Chapter 26

Exploring the Therapeutic Benefits of Olive Oil for Arthritis Management

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ABSTRACT

Olive Oil has been researched for its potential osteo-protective properties. The objective of this study is to present an updated summary of the available data on the osteo-protective effects of Olive Oil. Studies reveal that Olive Oil may improve the health of bones, including the prevention of osteoporosis, improvement of bone mineral density, and reduction of bone loss in various animal models. In addition, Olive Oil has been shown to possess anti-inflammatory and antioxidant properties, which may contribute to its protective effects on bone health. Olive Oil improves the bone health, like it exerts beneficial effects on osteo tumor cells, osteosarcoma in children, bone remodeling, alveolar bone loss, rheumatoid arthritis, osteoporosis, and post-menopausal osteoporosis. The phenolic and flavonoid compounds inhibit tumor cell growth and their potential therapeutic use in osteosarcoma treatment in children. Phenolic compounds like oleuropein may affect bone remodeling, a critical process that involves the resorption and formation of bone tissue. The chapter also discusses oleuropein's potential for treating osteoporosis, a widespread bone condition characterized by lower bone density and enhanced fracture risk. Specifically, examines oleuropein's impact on post-menopausal osteoporosis, a type of osteoporosis that affects women after menopause. The findings suggest that olive oil has potential as a natural osteo-protective agent and warrants further investigation.

KEYWORDS
Olive Oil, Oleuropein, Osteoporosis, Bone cancer, Bone mineral density, Anti-inflammatory

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INTRODUCTION

Oleaeuropaea Linn. (Oleaceae) in the mediterranean area is essential elements of Mediterranean cuisines are its fruits and oil (MDs). The MD, which has been shown to minimize the risk of several illnesses and ailments, must include olive oil as a key ingredient (Ahamad et al., 2019). The most significant hydrophilic phenolic component in olives and olive oil is the glycoside known as oleuropein.

Oleuropein may be hydrolyzed chemically or enzymatically to yield a variety of derivatives, including the aglyonic and hydroxytyrosol forms that are present in olive oils (Otero et al., 2021). The anti-atherogenic, anti-hepatotoxic, hypoglycemic, anti-inflammatory, anticancer, antiviral, and immunomodulator effects of olive tree polyphenols may be the cause of some of this plant's medically significant traits (Otero et al., 2021).The prevention of illness has taken precedence over its cure as knowledge has developed. Studies examining diverse phenolic compounds have expanded as researchers look for natural substances with potent pharmacokinetic effects.

Oleuropein is a potential phenolic substance that has a favorable impact on bone tissue in this regard (Bendini et al., 2007). Additionally to scavenging free radicals and reactive oxygen species, olive tree polyphenols particularly stimulated endogenous antioxidant enzymes including glutathione S-transferase and glutathione peroxidase (Recinella et al., 2022). Oleuropein might stop periodontitis and its associated bone loss and inflammation (Taskan et al., 2019a).

Osteoarthritis (OA) is a complicated, late-onset disease of the joints that is characterized by alterations in the

synovium and subchondral bone as well as a gradual failure of the extracellular cartilage matrix (ECM). The most prevalent kind of arthritis in the world is OA, which is also the sixth biggest cause of disability (Meiss et al., 2021).Future estimates indicate that the social and economic costs associated with OA will increase. As a result, there is a pressing necessity to find novel possibilities for the adoption of preventative and intercede methods in order to control OA, especially in light of the multiple difficulties connected with its treatment (Morales-Ivorra et al., 2021). A slowly developing heterogeneous joint disease that causes severe functional impairment, joint pain, stiffness, and deformity as well as high medical expenses (Murray et al., 2012; Xu et al., 2021a). Although the exact cause of knee OA is unknown, a number of risk factors, including advanced age, obesity, joint damage, and specific activities, have been linked to an elevated risk for incident OA (Atkinson et al., 2021; Xu et al., 2021a).

The most prevalent kind of metabolic bone disorder, often known as osteoporosis, is a skeletal condition that causes weaker bones and raises the risk of fracture. Although both sexes can be affected by osteoporosis, which often results from aging and frequently affects women more than men. It can happen at any age (Osteoporosis and Prevention, 2001; Föger-Samwald et al., 2020). Due to population ageing, it is predicted that the prevalence of osteoporosis would dramatically rise in the future (Akkawi and Zmerly, 2018). Women who have postmenopausal osteoporosis (PMOP) typically have bone loss and an increased risk of bone fractures as a result of the marked decrease in estrogen in the body after menopause (Liu et al., 2022). More than 200 million women suffer osteoporosis worldwide, according to pertinent statistics. Meanwhile, the number of people who suffer from fractures brought on by osteoporosis will twofold by 2050, placing a huge financial and medical strain on the world's health system (Pisani et al., 2016).

Long-term, it was extremely likely that the medication would raise the patient's risk of osteonecrosis and their chance of developing cancer. Raloxifene and hormone replacement therapy are additional options for postmenopausal women to take in order to avoid osteoporosis (Kanis et al., 2020). Therefore, the majority of postmenopausal women search for natural plant medicines to substitute conventional medication therapy due to the pill's varied negative effects (Cano et al., 2020). New medications for the treatment of several human disorders, including PMOP, often start with components taken from natural plants. Olive oil is popular among Mediterranean coastal residents (Castejón et al., 2017).

