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Nigella Sativa as biocoating / osteogenic agent

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ABSTRACT

Nigella sativa, a medicinal plant rich in bioactive compounds such as thymoquinone, has gained attention as a natural osteogenic and antimicrobial agent for biomedical applications, particularly in implantology. Its incorporation as a biocoating on hydroxyapatite and metallic implants has demonstrated enhanced osteoblast differentiation, improved osseointegration, and significant antimicrobial activity against oral pathogens. The plant's anti-inflammatory and antioxidant mechanisms further support bone regeneration by reducing oxidative stress and inflammatory cytokine production. Comparative studies reveal that Nigella sativa performs on par with or superior to other natural osteogenic agents like curcumin and green tea extract. While in vitro and in vivo findings confirm its promising osteoinductive and biocompatible properties, further studies are warranted to establish standardized formulations, assess long-term toxicity, and validate clinical safety for implant-based applications..

Keywords: Nigella sativa, Thymoquinone, Hydroxyapatite, Biocoating, Osteogenesis, Osseointegration, Antimicrobial, Osteoporosis, Bone Tissue Engineering, Implantology

INTRODUCTION

The plant kingdom not only sustains environmental balance and produces life-giving oxygen but also plays a crucial role in human nutrition, serving as an essential source of contemporary medicines. Foods derived from plants fulfill fundamental nutritional needs, promote bodily health, and offer protection against various diseases by enhancing the immune system. In recent years, the terms 'nutraceuticals' and 'functional foods' have gained traction among health-conscious consumers, highlighting the strong correlation between a nutritious diet and increased life expectancy.1 These ideas have also piqued the interest of dietitians, nutritionists, food scientists, medical professionals, and the food and pharmaceutical sectors. As the global market for functional foods continues to grow, significant research efforts are being directed towards investigating traditional foods that exhibit potential health benefits. Within the diverse array of functional food components, minor yet essential ingredients, such as herbs and spices, commonly utilized as flavor enhancers and preservatives, are rich in bioactive compounds.2 While these culinary herbs and spices are primarily employed in cooking, they are also recognized for their nutraceutical properties, possessing substantial health-promoting capabilities.3

NS is a dicotyledonous plant belonging to the Ranunculaceae family. It is also known as “crowfoot” or “buttercup”. Ranunculus is the largest genera from the family of more than 2000 flowering plants, with 43 genera widely distributed around the globe. Reports about the chemical constituents of NS suggested the presence of oils, carbohydrates, proteins, and fibres. Several experimental studies have suggested the medicinal importance of NS, which is primarily due to the presence of quinone constituents (TQ).

Large amounts of carbohydrates, proteins, fats, vitamins, minerals, and fiber make the seed nutrition rich. Several amino acids have also been detected in the plant, such as aspartate, glutamate, arginine, methionine, and cystine. Vitamins identified in black seed include folic acid, niacin, thiamine, and pyridoxine. Minerals such as calcium, iron, phosphorus, zinc, and copper are also found in it. A phytochemical investigation of black seeds revealed the presence of sterols, alkaloids, essential oil, and saponins. The seeds of this herb contain palmitic acid (20.4%) and linoleic acid (64.6%) as primary fatty acids in a fixed oil (26–34%). From the nutrient pool of NS, the bioactive compound TQ has been identified as possessing significant medicinal potential.

Nigella sativa's essential oil and extracts have been successfully used to coat hydroxyapatite (HAP) scaffolds, a standard biomaterial for bone implants. This biocoating not only enhances osteogenesis—promoting bone cell differentiation and tissue regeneration—but also imparts antimicrobial properties, reducing the risk of post-implant infections. For example, one study demonstrated that Nigella sativa-coated HAP scaffolds significantly improved cellular differentiation of osteoblasts and myoblasts compared to HAP alone, presenting a promising low-cost material for both hard and soft tissue engineering. The bioactive components of Nigella sativa, such as thymoquinone, further contribute by stabilizing the osteoinductive environment and augmenting biocompatibility.[4,5]

