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Review Article

Possible roles of *Eucomis autumnalis* in bone and cartilage regeneration: A review

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Abstract

In response to the recent alarming prevalence of cancer, osteoarthritis and other inflammatory disorders, the study of anti-inflammatory and anticancer crude medicinal plant extracts has gained considerable attention. Eucomis autumnalis is a native flora of South Africa with medicinal value. It has been found to have anti-inflammatory, anti-bacterial, anti-tumor/cancer, anti-oxidative and anti-histaminic characteristics and produces bulb that have therapeutic value in South African traditional medicine. Despite the widely acclaimed therapeutic values of Eucomis autumnalis, its proper identification and proper knowledge, morphogenetic factors are yet to be efficiently evaluated. Similar to other plants with the same characteristics, E. autumnalis extract may stimulate bone formation and cartilage regeneration by virtue of its anti-inflammatory properties. This review provides data presented in the literature and tries to evaluate the three subspecies of E. autumnalis, highlighting their geographical location in South African provinces, their toxicity effects, as well as their phytochemistry and anti-inflammatory properties. Biologically active components, pharmacological importance and some environmental factors that can affect E. autumnalis are presented. The review also discussed the novel potential roles of E. autumnalis in regenerative medicine. Proper knowledge of the E. autumnalis plant and its possible role in bone and cartilage regeneration will help in addressing and clarifying its use in the production of drugs and for other therapeutic purposes, especially in the treatment of inflammatory diseases and cancer.

Keywords: *Medicinal plants, inflammatory diseases, toxicity, phytochemicals, bone regeneration*

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INTRODUCTION

In developing countries, traditional medicine is still used in the primary treatment of many diseases, although few of these remedies have been reported scientifically in the literature. In response to the accelerating rate of cancer, osteoarthritis (OA) and obesity worldwide, the study of anti-inflammatory and anticancer crude medicinal plant extracts has gained considerable attention, perhaps because the current available treatment methods for these defects are expensive, have devastating side effects or are incapable of restoring all the normal biomechanical characteristics completely in damaged human tissues and organs [1-3].

The worldwide alarming prevalence of OA, arthritis, osteoporosis, atherosclerosis and rheumatoid arthritis, with few, if any, current effective treatment measures, cannot be overlooked. In Canada, 4.5 million people older than 15 years have arthritis and it is estimated that 7 million people will have arthritis by 2031 [4]. It has been estimated that 27 million Americans will suffer from OA by 2020. Studies have shown that joint disease will be at increase in South African because 70 % of their women are overweight or obese. This paves way for an upsurge of joint diseases if no health measures are taken [5].

A cell-based approach to using stem cells and herbal solutions for stimulation, protection and anti-inflammatory purposes in the regeneration and repair of bone, tissues, organs and cartilage in transplantation is promising both in tissue engineering and for therapeutic uses [6].

According to a World Health Organization (WHO) report, 80 % of people in Africa (South Africa) depend upon herbal drugs for their therapeutic effectiveness [7], yet little is known about medicinal plants, their extracts and morphogenetic factors.

Indigenous medicinal plants have been used traditionally as a major source of drugs for the treatment of various illnesses, including OA, asthma, cancer, heart disease, tuberculosis, swollen ankles and hypertension [8,14,45]. Extracted compounds of medicinal plants are usually employed as inputs in toxicology, phytochemicals, pharmaceuticals and other chemical industries [7,8,14]. Proper identification and knowledge of medicinal plants and their morphogenetic factors is of paramount importance. In South Africa, studies have documented reports on *Eucomis autumnalis* (*E.autumnalis*) and other medicinal herbs used in ethno-therapy of wound healing, pain relief, inflammatory diseases, fractures, teething, backache and other ailments [8,14,7,9,10]. *E. autumnalis* is the most commonly used herbal remedy for post-operative recovery and the treatment of bone fractures [Table 1] in South Africa. Table 1 also shows *E. autumnalis* plant, common names, its geographical location and some diseases where it has been locally employed.

E. autumnalis (Mill.) also known as pineapple lily, is native to South Africa. Because of its antibacterial and antifungal compounds, the bulbs of *E. autumnalis* are used in Southern African traditional medicine. The anti-inflammatory activity of the *E. autumnalis* plant depends on age, season, fertilization and growth conditions [15,17,18].