Oleuropein, the primary component of olive oil, has been widely used in clinical medicine to combat inflammation, as an antioxidant, and as an anticarcinogenic agent. Anti-inflammatory and antioxidant treatment can reduce postmenopausal osteoporosis (Izadi et al., 2016; Schwingshackl et al., 2017). Bone cancer causes abnormalities in bone growth and destruction by drastically disrupting the healthy coupling between osteoclasts and osteoblasts. Due to these anomalies in bone remodeling, patients have intense bone pain, a higher risk of fracture, increased tumor development, and greater chemotherapy resistance in the tumor cells (Burr, 2019). Osteolytic bone disease, which can cause excruciating bone pain, numerous pathological fractures, and increased mortality, is frequently developed by multiple myeloma (MM) patients (Roodman, 2010; Adamik et al., 2019). Systemic delivery of anticancer medications, bone-modifying medicines, radiopharmaceuticals, or any combination of these may have a deleterious impact on the normal metabolic turnover of bone tissue, which might be harmful to cancer patients (Leto et al., 2021a). The need to find novel drugs that have the potential to be helpful in stopping the spread and proliferation of cancerous cells in the bone while also having minimal negative effects (Makhoul et al., 2016; D'Oronzo et al., 2019).

Natural products appear to generally be easily accessible, not harmful to healthy human cells, and have the potential to function as many targets since they could interfere with different signaling pathways that control the development of cancer (Sun et al., 2019). Due to these qualities, natural products can be used therapeutically in many ways to cure cancer. One of the primary bioactive phenolic compounds found in olive leaves (*Oleaeuropaea L., Oleaceae*), unprocessed olive drupes, and, in the aglycone form, in olive oil, reveals a broad spectrum of therapeutic benefits that may clarify the therapeutic advantages of this molecule seen in a wide range of pathological processes in people, such as persistent inflammation linked to bone damage and human malignancies (Casaburi et al., 2013; Castejón et al., 2020). In this chapter we will highlight the osteoprotective effects of olive oil, we mainly focused on the main phenolic compound Oleuropein and its beneficial effects.

Impact on Osteo-tumour Cells

After the lung and the liver, the skeleton is where metastatic illness occurs most frequently (Leto et al., 2021b). Current clinical approaches for treating primary malignant bone tumors or bone metastases include systemic therapies like chemotherapeutic, hormone replacement therapy, immunotherapy, bone-modifying medications, small amounts of radioactive materials, as well as regional treatments such radiotherapy, endovenous, and surgery (D'Oronzo et al., 2019). Sadly, to yet, none of these treatment alternatives has demonstrated to have a favorable clinical effect on patients' survival. In addition, systemic administration of anticancer medications, bone-modifying medicines, radiopharmaceuticals, or any combination thereof, may have a deleterious impact on the normal metabolic cycle of bone tissue, which would be unfavorable for cancer patients (Makhoul et al., 2016).

Thus, there is a need to find novel drugs with the potential to stop the development and migration of malignant bone cells while also having low toxicity and few adverse effects. Natural products appear, in general, to be 1), easily accessible, ii) not harmful to live cells; iii) potentially acting as several targets and may impact on biochemical reactions that control cancer progression (Sun et al., 2019; Kapinova et al., 2019).

There are several advantages to adopting natural products for medicinal purposes in cancer prevention and treatment. Several phenolic molecules generated from extra virgin olive oil (EVOO) have anti-invasive, anti-metastatic, and anti-proliferative characteristics, according to expanding experimental data (Castejón et al., 2020; Hassen et al., 2020).

These compounds therefore appear to hold promise as possible cancer therapies. Olive leaves (*Oleaeuropaea L., Oleaceae*), natural olive drupes, and, in the aglycone form, olive oil are all known to include one of the key bioactive phenolic compounds., in particular, oleuropein (OLe), demonstrates a wide range of medicinal properties that may explain the curative properties of this chemical seen in several human pathological conditions, such as autoimmune disorders linked to bone loss and cancer (Rigacci and Stefani, 2016).

Mechanism

Through several mechanisms implicated in the early stages of cancer progression and the control of bone remodeling processes, OLe may exercise its chemo-preventive and therapeutic effects on cancer-related bone disorders (Castejón et al., 2020; Hassen et al., 2020)

Due to this molecule's antioxidant, anti-inflammatory, and innate immunity capabilities, OLe appears to have protective benefits on bone health. The ability of OLe to suppress the production of reactive oxygen species (ROS), act as spontaneous redox breakers, or serve as a metal ion chelating agent, among other potential activities, has been related to its antioxidant characteristics. OLe's inhibitory action on mitogen-activated protein kinase (MAPk) and nuclear factor-kB (NF-KB) signaling molecules is what causes the anti-inflammatory and anti-carcinogenic properties of the compound (Rigacci and Stefani, 2016; Hassen et al., 2020).