Compelling in vivo and in vitro research has established that Nigella sativa augments bone healing by increasing osteoblast (bone-forming cell) activity and upregulating critical bone turnover markers like bone-specific alkaline phosphatase (bALP) and osteoprotegerin (OPG). Particularly at higher dosages (e.g., 400 mg/kg in animal models), Nigella sativa promotes osteoblast proliferation and survival, contributing to more robust and mature bone formation in defect models. Additionally, thymoquinone, the principal active compound, is involved in stimulating osteoblast differentiation and mineralization, especially via the ERK pathway. Histological studies show that application of Nigella sativa oil led to more mature woven bone and a higher rate of new bone tissue formation in animal jaws when compared to uncoated controls.[6,7]

The underlying mechanisms for Nigella sativa's efficacy include potent antioxidant actions that scavenge free radicals, mitigate inflammatory responses, and modulate cytokine activity—key processes in bone regeneration and implant integration. Nigella sativa suppresses oxidative stress-induced bone loss and inhibits pro-inflammatory cytokines, which play a role in pathological bone resorption seen in osteoporosis and delayed bone healing. Collectively, these actions enhance the microenvironment at the implant site, ultimately favoring bone regeneration, reducing inflammation, and expediting healing.

The combination of osteogenic stimulation and antimicrobial biocoating positions Nigella sativa as a multifunctional agent in dental, orthopedic, and maxillofacial applications. Research supports its integration into next-generation biomaterials for bone defect repair, scaffold engineering, and as a protective coating for metallic or composite implants. As clinical interest grows, further trials are anticipated to optimize dosing, formulation, and long-term outcomes in human models.

Botanical Profile of Nigella sativa

Nigella sativa L., commonly known as black cumin, black seed, or kalonji, is an annual herbaceous plant belonging to the family Ranunculaceae. It is native to the Mediterranean region and Southwest Asia but is now widely cultivated across the Middle East, North Africa, India, and Southern Europe for its medicinal and culinary uses. The plant has been used for thousands of years in traditional systems of medicine, including Unani, Ayurveda, and Islamic medicine, where it was referred to as a "seed of blessing" due to its wide therapeutic potential. Ancient records indicate its use by the Egyptians and Greeks for ailments ranging from respiratory and gastrointestinal disorders to immune enhancement, reflecting its long-standing ethnopharmacological significance.[8]

The pharmacological potential of Nigella sativa is primarily attributed to its rich and diverse phytochemical composition. The seeds contain about 30–40% fixed oil and 0.4–2.5% volatile oil, along with proteins, alkaloids, saponins, and flavonoids. The major bioactive compound of the volatile oil is thymoquinone (TQ), which is known for its potent antioxidant, anti-inflammatory, and anticancer effects. Other significant constituents include nigellone (dithymoquinone), thymohydroquinone, carvacrol, p-cymene, α-pinene, and trans-anethole, which collectively contribute to the plant's biological activities. The fixed oil fraction is rich in unsaturated fatty acids such as linoleic acid, oleic acid, palmitic acid, and stearic acid, while the presence of alkaloids (nigellidine, nigellicine), flavonoids, and tannins further enhances its pharmacological potential. These compounds act synergistically to produce the therapeutic benefits associated with the plant.[9,10]

Among its well-documented pharmacological activities, Nigella sativa exhibits strong anti-inflammatory properties, mainly due to thymoquinone, which suppresses inflammatory mediators and signaling pathways. TQ inhibits the activity of enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), thereby reducing the production of prostaglandins and leukotrienes responsible for inflammation. It also downregulates the expression of nuclear factor kappa-B (NF-κB) and pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), contributing to its potent anti-inflammatory effect. Experimental studies have demonstrated that thymoquinone effectively reduces inflammation and edema in animal models, showing results comparable to conventional non-steroidal anti-inflammatory drugs.

