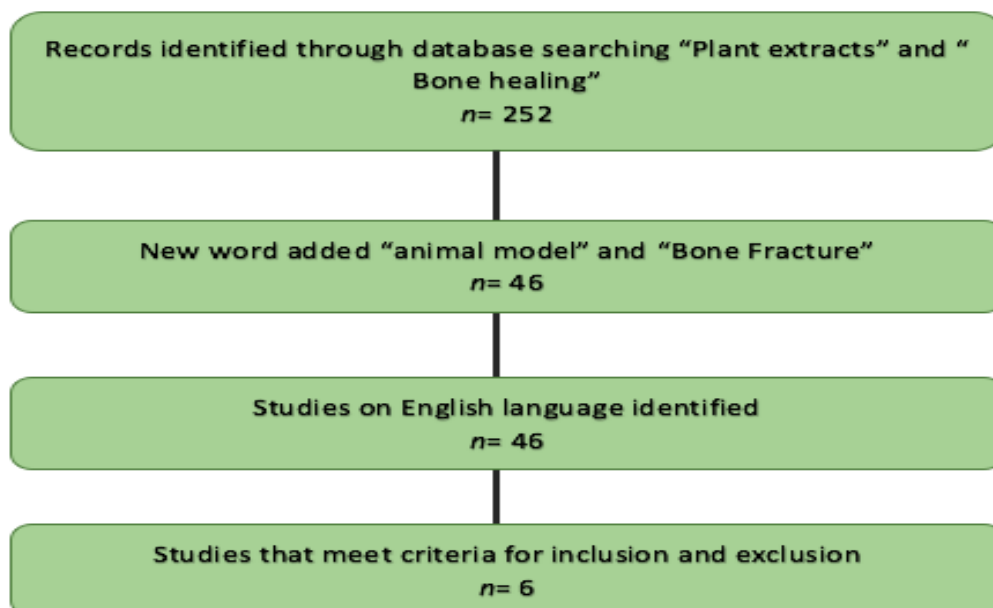


Figure 2 Flow chart diagram of included studies

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## RESULT

There are 6 studies that considered eligible for the criteria in the **Table 1**,

**Table 1 Summary of the included studies**

Title	Study ID	Used Parts	Solvent used for extraction	Animal Model
Repair of critical calvarias defects with systemic <i>Epimedium sagittatum</i> extract	Burim et al., 2016 <sup>25</sup>	Dried Leaves	Water/Ethanol	Wistar albino rats
Grape seed extract supplement increases bone callus formation and mechanical strength: an animal study	Gurger et al., 2019 <sup>26</sup>	Seed	1% carboxymethyl cellulose	Wistar-Albino
The effects of <i>Nigella sativa</i> seed extract on bone healing in an experimental model	Ezirganli et al., 2016 <sup>27</sup>	Seed	?	Wistar albino rats
Tanshinol alleviates osteoporosis and myopathy in glucocorticoid-treated rats	Chen et al., 2017 <sup>28</sup>	root	?	Sprague-Dawley rats
Root bark of <i>Sambucus williamsii</i> Hance promotes rat femoral fracture healing by the BMP-2/Runx2 signaling pathway	Yang et al., 2016 <sup>29</sup>	root bark	Ethanol	Sprague-Dawley rats
The effect of aqueous extract of <i>Prunus dulcis</i> on tibial bone healing in the rabbit	Anaraki et al., 2021 <sup>30</sup>	seed	Water	New Zealand white rabbits

## DISCUSSION

NSAIDs have long been a vital component of our strategy for pain management in post-traumatic environments. Owing to their strong analgesic and anti-inflammatory effects and fewer side effects than opioids, NSAIDs play an essential role in immediate pain following fracture or during the postoperative period after fracture repair.<sup>10</sup> However, research comparing NSAIDs and opiates has found that NSAIDs are at least as effective as opiates, and some research even suggests that NSAIDs might reduce pain ratings more effectively. Despite the advantages of NSAIDs, several studies have reported negative effects of NSAIDs. According to existing literature, NSAIDs treatment could inhibit shattered bones from healing. A meta-analysis by Pountos et al. reported that the study found no evidence of associations between various NSAIDs or even selectivity toward the enzymes COX-1 or COX-2 to explain the inhibition of bone healing.<sup>6</sup> Pountos et al. found that NSAIDs appear to impact the stage of mesenchymal stem cells, leading to the development of functional chondrocytes. Endogenous generation of PGE-2 did not bear this impact. The process appears to be the downregulation of the expression of important molecules like TGF-3.<sup>19</sup>