As a result of these occurrences, the synthesis of several subsequent molecular signaling pathways that regulate the immune-inflammatory response is reduced. TNF (tumor necrosis factor), IL-1 (interleukin-1), IL-6 (interleukin-6), and IL-8 (interleukin-8) (IL-8), Prostaglandins and MCP-1, a monocyte chemoattractant protein (PGs), particularly enzymes and prostaglandin E2 (PGE2) for example cyclooxygenase-2 (COX-2) and matrix metalloproteinases (MMPs) as well as the inactivating form (iNOS). These findings are in line with experiments demonstrating that OLe's bone-protective benefits appear to be mostly caused by its regulatory impact on inflammatory signaling networks instead of by directly affecting bone metabolism (Chin and Ima-Nirwana, 2016; Castejón et al., 2017; Leto et al., 2021b).

The discovery that several chronic inflammatory bone conditions and cancers related to bones have shared molecular mechanisms in their pathogenesis may help to partially explain why it is believed that one of the key pathogenic mechanisms that may favor the location and proliferation of tumor cells in the bone tissue is chronic inflammation (Roca and McCauley, 2015; Ritter and Greten, 2019; Vallée et al., 2019)

Experimental research indicates that persistent inflammation may act as a catalyst for the development of cancer in its early stages. These results may also help to partially explain the observation that some cancer cell types appear to thrive and spread more readily in bone tissue when osteoporosis and other autoimmune bone diseases alter the osteo microenvironment (Leto et al., 2021b).

Osteosarcoma in Children

Among the most prevalent bone cancers in children and teens is osteosarcoma. The main clinical problem with OS is how aggressive and likely it is to metastasize (Zhang et al., 2018). Osteosarcoma is treated surgically in addition to chemotherapy, typically doxorubicin and cisplatin (Otoukesh et al., 2018). Tragically, the 5-year survival rate of 60–70% has held steady over the past two decades, and no additional improvement has been shown with the current treatment(Harrison et al., 2018). As added 2-methoxyestradiol in our tests to examine the anticancer potential of oleuropein when combined with powerful chemotherapy (2-ME). A naturally occurring 17-estradiol metabolite recognized for having anticancer effects is 2-ME. 2-ME, marketed as Panzem, is now being assessed in active clinical studies for the treatment of solid tumors (Bruce et al., 2012). 2-ME's anticancer efficacy is solely dependent on its ability to prevent angiogenesis and trigger cell death by chasing cells that are actively growing (Lis et al., 2004).

Quiescent cells are therefore less susceptible to 2-ME. Additionally, the antitumoral action of 2-ME against several cancer cell types involves the production of nitro-oxidative stress (Gorska et al., 2015). Oleuropein has the ability to inhibit the growth of both highly and lowly metastatic SaoS2 OS cell lines, although this was done without looking at the compound's ability to inhibit migration. Oleuropein was combined with the brand-new, very effective anticancer drug 2-ME to examine any potential synergism in the OS cellular model. It is yet unclear how the two chemicals work together synergistically (Przychodzen et al., 2019). The overall beneficial effects of Oleuropein on the bone's health is schematically represent Fig. 1.

Bone Remodeling

Bone is a dynamic, complex structure that is always changing. Osteoclasts remove worn-out or broken bone from the body, and osteoblasts then replace it with freshly produced bone. To keep the skeleton healthy, there must be a suitable balance between bone growth and degradation. In order to eliminate microfractures and ischemia fractures in bones, replacing the main bone with bone remodeling appears to become crucial in order to establish a good equilibrium of Ca^{+} or K^{+} and secondary bone that is more mechanically strong (Ramesh et al., 2021).The coordinated action of four different cell types, including osteoblasts, osteoclasts, and bone-lining cells, is necessary for bone remodeling, which comprises four

phases: activation phase, resorption phase, reversal phase, and formation phase (Parra-Torres et al., 2013).The presence of numerous nuclei, the expression of calcitonin receptor and tartrate-resistant acid phosphatase (TRAP) are distinguishing characteristics of osteoclasts, which are cells derived from the myeloid (Hayman, 2008)

The cytokines Colony Stimulating Factor-1 (CSF-1) and receptor Activator of Nuclear Factor-kappa B (NF-kB) regulate the survival and growth of osteoclast precursor cells (Raggatt and Partridge, 2010). Using alpha-v beta integrin, osteoclasts interact with the surface of bone after differentiating and transferring signals that control how the cytoskeleton is organized. Spleen tyrosine kinase (SYK), VAV3 Ras-related C-Src, guanine nucleotide exchange factor (GEF), and All of the gates are opened in response to the signals (Teitelbaum, 2007). In order to break down the bone's matrix and mineral components, proteases like cathepsin K (CTSK) and hydrochloric acid are secreted into an extracellular lysosomal area and create microscopic trenches on the bone's trabeculae surface (Boyce et al., 2009).