Although the therapeutic values of *E. autumnlis* are widely acclaimed (Table 1), they are yet to be rigorously evaluated in terms of their safety. Many studies have recorded complications arising from the administration of some medicinal plants. This review evaluates the biologically active components and pharmacological importance of *E*. *autumnalis.* The classification, geographical distribution of *E. autumnalis* subspecies and its phytochemical properties are also highlighted. This work discusses some effects of environmental factors on *E. autumnalis* and its possible role in bone and tissue regeneration as well.

Knowledge of the above-mentioned properties of *E. autumnalis* will help in addressing and clarifying its use in the production of drugs and for other therapeutic purposes, especially in the treatment of inflammatory diseases and cancer. *E. autumnalis* plant species are extensively used

Table 1: Common names, family, geographical location of *E. autumnalis* with its medicinal uses

Common name	Scientific name	Family	Parts Used	Medicinal Uses	Geographical Location	References
Pineapple flower, wilde pynappel (Afrikaans), Umathunga (isiZulu)	*Eucomis autumnalis*	Asparagacea-e	Bulb	Treatment of backache, post-operative recovery, fracture healing, inflammation, fever, hangover, stomach aches, syphilis and urinary complaints	Mpumalanga, Gauteng, Limpopo, Free State and Eastern Cape	[8, 12, 13 14,16, 17]

in South Africa for both traditional and pharmacological needs because of their anti-inflammatory and anti-cancer properties and very limited toxic effect.

Classification/geographical location

E. autumnalis belongs to the Asparagaceae family. It is a deciduous, summer-growing bulb plant with very decorative raceme inflorescences composed of numerous star-shaped, greenish-white and sweetly scented flowers. The bulb is about 8-10 cm in diameter and ovoid in shape [18,33,19,17]. The flowers are produced in mid- to late summer (December to February) and the fruit is in the form of a trilocular capsule containing shiny, black rounded seeds. Its specific name, *autumnalis,* refers to its flowering and fruiting time.

E. autumnalis is divided into three subspecies and can be identified by the structure of the stalk of the inflorescence (peduncle) and geographical location, but generally the peduncle is either club-shaped or cylindrical. The subclasses of *E autumnalis* are *E. autumnalis amaryllidifolia, E. autumnalis autumnalis* (*undulata*) *and E. autumnalis clavata* (Figure 1).

Fig 1: The three subspecies of E. autumnalis medicinal plant. A; *E.autumnalis amaryllidifolia*, B; *E.autumnalis undulata* and C; *E. autumnalis clavata.*

Figure 1: The three subspecies of *E. autumnalis* medicinal plants. A; *E. autumnalis amaryllidifolia*, B; *E.autumnalis undulata* and C; *E. autumnalis clavata*

Eucomis undulata and Fritillaria autumnalis subsp (cylindrical), are types of *E. autumnalis* subspecies found on mountain slopes, in open grassland and forest margins in the Eastern Cape, Northern Province, Zimbabwe and Malawi. They form a dense rosette of strap-like leaves with undulating edges and white or green flowers on spikes around 60 cm high. *Eucomis robusta and Eucomis clavata subsp* (club shape) grow in open grassland and marshes in Lesotho, KwaZulu-Natal, Mpumalanga, the eastern Free State and Gauteng. The leaves of this species have margins that are crispy and wavy. Their green flowers are creamy green on a stout stem, club-shaped and tightly packed. The third subspecies of E. autumnalis is *Eucomis amaryllidifolia subsp.* It is a rarer subspecies with linear, thick ovate prostrate leaves and a club-shaped peduncle. These plants are found among rocks on the mountain slopes of the Western Free State and Eastern Cape [14,20,21,28,17]. Apart from South Africa, *E. autumnalis* can also be found in Zimbabwe, Malawi, Botswana and California.

