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Study of the Osteoinductor Property in Bone Repair of the Species *Zingiber Zerumbet* (Bitter Ginger)

Estudo da Propriedade Osteoindutora na Reparação Óssea da Espécie Zingiber Zerumbet (Gengibre Amargo)

Estudio de la Propiedad Osteoinductiva en Reparación Ósea de la Especie Zingiber Zerumbet (Bitter Ginger)

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Abstract
Zingiber zerumbet is a species that is part of the Zingiberaceae family, one of the largest families in the plant kingdom, being considered a perennial, aromatic and tuberculin plant. This species has been used in different sectors as food due to its nutritional properties. The main chemical compounds found in Z. zerumbet are terpenes and polyphenols. Zerumbone, a sesquiterpene, is the main bioactive compound of Z. zerumbet and is widely studied for its medicinal properties. Although many studies have already reported on its pharmacological properties, extract and metabolites granted from the species of Z. zerumbet exhibited anti-inflammatory, antioxidant, antidiabetic, anticancer, antimicrobial, analgesic and antiviral properties. Several biomaterials have been developed to fill or rebuild bone defects, among these, the herbal ones that have substances with high antioxidant potential stand out, not which this one has a role in the bone recovery process. Therefore, this mini-review provides an overview of the main aspects related to the properties of bioactive compounds found not extracted from Z. zerumbet species, with the objective of demonstrating the importance of extracted actives and used in future osteoinductive solutions.
Keywords: *Z. Zerumbet*; Antioxidants; Osteoinductive; Potential.

Resumo
Zingiber zerumbet é uma espécie que faz parte da família *Zingiberaceae*, uma das maiores famílias do reino vegetal, sendo considerada uma planta perene, aromática e tuberculífera. Esta espécie vem sendo utilizada em diferentes setores, como alimentício devido as suas propriedades nutritivas. Os principais compostos químicos encontrados em *Z. zerumbet* são terpenos e polifenóis. Zerumbone, um sesquiterpeno, é o principal composto bioativo de *Z. zerumbet* e é amplamente estudado por suas propriedades medicinais. Embora muitos estudos já tenham relatado sobre suas

propriedades farmacológicas, extrato e metabólitos isolados da espécie de *Z. zerumbet* exibiram propriedades antiinflamatória, antioxidante, antidiabético, anticâncer, antimicrobiano, analgésico e antiviral. Diversos biomateriais tem sido desenvolvido para preencher ou reconstruir defeitos ósseos, dentre esses destaca-se os fitoterápicos que possuem substancias com alto potencial antioxidante, no qual este possui uma participação no processo de reparação óssea. Portanto, esta mini-revisão fornece uma visão geral dos principais aspectos relacionados às propriedades dos compostos bioativos encontrados no extrato da espécie de *Z. zerumbet*, com o objetivo de demonstrar a importância de ativos extraídos e utilizados em tratamentos futuros de reparação osteoindutora.
Palavras-chave: *Z. zerumbet*, Antioxidantes; Osteoindutor; Potencial.

Resumen
Zingiber zerumbet es una especie que forma parte de la familia Zingiberaceae, una de las familias más grandes del reino vegetal, siendo considerada una planta perenne, aromática y tuberculífera. Esta especie ha sido utilizada en diferentes sectores, como el alimentario por sus propiedades nutritivas. Los principales compuestos químicos que se encuentran en Z. zerumbet son los terpenos y los polifenoles. Zerumbone, un sesquiterpeno, es el principal compuesto bioactivo de Z. zerumbet y es ampliamente estudiado por sus propiedades medicinales. Aunque muchos estudios ya han informado sobre sus propiedades farmacológicas, el extracto y los metabolitos aislados de especies de Z. zerumbet exhibieron propiedades antiinflamatorias, antioxidantes, antidiabéticas, anticancerígenas, antimicrobianas, analgésicas y antivirales. Se han desarrollado varios biomateriales para rellenar o reconstruir defectos óseos, entre los que se destacan los medicamentos a base de plantas que poseen sustancias con alto potencial antioxidante, en las que tiene participación en el proceso de reparación ósea. Por lo tanto, esta minirevisión brinda una visión general de los principales aspectos relacionados con las propiedades de los compuestos bioactivos encontrados en el extracto de la especie de Z. zerumbet, con el objetivo de demostrar la importancia de los activos extraídos y utilizados en futuros tratamientos de reparación osteoinductiva.
Palabras clave: *Z. zerumbet*; Antioxidantes; Osteoinductor; Potencial.

1. Introduction

Zingiberaceae are the largest families in the plant kingdom. Its plants tend to be of high medicinal value and provide many useful products for food, spices, medicines, tinctures, perfumes and aesthetics (Koga, Beltrame and Pereira, 2016), it has approximately 141 species, among which stands out the species *Zingiber zerumbet* (L) Smith is a wild ginger, also known as bitter ginger. This species can be found naturally in humid and shady lowland locations.