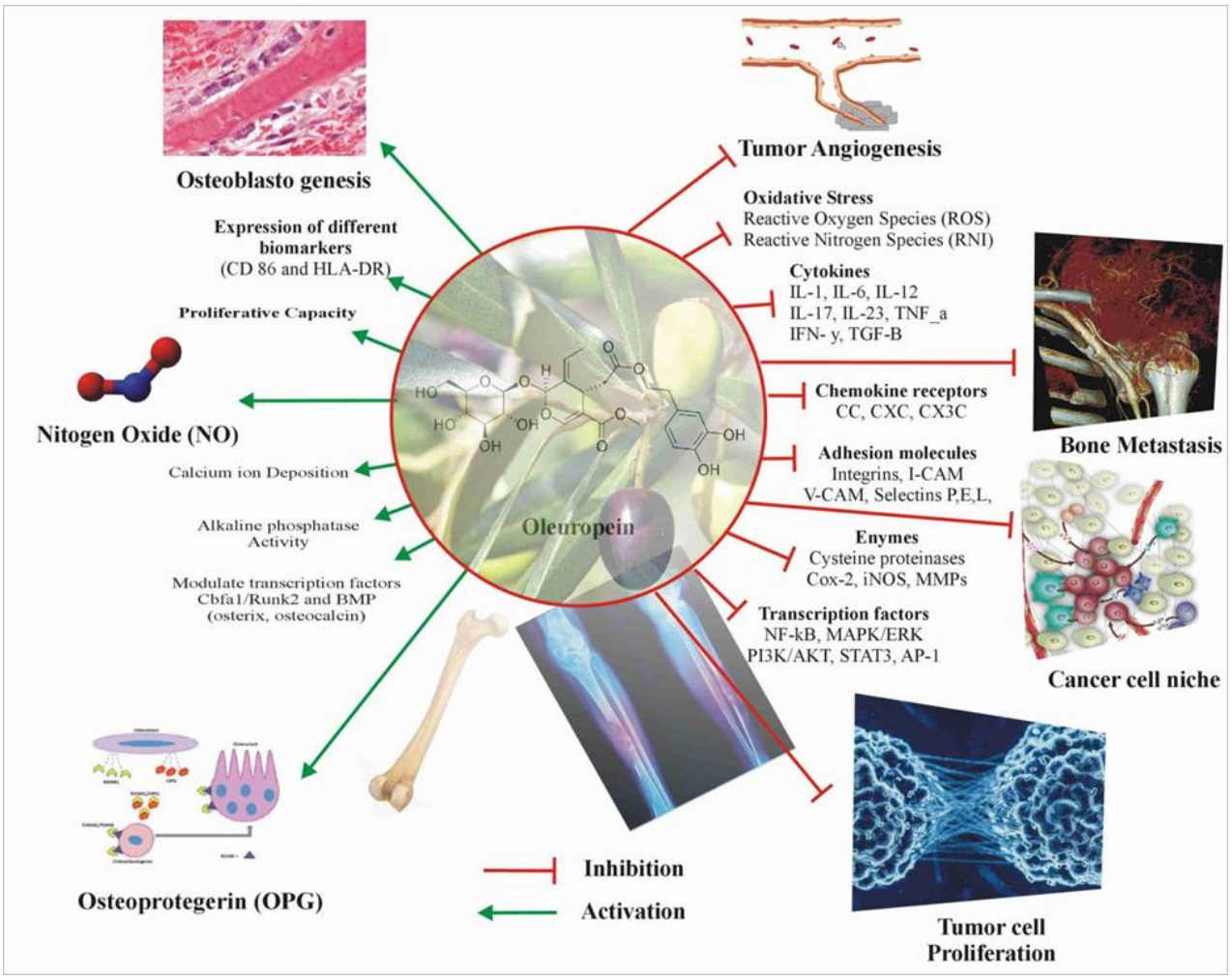

Fig. 1: Inhibition effects oleuropein on bone cancer such as tumor angiogenesis, oxidative stress, cytokines, chemokine receptors, adhesion molecules, enzymes, transcription factors, bone metastasis, cancer niche, and tumor cell proliferation. These processes are typically associated with the progression of cancer. On the other hand, activation affects processes such as osteoblast genesis, expression of different biomarkers, nitrogen oxide and osteoprotegerin production, calcium ion deposition, alkaline phosphatase activity, and proliferative capacity. These processes are typically associated with the maintenance and growth of healthy bone tissue.

A number of osteotropic substances, including Interleukin-11 (IL-11), IL-1, PTH, and 1,25-(OH)2D3, indirectly promote the production of osteoclasts by stimulating RANKL on the surface of osteoblasts and then associating RANK on osteoclast precursors(Hofbauer and Heufelder, 2000). Due to that signaling pathways like the Ak strain transforming (AKT) route, the c-Jun N-terminal kinase (JNK) system, p38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK) pathway, and NF-B are all active (Nakchbandi et al., 2001).

Osteoclast genesis is regulated by a number of additional proteins connected to RANK-activated signaling pathways (Boyce et al., 1992). Numerous variables, most notably osteoprotegerin (OPG), that are considered as a false receptor for RANKL, restrict the development of osteoclasts and the activation that follows. The balance of RANKL/OPG is an important factor in determining the strength of bone (Takayanagi, 2005).