Phytochemistry of *E. autumnalis*

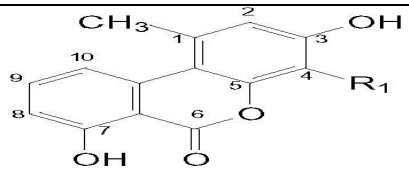
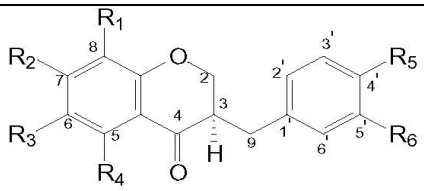
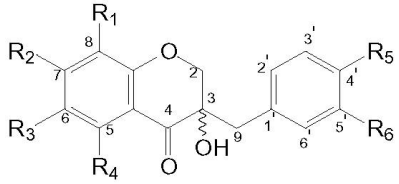
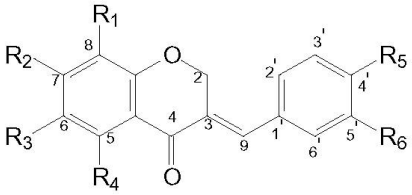
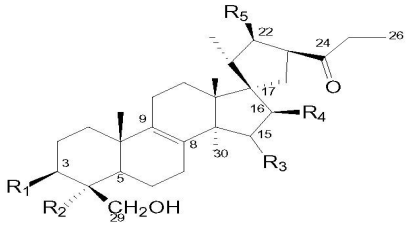
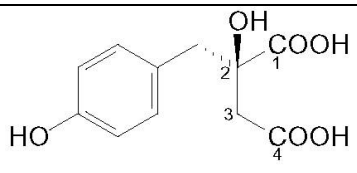
In the genus *Eucomus*, many constituents such as homoisoflavanones and triterpenoid glycosides have been isolated from the bulbs of several of the species investigated. The homoisoflavanones are usually found in the waxy layer between the storage leaves of the bulb and the terpenoids in the bulb tissue [14,12,16,22,23]. *E. autuimnalis* species have been phytochemically investigated and compounds have been profiled. In all, three homoisoflavanones, two dibenzo-α-pyrones (structure corresponding to xanthones), two spirocyclic nortriterpenoids (structure of these compounds confirmed by the x-ray structure of p-bromobenzene sulphate derivative) and an acid compound have been isolated (Table 3). Moreover, *E. autumnalis* leaves, bulbs and roots are known to inhibit the synthesis of prostaglandin, thereby protecting the cyclooxygenase enzymes COX-1 and COX-2 [12,16,24,25].

Anti-inflammatory properties

The most popular traditional use of *E. autumnalis* species has been for anti-inflammatory and fracture purposes (Table 1), hence they are recommended to be used in the manufacturing of non-steroidal anti-inflammatory drugs (NSAID). The anti-inflammatory capacity of *E. autumnalis* varies according to the part of the plant [26,27,12,16]. Generally, anti-inflammatory activity in the *E. autumnalis* plant depends on age, season, fertilization and growth conditions [17,18,24,25].

During inflammation, prostaglandins are involved and are responsible for the sensation of pain. Numerous studies have investigated the anti-inflammatory effects of *E. autumnalis* by evaluating the efficacy of its extracts for prostaglandin synthesis. This in vitro assay tends to measure the degree of inhibition of Cyclooxygenase enzyme activity. Cyclooxy-genase exists in two isoforms, COX-1

Table 2: *E. autumnalis* phytochemical isolated compounds and their general structure

No	Compound name	General structure	Description	References
1	Dibenzo-α pyrones		Isomeric methylxanthones have also been identified from the genus *Drimiopsis*. Two types have been isolated from E. autumnalis (autumnariol).	[12, 14, 30]
2	Homoiso-flavanones or 3-benzyl-4-chromanones	--	They are usually found in the asparagaceae group. Reported first in 1967 from the genus *Eucomis* and are found concentrated in the waxy, scale-like layers of the bulb. So far, only three types have been isolated in *E. atumnalis.*	[12, 30, 31]
2a	3-Benzyl-4-chromanone		It is the most common class of homoisoflavonoids with a 16-carbon skeleton formed. The benzyl group is attached at the 3-position.	[12, 14, 31]
2b	3-Hydroxy-3-benzyl-4-chromanones		In this group, they have hydroxyl group attached at the 3-position and their 3-hydroxy-3-benzyl-4-chromanones occur as a mixture of C-3 epimers	[12, 16, 32]
2c	3-Benzylidene-4-chromanone		They have a double bond attached at the 3-position.	[12, 14, 31]
3	Spirocyclic nortriterpenoids		They are characterized by a basic lanosterol triterpenoid skeleton losing one terminal methyl of the side chain. Two of these compounds have been isolated from *E. autumnalis*	[12, 14, 31]
4	Aromatic or acid compounds		R-(-)-2-(4'-hdroxybenzyl-malic acid has been isolated from *E. autumnalis*	[35, 12]

and COX-2 [33,27,12,16]. Generally, studies have observed *E. autumnalis* to selectively inhibit COX-2, with little interference with COX-1. This property/characteristic makes *E. autumnalis* plant extract potentially anti-inflammatory and non-ulcer genic, hence it is frequently employed by traditional healers in wound/fracture healing and post-surgery treatment (Table 1). *E. autumnalis* therefore has a considerable interesting quality for therapeutic use.