Nigella sativa also possesses strong antioxidant activity, which plays a crucial role in protecting tissues against oxidative stress and cellular damage. Thymoquinone and other phenolic constituents act as free radical scavengers, enhancing the levels of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). This antioxidant defense mechanism helps in maintaining cellular integrity by preventing lipid peroxidation, DNA damage, and protein oxidation. Studies have shown that supplementation with Nigella sativa oil or extract can restore antioxidant enzyme activity and protect against oxidative stress-induced organ damage, confirming its role as a natural antioxidant.[11-13]

In addition, Nigella sativa demonstrates remarkable antimicrobial activity against a wide spectrum of pathogens, including Gram-positive and Gram-negative bacteria, fungi, and certain parasites. Thymoquinone and other volatile oil components disrupt microbial cell membranes, inhibit enzyme systems, and interfere with microbial replication. The seeds and their extracts have been shown to inhibit the growth of Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, and Aspergillus niger. Furthermore, the combination of Nigella sativa extracts with conventional antibiotics enhances antibacterial efficacy, indicating synergistic effects that could help combat antibiotic-resistant infections.

Overall, Nigella sativa is a pharmacologically rich plant with multifaceted therapeutic properties. Its primary bioactive compounds, particularly thymoquinone and nigellone, play key roles in conferring anti-inflammatory, antioxidant, and antimicrobial benefits. The combination of traditional use and modern pharmacological validation underscores Nigella sativa as a valuable natural agent with significant potential in preventive and therapeutic medicine.

Biological Basis for Osteogenesis

Bone healing and regeneration are complex biological processes that involve a well-coordinated series of cellular and molecular events aimed at restoring the structural and functional integrity of the skeletal system. Osteogenesis, or new bone formation, is primarily carried out by osteoblasts derived from mesenchymal stem cells (MSCs), which differentiate under the influence of various growth factors and signaling molecules. The bone healing process generally occurs in three overlapping phases: inflammation, repair, and remodeling. During the inflammatory phase, cytokines and growth factors such as transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and bone morphogenetic proteins (BMPs) are released at the injury site, attracting MSCs and osteoprogenitor cells. The repair phase is characterized by the formation of a soft callus composed of cartilage and fibrous tissue, which later mineralizes to form a hard bony callus. In the final remodeling phase, immature woven bone is replaced by mature lamellar bone, restoring the bone's original structure and mechanical strength.

Osteoinduction refers to the process by which osteogenesis is stimulated in undifferentiated mesenchymal cells, prompting their transformation into osteoblasts. This process is mediated by bioactive molecules such as BMPs, TGF-β, insulin-like growth factors (IGFs), and fibroblast growth factors (FGFs), which act through specific receptor-mediated signaling pathways. Among these, BMPs play a central role by initiating the Smad signaling cascade, leading to the upregulation of osteogenic genes such as RUNX2, osteocalcin, and alkaline phosphatase (ALP). The local microenvironment, including oxygen tension, mechanical stimuli, and extracellular matrix (ECM) composition, also influences osteoinduction by regulating cell adhesion, proliferation, and differentiation. Together, these factors ensure the controlled and sustained formation of new bone tissue during the healing process.

Bioactive coatings on implant surfaces have gained significant attention for their role in enhancing osteointegration—the stable and functional connection between living bone and the surface of a load-bearing implant. Osteointegration depends on the ability of the implant to promote cellular adhesion, proliferation, and differentiation of osteogenic cells at the bone-implant interface. Traditional metallic implants such as titanium possess excellent mechanical properties but limited bioactivity, leading to slow or incomplete integration. To overcome this limitation, bioactive coatings composed of materials like hydroxyapatite, calcium phosphate, bioactive glass, and polymeric or natural compounds have been developed to mimic the mineral phase of bone and improve biological interactions.