Osteoblasts are produced by neural crest progenitor cells and mesodermal cells, which later differentiate into

osteocytes and proliferating preosteoblasts (Komori et al., 1997). Runt-related transcription factor 2 (RUNX2) is required for the development of the Osteoblast genesis parent cell. RUNX2 controls sclerostin, dentin matrix protein 1, receptor activator of nuclear factor kappa-B ligand, osteocalcin, osteocalcin (OCN), vascular endothelial growth factor (VEGF), and RANKL throughout cell growth (Lian et al., 2006) PTH, endothelin-1, fibroblast growth factor (FGF), bone morphogenetic proteins (BMPs), insulin-like growth factor (IGF), and Osterix (OSX) all regulate osteoblast development. Wingless-related integration site (Wnt) signalling pathways are activated by BMP and PTH (Westendorf et al., 2004). Fully formed osteoblasts coexpress Type I collagen and alkaline phosphatase, which are necessary for the bone mineralization and formation of bone matrix (Murshed et al., 2005). Mineralization regulators including RANKL, osteopontin (OPN), osteonectin (ON), and OCN are produced by grown osteoblasts and are necessary for osteoclast differentiation. Osteocytes, which are immersed in mineralized matrix, or lining cells, which cover the edges of the bones, are the final forms of osteoblasts (Eriksen, 2010). As a result, the balance between bone formation by osteoblasts and bone resorption by osteoclasts, which is intricately related and regulated by a multitude of pathways, transcription factors, and released chemicals, determines the overall integrity and structure of the bone (Ramesh et al., 2021).

Alveolar Bone Loss

The permanent effect of severe inflammation, which is also present in metabolic bone illnesses including osteoporosis and rheumatoid arthritis, is alveolar bone loss. By inducing osteoclastic development and activity, which causes bone loss, NF-KB is a crucial transcriptional factor controlling inducible genes that cause inflammation and the destructive process (Taskan et al., 2019a).

Lipopolysaccharides can activate neutrophils, which increases levels of IL-8, MCP-1, and TNF, which sets off a series of inflammatory processes. Neutrophil activation is the initial stage of inflammation. Neutrophils stimulated by LPS phosphorylate p38 MAPK, ERK, and JNK and move NF-KB17. Oleuropein reduced the activity of p38 MAPK, ERK1/2, and JNK and inhibited the movement of NF-KB from the cytosol to the nucleus, which is essential for activating NF-KB.TNF, IL6, MMP1, MMP3, and COX2 levels were reduced in IL-1-induced synovial fibroblast cells along with a downregulation of the MAPK and NFKB pathway (Woźniak et al., 2018). Oleuropein suppressed NF-KB and MAPK activation and lowered the production of COX2, iNOS, MMP1, and MMP13 in both fibroblasts and the osteoarthritis chondrocytes. All of these studies point to oleuropein's potent anti-inflammatory effectiveness.

Effect on Rheumatoid Arthritis

Rheumatoid arthritis (RA), an unexplained chronic inflammatory disease, primarily affects joints and eventually results in joint deterioration. It is currently believed that immune cells and the associated proinflammatory mediators are involved in all systemic autoimmune disorders, including RA (Rosillo et al., 2019). *Extra virgin olive oil* is ingested because of its tiny yet very bioactive components. Some of them have demonstrated indications of anti-inflammatory and antioxidant properties, including phenolic compounds comprising hydroxytyrosol (HTy), tyrosol, and oleuropein. The studies have shown that consuming extra virgin olive oil (EVOO) enhanced with polyphenolic extract (PE) can decrease the progression of damage in a collagen-induced arthritis (Aparicio-Soto et al., 2016).

Synovial fluid (SF) participates in continuing inflammatory responses as a substantial cell population in the RA invasive lesion. In the current work, PE from EVOO is shown for the first time to be able to restrict the activation of SW982 human synovial cells produced by IL-1 and reduce the inflammatory response (Tanaka, 2001). SF inflammatory alterations are crucial to the development of RA. This is due to the fact that TNF-, IL-1, and IL-6, pro-inflammatory cytokines that are known to have a significant role in the pathophysiology of RA, are overproduced during the synovial response in RA patients. IL-6 levels are associated with the development of rheumatoid factors and an increase in serum c-globulin (Sommerfelt et al., 2013).Early joint swelling, chronic joint inflammation, and the ensuing erosive changes in cartilage and bone are thought to be caused by TNF-, a pro-inflammatory molecule produced by macrophages and T cells. The current work showed, for the first time, that treatment with PE derived from EVOO substantially decreased IL-1-induced TNF- and IL-6 production in human synovial SW982 cells (Rosillo et al., 2014).

According to research they identify the arthritis-related pharmacological properties of olive leaf extract. The phenolic compound in olive leaves is linked to a decreased risk of arthritis, as well as many other diseases, as antioxidants reduce the harmful effects of free radicals on the body (Alethari et al., 2021). They also act as a scavenger, suppressing the production of reactive oxygen species in various experimental systems, including cell damage from H_2O_2exposure.Arachidonic acid metabolism and phospholipase C activation are likely to be involved in the process, which lowers hydrogen peroxide. Olive leaf extract has improved and accelerated the recovery from arthritis (Tahmasebi et al., 2021).