The use of plant extracts in therapy is very promising because of the benefits they contain with minimal side effects. Numerous plants have been used for various therapeutic purposes. Most plant parts have been used as extracts and may have anti-inflammatory and antioxidant properties. Neto et al. found that administration of systemic high icariin content in *Epimedium sagittatum* extracts can cause bone neoformation, lower osteocyte and osteoclast densities, and change the typical processes of bone deposition and remodeling in critically sized bone defects. Burger et al. in their studies with grape extract with animal model that

osteotomy was performed to the right femurs showed that grape seed proanthocyanidin extract (GSPE) is a potent antioxidant, had a positive effect on bone healing and improved mechanical strength of the healing bone.<sup>31</sup> The study from Ezirganli et al. was to histologically evaluate the effects on bone healing of *Nigella sativa* seed extract applied on calvarial defects in an ovariectomized rat model. 32 female rats weighing 280 and 310 g, with an average age of 3 months were used in this study. A trephine burr was used on the calvarium of each rat to produce a flaw. The rats were divided into two groups (control and experimental), each with eight animals. A gelatin sponge blended with regular saline was used to transplant all the flaws. An orogastric tube was used to systemically administer the *Nigella sativa* seed extract to the experimental group. After two weeks, half of the animals in each group were slaughtered, and four weeks later, the remainder. The flaws in the control group were not entirely filled with bone that had grown back. The research groups had more osteoblast cells. There were more osteoclasts in the control group. Additionally, at both 2 and 4 weeks, the *Nigella sativa* group exhibited significantly more bone growth than the other groups (P<0.05). In this experimental osteoporotic model, systemic administration of *N. sativa* seed extract showed remarkably beneficial effects on improved bone healing.<sup>27</sup> From the study of Chen et al. used tanshinol, a major water-soluble active component of *Salvia miltiorrhiza*. This study investigated the potential therapeutic effects of tanshinol against glucocorticoid-induced osteoporosis and glucocorticoid-induced myopathy. A total of 96 *sprague-dawley* rats were randomly divided into five groups: a control group, a model group, and three model groups that received calcitriol (tanshinol) at doses of 25, 50, or both. Prednisone acetate was administered to all the model groups for 90 days to induce glucocorticoid-induced

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osteoporosis. All of the animals underwent surgery to create bone defects in the right proximal tibia. After surgery, prednisone therapy was halted, but tanshinol or calcitriol treatment was continued until the endpoint. At the experimental endpoint, tanshinol 25 mg/kg significantly reduced glucocorticoid-induced loss of bone mineral density by 12.5% compared to the model group, improved mechanical bone strength, increased trabecular number significantly by 11%, and decreased trabecular separation by 28%. Tanshinol also promoted bone production and inhibited bone resorption, which enhanced the bone microarchitecture and halted glucocorticoid-induced bone loss. Tanshinol also sped up bone fracture mending and lessened the muscular atrophy brought on by glucocorticoid therapy, according to results of bone defect repair and muscle weight measures. Additionally, qRT-PCR results revealed that calluses from the tanshinol groups had 1-fold higher transforming growth factor-beta mRNA levels and nearly 6-fold higher vascular endothelial growth factor mRNA expression. Tanshinol also protected against glucocorticoid-induced increase in muscle ubiquitin mRNA levels. These results suggest that tanshinol may protect against glucocorticoid-induced osteoporosis and glucocorticoid-induced myopathy, which calls for additional follow-up studies.<sup>28</sup>

Yang et al. studied *Sambucus Williamsii* Hance (SWH), a plant from the family *Caprifoliaceae*, which has a long medical history of use as an effective folk treatment for fracture bruises. In this study, the mechanism of action of *Sambucus Williamsii* Hance root-bark extracts in relation to the BMP-2 signaling pathway was examined along with the effects of these extracts on the healing of rat fractures. This study discovered that EE-rbSWH significantly accelerated fracture healing by promoting bone formation at every stage of fracture healing, mainly by raising the BMD level at the fracture site, serum ALP and BGP levels, and the quantity of calcified nodules in BMSC. According to mechanistic studies, EErbSWH can speed up the healing of fractures by increasing the expression of BMP-2, BMPRII, BMPRII, and Runx2 at the site of the fractures in rats. This showed *Sambucus Williamsii* Hance root-bark extracts in 50% ethanol can accelerate the healing of fractures by attracting osteoblasts to the location of the break and activating the BMP-2 signaling pathway.<sup>29</sup> This is also consistent with Anaraki et al.'s study, which showed that tibial bone healing may be speed up in a rabbit model of lesions on the bone by utilizing *prunus dulcis* extract at a level of 300 mg/kg.<sup>30</sup>

## CONCLUSION

The outcomes of this study showed that the usage of plant extracts promotes bone healing by enhancing osteogenesis, the rate of calcification, and the creation and mineralization of bone callus, hence expediting the process of new bone formation on the fracture location. These benefits may be connected to the antioxidant and anti-inflammatory

properties of these extracts. From these results it can be concluded that plant extracts can potentially substitute for NSAIDs in postoperative bone healing as anti-inflammation. However, it is challenging to comprehend and apply data in research for the human condition due to the methodological flaws revealed in some studies. Therefore, in order to compare the research more effectively and enable future trials to be adapted, more thorough methodological descriptions are required. Beyond that, to find further potential for its usage as a bone healing therapy, research with other plant extracts must also be conducted.

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