These bioactive coatings function by releasing ions and signaling molecules that stimulate osteoblast activity and extracellular matrix mineralization. For example, calcium and phosphate ions released from hydroxyapatite coatings promote nucleation and deposition of bone-like apatite, while bioactive glass coatings generate a silica-rich layer that supports protein adsorption and cell adhesion. Moreover, coatings incorporating osteogenic agents such as growth factors, peptides, or plant-derived compounds (e.g., Nigella sativa extract or thymoquinone) can further enhance osteoinduction and accelerate bone healing. By combining mechanical stability with biological functionality, bioactive coatings bridge the gap between artificial implants and natural bone tissue, thereby ensuring long-term implant success through improved osteointegration and bone regeneration.[12-14]

Osteogenic Potential of Nigella sativa

Osteoporosis is a condition that progresses silently, leading to a decrease in bone mass, changes in the microarchitecture of bone, and an increase in the risk of fractures due to weakened bone strength. It is estimated that around 200 million women worldwide are impacted by this condition, with approximately 8.9 million fractures occurring each year as a result of osteoporosis. The World Health Organization (WHO) characterizes osteoporosis by measuring bone mineral density (BMD) using DEXA (dual energy X-ray absorptiometry), which is expressed in terms of Z-scores and T-scores. A BMD that falls within 1 standard deviation on this scoring scale is deemed normal, a score between 1 and 2.5 indicates osteopenia (a reduction in bone mass), and a score exceeding 2.5 is classified as osteoporosis.

Osteoporosis is categorized into primary and secondary types based on underlying causes. Primary osteoporosis can affect individuals of both genders but is predominantly observed in postmenopausal women, whereas secondary osteoporosis arises from specific medical conditions such as hypogonadism or celiac disease, as well as from the use of certain medications like glucocorticoids. The risk factors associated with osteoporotic fractures are numerous and include low peak bone mass, hormonal influences, the use of steroid medications, smoking, insufficient physical activity, inadequate intake of calcium and vitamin D, racial background, small body size, and a personal or familial history of fractures. In postmenopausal women, osteoporosis significantly increases the likelihood of hip and vertebral fractures, as well as the risk of falls, which in turn contributes to higher rates of morbidity and mortality in this population.

Nigella sativa has emerged as a promising natural agent with significant osteogenic potential, attributed mainly to its rich phytochemical composition, particularly thymoquinone (TQ), nigellone, and various essential fatty acids, alkaloids, and flavonoids. These bioactive compounds act synergistically to modulate bone metabolism by promoting osteoblast differentiation, enhancing bone formation, and inhibiting osteoclastic bone resorption. The seeds and their extracts have been extensively studied for their antioxidant, anti-inflammatory, and osteoprotective effects, which collectively contribute to their ability to support bone regeneration and repair.

The osteogenic activity of Nigella sativa is primarily linked to the action of thymoquinone, which influences several signaling pathways involved in bone formation. TQ has been shown to stimulate the differentiation of mesenchymal stem cells into osteoblasts by upregulating osteogenic markers such as alkaline phosphatase (ALP), osteocalcin, and runt-related transcription factor 2 (RUNX2). These markers are critical for the synthesis and mineralization of the bone matrix. Furthermore, TQ enhances the expression of bone morphogenetic proteins (BMPs) and activates the Wnt/β-catenin signaling pathway, both of which play vital roles in osteoinduction and bone tissue development.

In addition to promoting osteoblastogenesis, Nigella sativa also exhibits inhibitory effects on osteoclast activity, thereby reducing bone resorption. Thymoquinone suppresses osteoclast differentiation by downregulating the receptor activator of nuclear factor-kappa B ligand (RANKL) and nuclear factor of activated T-cells cytoplasmic 1 (NFATc1), both of which are essential regulators of osteoclast formation. By maintaining a favorable balance between bone formation and resorption, Nigella sativa contributes to overall bone homeostasis and prevents bone loss conditions such as osteoporosis.

The antioxidant and anti-inflammatory properties of Nigella sativa further strengthen its osteogenic capacity. Oxidative stress and chronic inflammation are known to impair bone healing and regeneration by disrupting osteoblastic function and promoting osteoclastic activity. Thymoquinone, a potent antioxidant, scavenges reactive oxygen species (ROS) and enhances the activity of endogenous antioxidant enzymes like superoxide dismutase and catalase. Additionally, it reduces the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, thereby creating a microenvironment conducive to osteogenesis.