Osteoporosis

The loss of bone mass and the microstructural breakdown of bone tissue are the two characteristics that characterize the skeletal disease known as osteoporosis. Osteoporosis, often known as "porous bone," causes bones to become increasingly brittle and prone to breaking (Jiang et al., 2021). However, considerable improvements in osteoporosis therapy over the previous 50 years, including the widely accessible nature of numerous efficient pharmaceutical therapies, have changed the perception that the condition is a natural part of aging (Clynes et al., 2020).

Osteoporosis-related fractures are expensive, costing the US and the UK $17.9 billion and £4 billion, respectively, each year (Clynes et al., 2020; Chandran and Kwee, 2022)**.** Osteoporosis is challenging to diagnose clinically because fracture criteria may exclude populations that would benefit from therapy and because the original 1994 World Health Organization (WHO) account by bone mineral density (BMD) alone (2.5 standard deviations below the young adult female mean) may not have taken other risk factors into account (Aggarwal et al., 2021). A person's risk of a fracture may now be quantified using clinical risk variables like age and alcohol consumption, with just a partial focus on BMD (Chotiyarnwong et al., 2022), thanks to risk calculators such as the online FRAX® algorithm (Clynes et al., 2020). According to a study by the United States surgeon general, 10 million Americans older than 50 are thought to be suffering from osteoporosis, and a further 34 million could be at risk (BRANNON, 2020). Approximately 1.5 million fractures caused by fragility in the USA occur annually as a result of osteoporotic fractures. In the UK, epidemiological studies indicate that a single in 5 men and one in two females older than 50 may sustain a fracture due to osteoporosis over their lifetime, indicating a comparable disease burden (Wu et al., 2019).

An individual's peak skeletal growth occurs during their fourth decade, and their following rate of bone loss determines their bone mass in old age. Bone mass is a recognized sign of bone strength (Yu and Wang, 2022). The likelihood of fractures should be highest when bone mass (and thus bone strength) is at its lowest points. In reality, there is a bimodal age-related variation in fracture incidence, with the young and the elderly experiencing the highest rates (Rizzoli et al., 2021). Younger males get fractures more frequently than females, but above the age of 50, female fracture rates are nearly twice as high as male rates. Long bone fractures, which are the most frequent type of fracture in young individuals, are brought on by serious trauma. According to studies, bone mass is still a substantial and important risk factor for fracture in this cohort, in addition to the severity of the trauma. The forearm, hip, and spine are the places where older persons are most vulnerable to fractures (Clynes et al., 2020). Bone remodelling is directly influenced by bone cells such osteoclasts, osteoblasts, and osteocytes (Kitaura et al., 2020). Together, osteoblasts from mesenchymal stem cells (MSCs) and osteoclasts from tissue-specific macrophage polykaryons develop and disintegrate bone to maintain the mineral balance and strength of the bone. The malfunctioning of each cell type may cause bone loss (Noh et al., 2020).

The oleuropein has ability to stimulate the activity of bone-forming cells (García-Martínez et al., 2016), known as osteoblasts(Horcajada and Offord, 2012), while also inhibiting the activity of bone-resorbing cells (Hagiwara et al., 2011), known as osteoclasts. This oleuropein helps to promote bone growth and prevent bone loss. The supplementation with oleuropein was able to improve bone mineral density and reduce the risk of fractures in rats with induced osteoporosis (Chin and Ima-Nirwana, 2016). Similarly, the oleuropein may have a positive effect on bone mineral density and may help to prevent bone loss (Taskan et al., 2019b). While the research on the effects of oleuropein on osteoporosis is promising, more studies are needed to determine its effectiveness and safety in humans.

Post-Menopausal Osteoporosis

The metabolic bone disease (Xu et al., 2021b) osteoporosis, which is becoming more and more of an epidemic due to a constant rise in incidence, is a major social and medical issue in advanced economies (Rossi et al., 2018). Once a person reaches the age of 50 and above (Cannarella et al., 2019), their bone mass begins to naturally decline (Aspray and Hill, 2019). As a result, the bone remodeling cycle alters, making their bones more brittle and increasing their risk of bone fractures (Bijelic et al., 2017).

Numerous factors that may be divided into the categories of risk factors that can be changed and those that cannot be changed are involved in osteoporosis (Pisani et al., 2016). Recent studies (Li et al., 2020) demonstrate that smoking (Li et al., 2020) holds a significant place among the various risk factors for osteoporosis that are linked to unhealthy lifestyle choices (Lems, 2015) because it causes alterations in the level of microarchitecture of trabecular bone (Rupp et al., 2019) that reduce the bone's resistance to mechanical stress and friction (Li et al., 2020). Smokers have an increased chance of developing osteoporotic fractures regardless of their gender (Ratajczak et al., 2021). Women who smoke are approximately two times more likely than women who don't smoke to develop osteoporosis (Bijelic et al., 2017). Findings (Bijelic et al., 2017) are in line with those of previous academic research, which found that smokers (31.3%) had a substantially greater prevalence of osteoporosis than did ex-smokers (28.6%) or non-smokers (7.5%).