This type of wild ginger, the crude extract, as well as the active compounds extracted from the rhizome and leaves of *Z. zerumbet*, have been reported to have several pharmacological properties, including anti-inflammatory (Jalil et al., 2015), antitumor (Abdelwahab et al., 2015), antioxidant (Rout et al., 2012), antibacterial (Kumar et al., 2013), antiviral (Epstein-Barr virus) (Murakami et al., 2012), analgesic (Somchit et al., 2015) and antiallergic (Tewtrakul and Subhadhirasakul, 2017).

Scientific investigations have elucidated several ways that compounds interfere with bone health. Through several mechanisms, they can favor the formation of bone tissue and/or attenuate its reabsorption, or even help in the regeneration process indirectly, such as promoting blood supply to the injured region. From these investigations it was discovered, for example, that bone pathophysiology is associated with oxidative stress and therefore, antioxidant compounds have the potential to positively affect bone metabolism (Cavassani et al., 2018).

Zerumbona, the major compound in the essential oil of *Z. zerumbet*, has gained prominence for revealing properties such as antioxidant activity (Shieh, 2015).

Zingiber zerumbet (L.) Smith and its major component, zerumbone, have high antioxidant/anti-inflammatory potential, thus contributing to the investigation of new therapies or pharmacological mechanisms.

2. Methodology

Among the researches that synthesize findings about a certain phenomenon investigated in primary studies, several terms have been used: integrative review, traditional review, narrative review, systematic review, meta-analysis, metasynthesis, metasumarization, among others (Soares et al., 2014). To achieve the objectives proposed in this study, the chosen method was

the Integrative Review, which includes the analysis of relevant research that supports decision-making, allowing the incorporation of these findings in the research. This type of study is a strategy for identifying and analyzing existing evidence, when the production of scientific knowledge is not sufficiently grounded (Lucia & Robazzi, 2012).

The study aimed to carry out a systematic review of the literature, searching through research in bibliographic data platforms such as Scopus, Scielo and PubMed that addressed the keywords [“Property”, “Osteoinducer”, “Zingiber” “Zerumbet”].

The inclusion criterion consisted of studies comprising the English and Portuguese languages, this research was not limited to the maximum and minimum time, but sought a maximum period of 10 years. Exclusion criteria are articles that do not include such keywords. In total, 2.014 scientific articles were found, of which only 19 were suitable for the research, for discussion throughout the article.

3. Results and Discussion

3.1 Chemical Compounds of *Zingiber zerumbet* Species

Zingiber zerumbet (L.) Roscoe ex Sm., Zingiberaceae, is a perennial, aromatic, tuberous plant that grows in humid places. Also known as bitter ginger, *Z. zerumbet* (L.) Smith is traditionally found throughout Asia, where it is widely used in food, drink and for ornamental purposes (Andreo and Jorge, 2013).

In Brazil, *Z. zerumbet* is found in the Amazon region, in Taruma-mirim and Puraquequara (rural areas of Manaus, Amazonas, Brazil). The main chemical compounds found in *Z. zerumbet* are terpenes and polyphenols (Koga, Beltrame and Pereira, 2016). Its various studies are directly related to the therapeutic potential referring to the chemical composition, where it is worth mentioning the presence of sesquiterpene, flavone, flavonoid glycosides from *Z. zerumbet* species (Sidahmed *et al.*, 2015). Attempts to identify bioactive compounds of the species began in 1944 with the identification of humulene, monoterpenes and zerumbone (Varier, 2012). High proportions of (Z)-nerolidol (22-36%) were found in extracts of stems, leaves and flowers, where zerumbone is predominant in leaves (Sulaiman *et al.*, 2012).

3.2 Pharmacological and Toxicological Action of *Zingiber zerumbet* Species

From a medicinal point of view, the species *Z. zerumbet* has a high potential for cultivation, being the matrix of food products due to the fact that it enhances the nutritional absorption functions of food.

In Chinese medicine, *Zingiber zerumbet* rhizomes are used to treat coughs, colds, diarrhea, vomiting and abdominal pain associated with colds (fresh rhizome); uterine bleeding and blood in the urine (charred fresh rhizome); swelling of the abdomen and edema (rhizome); digestive disorders and chronic bronchitis (dry rhizome) (Corrêa, 2013).

The species Zingiber zerumbet contains zerumbone, a cytotoxic compound used in China for the treatment of cancer (Pinheiro, 2015).