Experimental studies have validated the osteogenic effects of Nigella sativa in both in vitro and in vivo models. Animal studies have demonstrated that supplementation with Nigella sativa oil or thymoquinone improves bone density, enhances calcium deposition, and accelerates fracture healing. In ovariectomized rat models of osteoporosis, TQ supplementation increased bone mineral content and trabecular thickness while decreasing markers of bone resorption. In cell culture studies, Nigella sativa extracts have shown to increase osteoblast proliferation and mineralization, indicating direct stimulatory effects on bone-forming cells.

Therefore the findings suggest that Nigella sativa can act as a natural osteoinductive agent, capable of stimulating bone regeneration through multiple mechanisms—enhancing osteoblastic activity, suppressing osteoclastic bone loss, and modulating oxidative and inflammatory stress. Its potential use in bioactive coatings, bone graft materials, or dietary supplementation opens new avenues for developing natural, biocompatible strategies in bone tissue engineering and implantology.[15-20]

Nigella sativa as a Biocoating Agent

Nigella sativa has been explored as a natural biocoating agent due to its antimicrobial, antioxidant, and bioactive properties derived mainly from thymoquinone, nigellone, and other volatile oils. Edible coatings incorporating N. sativa oil have been shown to enhance the shelf life and quality of perishable foods. For instance, a study demonstrated that lemons coated with 100% N. sativa oil retained freshness and delayed spoilage longer than other treatments, indicating the oil's potential to act as an effective antimicrobial and oxidative barrier on biological surfaces

In agricultural and biomedical contexts, N. sativa extracts have been integrated into nano-emulsion and composite coating systems. Oil-in-water nano-emulsions containing N. sativa oil applied to maize seeds improved germination rates, root and shoot development, and protection against Penicillium verrucosum infection, confirming its effectiveness as a bioactive surface agent. Similarly, Nigella sativa seed extracts incorporated into hydroxyapatite/sodium-silicate glass coatings demonstrated antimicrobial activity against both Gram-positive and Gram-negative bacteria as well as Candida species, supporting its potential for use in implant coatings and other biomedical applications.[21-24]

Antimicrobial and Anti-inflammatory Properties in Implantology

Nigella sativa exhibits significant antimicrobial properties that contribute to its potential use in implantology. The bioactive constituent *thymoquinone* is primarily responsible for its broad-spectrum antibacterial and antifungal activity. Studies have demonstrated its effectiveness against oral pathogens such as *Staphylococcus aureus*, *Porphyromonas gingivalis*, and *Candida albicans*, which are commonly associated with peri-implant infections. When used as a biocoating or incorporated into implant materials, Nigella sativa extracts can inhibit bacterial adhesion and biofilm formation, reducing the risk of peri-implantitis and infection-related implant failures

In addition to its antimicrobial action, Nigella sativa possesses potent anti-inflammatory effects beneficial in the peri-implant healing phase. Thymoquinone suppresses pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, while enhancing antioxidant enzyme activity and reducing oxidative stress at the implant site. This dual action promotes favorable tissue healing and reduces inflammatory bone resorption around implants. These properties suggest that incorporating Nigella sativa into implant coatings may enhance osseointegration while minimizing inflammatory complications[25-27]

Comparative Evaluation with Other Natural Osteogenic Agents

Natural bioactive compounds have gained significant attention as alternatives to synthetic growth factors for enhancing bone regeneration and implant integration. Among these, *Nigella sativa* has emerged as a potent osteogenic agent, often compared with other plant-derived substances such as *Curcuma longa* (curcumin), *Camellia sinensis* (green tea), *Aloe vera*, and *Resveratrol*. These natural agents share common mechanisms such as the stimulation of osteoblast proliferation, inhibition of osteoclast activity, and modulation of oxidative and inflammatory pathways. However, *Nigella sativa* distinguishes itself through its combined antimicrobial, anti-inflammatory, and osteoinductive actions, making it particularly suitable for applications in implantology and bone healing environments where infection control is vital.