The olive oil and its polyphenols may have a beneficial effect on bone health, particularly in postmenopausal women (Chin and Ima-Nirwana, 2016).

The oleuropein, a polyphenol compound found in olives and olive oil, may have a positive effect on bone health (García-Martínez et al., 2016), particularly in postmenopausal women with osteoporosis (Chin and Ima-Nirwana, 2016). The oleuropein on bone cells in postmenopausal women helps to promote bone growth (Basharat et al., 2019) and prevent bone loss in postmenopausal women with osteoporosis (Chin and Ima-Nirwana, 2016). The supplementation has ability to improve bone mineral density and reduce the risk of fractures in the rats (Chin and Ima-Nirwana, 2016), suggesting that it may have potential as a treatment for postmenopausal osteoporosis. The literature on the effects of oleuropein on postmenopausal osteoporosis is limited. The available evidence suggests that oleuropein may have a positive effect on bone health in this population. However, more research is needed to determine the optimal dose, duration of treatment, and safety of oleuropein supplementation for postmenopausal osteoporosis prevention and treatment. Nonetheless, these

findings suggest that oleuropein may be a promising area for further investigation as a potential natural agent for the prevention and treatment of postmenopausal osteoporosis. The overall, olive oil on various bone-related conditions is diagrammatically represented in Fig. 2.

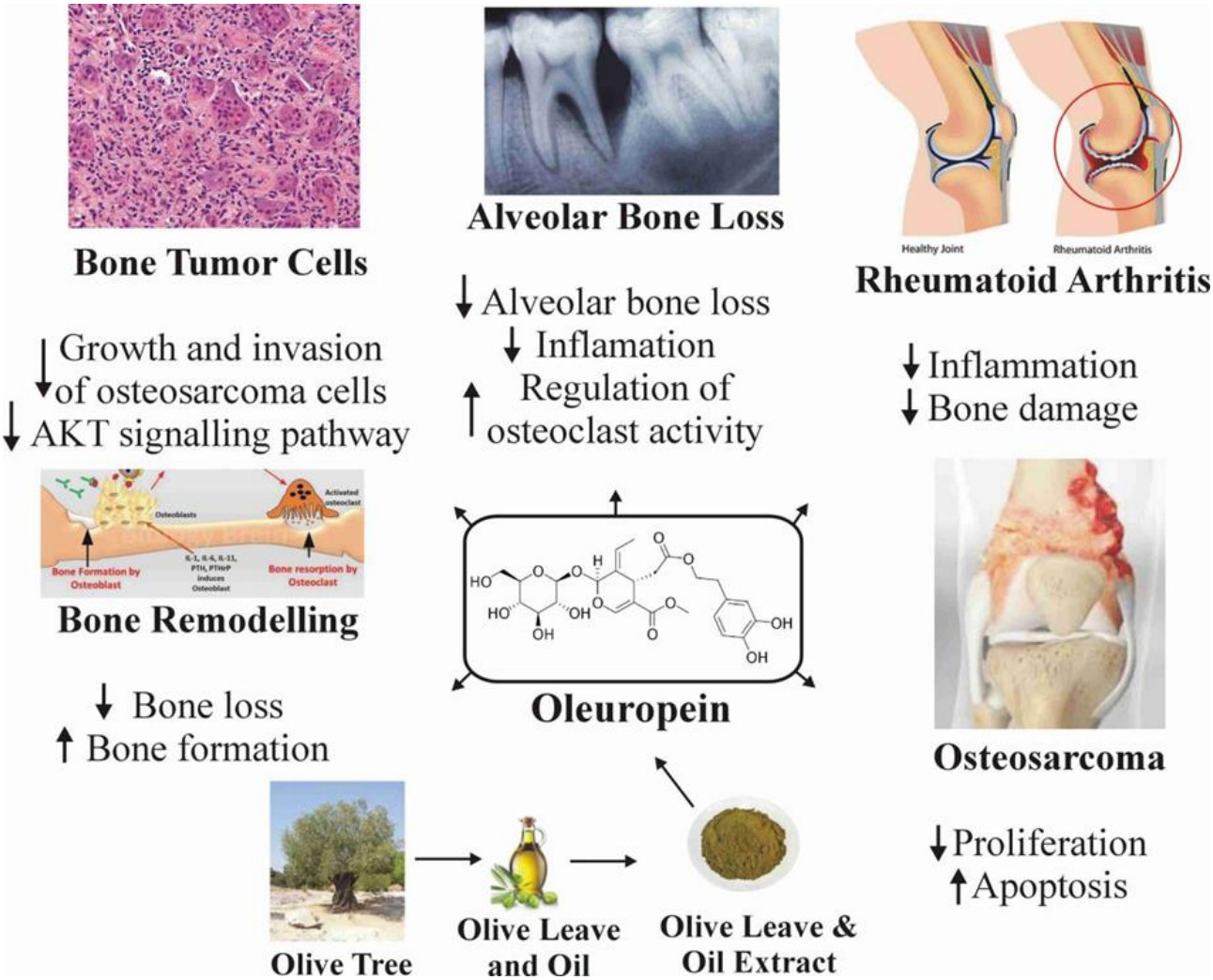

Fig. 2: Effects of oleuropein on various bone-related conditions, such as bone tumor cells, alveolar bone loss, rheumatoid arthritis, bone remodeling, and osteosarcoma.