Z. zerumbet ethyl acetate extract has been shown to have protective effects against ethanol-induced brain damage in rats by decreasing lipid and protein oxidation as well as increasing antioxidant activities. This suggests that *Z. zerumbet* has potential as a neuroprotective agent (Hamid *et al.*, 2018). The anti-inflammatory activity found in the species of *Z. zerumbet* occurs from the presence of an isolated natural cyclic sesquiterpene, where, from the significant dosage there was a significant suppression of the formation of granulomatous tissue (Sulaiman *et al.*, 2012).

Although many studies have reported the biomedical applications of *Z. zerumbet*, its antiallergic effects are due to its main bioactive compounds. Many important metabolites that have antiallergic properties are terpene compounds that can also be found in essential oil extracted from *Z. zerumbet* rhizomes, such as zerumbone, limonene and humulene. The rhizome

present in the plant parts of *Z. zerumbet* has been widely used for many studies due to its exceptional biomedical applications. Most of these studies showed that both the essential oil and the extract have several active metabolites (Tan, Israf and Tham, 2018).

3.3 Osteoinductive Property in Bone Repair

Osteoinduction is defined as the ability to produce pluripotent cells from an environment of non-bone union and to differentiate into chondrocytes and osteoblasts, with consequent bone formation. An osteoinductive material allows repair at a site that would normally not heal if not treated properly (Ahsan, 2015). Osteoconduction supports the growth of capillaries and host cells into a three-dimensional structure to form bone. The osteoconductive material guides the location of the repair in places where bone healing would not occur naturally (Bennettl *et al.*, 2012).

Osteoinduction is one of the main properties attributed to bone grafts. The term refers to the process by which mesenchymal stem cells, present in the tissue surrounding the graft site, are induced to differentiate into osteogenic lineage cells. This mechanism is related to the activity of the "bone morphogenetic protein" (BMP) present in the bone matrix (Cavassani et al., 2018).

When evaluating the osteoinductive function attributed to bone fragments from donor rats in 98% glycerin, performed in the subcutaneous and intramuscular tissue of recipient rats, a positive osteogenic response was noted, with the presence of fragments of calcified bone matrix, suggesting the presence of newly formed bone tissue. from osteoblastic activity (Cavassani, Moraes and Padilha Filho, 2018).

From the production of the gel extract of the species of Chenopodium ambrosioides (mastruz), containing saponins and tannins in its composition, it showed anti-inflammatory and osteoinductive effects, positively interfering in the quality of newly formed bone in osteoporotic rats (Trindade & Rodrigues, 2021).

Pinheiro Neto et al., (2021) evaluated the effect of mastruz poultice (*Chenopodium ambrosioides*) applied directly to the bone defect in rabbits, comparing it with sodium diclofenac and saline solution. The evolution of bone repair was verified after 30 and 45 days through histological analysis. This analysis revealed at 30 days a greater formation of mature bone tissue in the mastruz poultice group compared to the other groups. Therefore, they concluded that Chenopodium ambrosioides is a promising therapeutic agent for bone regeneration (Neto *et al.*, 2021).

Knowledge of bone metabolism also leads to the search for pharmacological alternatives. It is known, for example, that oxidative stress conditions the pathophysiology of bone tissue, which has motivated scientific investigations of substances with antioxidant potential. In this perspective, natural substances gain prominence, due to their potential to reduce and neutralize free radicals (Lee *et al.*, 2016).

Antioxidant compounds have direct or indirect action on bone metabolism. They can interfere with the recruitment of osteoprogenitor cells, favor osteoblastic differentiation and function, but mainly, attenuate osteoclastic differentiation and decrease the survival time of these cells (Andreo & Jorge, 2013). Thus, Zerumbone (2,6,10-cy-cloundecatrien-1-one, 2,6,9,9-tetramethyl), a cyclic sesquiterpene, is the major component of essential oils from the roots and leaves of *Zingiber zerumbet*, this substance has cytotoxic activity for cancer cells, having anti-inflammatory and antioxidant activity (Tan, Israf and Tham, 2018). Lako et al. (2007) investigating 70 fruits and vegetables found that the two ginger species studied Zingiber officinalle (white ginger) and *Zingiber zerumbet* (bitter ginger), reported that both have a high antioxidant potential.

4. Final Considerations

Studies carried out with *Z. zerumbet* have shown the immense potential of this medicinal plant in the treatment of several diseases. Its chemical composition reveals the presence of sesquiterpenes, monoterpenes and phenolic compounds are

the main compounds, since many of its chemical properties are attributed to the main sesquiterpene zerumbona, which is directly related as an osteoinductive potential, due to its antioxidant potential, which will be investigated and evaluated in further studies. The present study proved to be relevant for obtaining information on the importance of the extracted actives and used in future osteoinductive solutions, with a future estimate of applicability.

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