The osteogenic effect of *Nigella sativa* is primarily attributed to its active component, *thymoquinone*, which enhances alkaline phosphatase (ALP) activity, collagen matrix formation, and mineral deposition. In comparative studies, it has shown bone-forming potential similar to or greater than curcumin and green tea polyphenols, with added antimicrobial benefits that reduce the risk of peri-implant infections. Furthermore, *Nigella sativa* modulates the RANKL/OPG signaling pathway, maintaining bone homeostasis while promoting osteoblastic differentiation. This multifaceted action positions it as a promising candidate among natural agents for surface modification of implants to improve osseointegration and bone healing outcomes[28-30]

Toxicity and Biocompatibility Consideration

Toxicity and biocompatibility are critical parameters in evaluating the suitability of Nigella sativa and its bioactive compounds, particularly thymoquinone, for use as implant surface coatings. Several in vitro studies have demonstrated that Nigella sativa extracts exhibit dose-dependent cytocompatibility with osteoblast-like cells. At lower concentrations, thymoquinone promotes osteoblast proliferation, differentiation, and alkaline phosphatase activity, while higher doses may induce cytotoxic effects due to oxidative stress or apoptosis induction. Thus, optimizing concentration and release kinetics is essential to ensure sustained biological activity without compromising cellular viability.

In vivo studies have further supported the biocompatibility of Nigella sativa-based formulations. Animal models have shown minimal inflammatory response, absence of fibrous capsule formation, and enhanced bone regeneration around implants treated with Nigella sativa coatings compared to uncoated controls. The anti-inflammatory and antioxidant nature of its components contributes to reduced postoperative inflammation and improved osseointegration. Moreover, histological analyses often reveal increased new bone formation and better interfacial contact between bone and implant, suggesting that Nigella sativa enhances both biological and mechanical integration.

Despite these encouraging findings, the long-term toxicity profile of Nigella sativa-derived coatings remains inadequately explored. Potential concerns include variability in extract composition, stability of bioactive compounds under sterilization or physiological conditions, and the possibility of systemic absorption or degradation byproducts. Therefore, comprehensive biocompatibility assessments following ISO 10993 guidelines, including cytotoxicity, genotoxicity, and chronic exposure studies, are necessary before clinical translation. Establishing standardized extraction, purification, and coating protocols will be crucial to ensure reproducibility, safety, and regulatory approval for Nigella sativa-based implant coatings.[31-34]

Clinical Application and Future Scope

The integration of Nigella sativa (NS) into orthopedic, dental, and maxillofacial applications offers a promising strategy for treating osteoporosis and enhancing skeletal muscle regeneration. As a multifunctional biocoating for hydroxyapatite (HAP) and metallic implants, NS and its active constituent, thymoquinone, stimulate osteoblast differentiation while providing a critical antimicrobial barrier against pathogens like Staphylococcus aureus and Porphyromonas gingivalis.

Future research must prioritize the standardization of extraction protocols and formulations to ensure reproducible results across different medical platforms. While current in vitro and in vivo results are encouraging, extensive human clinical trials are necessary to validate long-term toxicity, biocompatibility, and controlled release kinetics. Advancing toward nanostructured composite coatings could further refine the delivery of these bioactive compounds, paving the way for next-generation, naturally-enhanced implant systems.

CONCLUSION

Nigella sativa represents a multifunctional natural agent with strong potential for enhancing bone regeneration and implant integration through its combined osteogenic, antimicrobial, and anti-inflammatory actions. The thymoquinone-rich biocoating not only promotes osteoblastic activity and osseointegration but also minimizes peri-implant infections, offering a biocompatible and cost-effective alternative to conventional synthetic coatings. However, to achieve clinical translation, rigorous evaluation of long-term biocompatibility, controlled release kinetics, and standardized extraction protocols is essential. Future research integrating Nigella sativa into nanostructured and composite coatings may pave the way for its use in next-generation dental and orthopedic implant systems

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