Table 1: Biological effect of Olive Leaves Extract on Bone Health

Effect of Oleuropein on Bone Health	Study Type	Result/Conclusion	Dosage and duration	References
Bone Tumor Cells	MG-63 an osteosarcoma cell line	↓ MG-63 cells proliferation ↓ The growth and invasion of osteosarcoma cells ↓ AKT signaling pathway	20 mL for 24 h of olive oil	(Gioti et al., 2021; Zheng et al., 2022)
Osteosarcoma in Children	osteosarcoma (OS) cells	↑ Metastatic OS cells ↓ Proliferation ↑ Apoptosis of MG-63 human osteosarcoma cells	1 µM - 250 µM for 24 to 48 h Oleuropein	(Przychodzen et al., 2019; Gioti et al., 2021)
Bone Remodeling	Rats	↑ Protective effects on bone mass ↓ Inflammation ↓ Bone loss ↑ Stimulates bone formation	2.5 ml for 100 days olive oil	(Puel et al., 2004, 2006)

Alveolar bone loss, inflammation, and apoptosis	Rats	↓ Alveolar bone loss in experimental periodontitis in rats ↓ Inflammation and regulating osteoclast activity ↓ Caspase-3 expressions ↑ Radiotherapeutic effects ↓ Osteoclastic activity ↓ Apoptosis ↑ Osteoblastic activity ↑ BMP-4 and bcl-2 expressions	15 mg /kg for 15 days or 12 mg/kg/day to 24 mg/kg/day for 14 days OLE	(El-Hady et al., 2018; Taskan et al., 2019a)
Bone loss in ovariectomy/inflammatory model	Rats	↓ Bone loss ↓ Inflammatory biomarkers	2.5 ml for 100 days Olive Oil	(Puel et al., 2006)
Anti-osteoclastogenic effects	in vitro	↓Transcriptional gene ↓ Osteoclastogenesis blood monocytes	25 and 50 µM for 6 days Oleuropein	(Rosillo et al., 2020)
Postmenopausal osteoporosis	Rats	↓ IL-6 ↓ MDA ↓ ALP ↓ P	200 µg/kg/dose Oleuropein	(Liu et al., 2022)
Antiproliferative activity	human osteosarcoma cell lines (MG-63 and Saos2)	↑ Regression ↓ Proliferation	247.4-475.0 µM and m 798.7-359.9 µM for 24, 48, 72 hours Oleuropein	(Moran et al., 2016)
Arthritis	Mice	↑ Anti-inflammatory effects ↓ Bone damage ↓ Oxidative and Nitrosative damage	40 µg/kg for7 Oleuropein	(Impellizzeri et al., 2011; Haloui et al., 2011)
Inflammation-induced bone loss	Rats	↓ Inflammation-induced osteopenia in OVX rats	0·15 g/kg for 80 days OLE	(Puel et al., 2004)
Antioxidant and Antimicrobial activities	In vitro	↓ ROS production ↑ Disturbance to cell membrane structure of bacteria	102.36 and 325.02 mg for 18–24 hr OLE	(Topuz and Bayram, 2022)

AKT: protein kinase B (PKB), also known as Akt, is the collective name of a set of three serine/threonine-specific protein kinases; OS: osteosarcoma; BMP4: bone morphogenetic protein 4; BCL2: b-cell leukemia/lymphoma 2 protein; IL-6: interleukin-6; MDA: malondialdehyde; ALP: nitrate, alkaline phosphatase; P: phosphorus; OVS rats: ovariectomized In order to study mandibular alterations, rats have been employed as a preclinical model of postmenopausal people; ROS: reactive oxygen species.

Conclusion and Future Directions

In conclusion, this book chapter provides a valuable contribution to the current understanding of oleuropein's potential role in promoting bone health and preventing bone-related diseases. The chapter highlights the need for further research to explore the mechanisms underlying oleuropein's effects on bone cells and the potential for developing oleuropein-based therapies for various bone-related conditions. Future research could focus on conducting clinical trials to evaluate the effectiveness of oleuropein-based interventions for preventing and treating bone-related diseases, such as osteoporosis and rheumatoid arthritis. Additionally, research could investigate the optimal doses and delivery methods for oleuropein to maximize its therapeutic potential. Moreover, further studies could explore the potential synergistic effects of oleuropein with other natural compounds found in olives and olive oil, as well as their interactions with conventional treatments for bone-related diseases. Overall, the findings of this review paper suggest that oleuropein holds promise as a natural compound with potential osteo-protective effects, and further research in this field could have significant implications for improving bone health and preventing bone-related diseases.

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