Effects of environmental factors

Plant protection programs, particularly those concerning plants grown for phyto-therapeutics, are focused on prophylactic treatments that encourage limited use of pesticides negatively affecting the environment. The popular bulb of *E. autumnalis* in the South African medicinal trade is currently becoming threatened in the wild and measures have been taken for its protection to counteract the depletion of the wild population.

Studies have observed that seed germination of *E. autumnalis* is influenced by light conditioning, cold stratification and a smoke-derived compound [34]. Light, temperature, moisture and chemical bio-stimulants such as smoke have been identified to be among the major environmental factors that can influence growth and development of seedlings of a number of plant species, including *E. autumnalis* [22,23,34]. [35] investigated not only the effects of sunlight intensity, temperature, watering frequency and smoke-water solutions on seedling and bulb development, but also the pharmacological properties of *E. autumnalis* bulbs exposed to different light conditions, temperature regimes, watering frequencies and smoke-water solutions. *They observed in their study that* sunlight intensity of 50 % achieved the best developed seedlings and bulb sizes, compared to 75 % and 100 % sunlight. The optimum temperatures for seedling development of *E. autumnalis* were found to be 30/15°C. Regular watering frequency (three times per week) produced the largest bulbs compared to less frequent watering. A smoke-water solution at a 1:250 v/v dilution stimulated growth and produced the largest bulbs when compared to dilutions of 1:500 and 1:1000 v/v smoke-water.
For the pharmacological properties against two Gram-positive, two Gram-negative and a fungus *Candida albicans*, the result showed an increase in the bioactivities of some of the extracts from the bulb exposed to different light conditions, temperature regimes, watering frequencies and smoke-water solutions compared to the control bulbs. Antimicrobial activity was also found to be very high in acetone extracts when compared to water extracts of *E. autumnalis* [24,34,35].

Furthermore, heavy metals in the environment affect medicinal plant extracts. Soil-plant and roots-microbes interactions play vital roles in regulating heavy metal movement from the soil to edible plant parts. Studies have observed that the accumulation of metals by both roots and leaves is proportional to the availability of metal concentration in the external medium, with factors such as reduced biomass, root light, shoot length and root length being common indicators of heavy metal toxicity [36-38]. Direct interaction between the metal and structural components in the environment causes visible changes at the cell, tissue and organ levels of medicinal plants. There is therefore every need for conscious site selection and suitable soil management to reduce heavy metal uptake by medicinal plants [27].

Over-exploitation is another environmental factor that can affect *E. autumnalis* subspecies. A study by [28] showed that the mean size of the bulbs decreased significantly between 1995 and 2001. This was believed to be an indication of over-exploitation. Another study also confirmed its decline as a result of over-exploitation [29].

Possible role of *Eucomis autumnalis* in osteoarthritis defects

OA is the best known form of arthritis, a chronic inflammatory progressive disorder of the joints, characterized by late onset degeneration of articular cartilage. Degeneration of articular cartilage is marked by the breakdown of cartilage matrix proteins. OA causes pain, synovial inflammation, joint deterioration and subchondral bone alteration [39,40]. It usually affects aged people but it can also affect young individuals [40-42].

OA is characterized by relatively few cells with low cell mobility owing to the neighboring matrix and a limited number of progenitor cells [43,44]. These factors retard cartilage regeneration and repair; as a result symptoms associated with OA occur [45]. The methods currently used to treat OA, such as NSAIDS and autologous chondrocyte implantation (ACI), mainly revolve around, i) pain management, ii) rehabilitation and iii) surgery to treat loss of joint function, with negative side effects. Furthermore, there are problems associated with donor site morbidity, difficulty in harvesting a large number of chondrocytes without causing substantial additional damage and the very high cost of treatment [46-48]. A positive outcome has been

reported for ACI, involving chondrocyte isolation from the cartilage, *in vitro* expansion and re-implantation into the cartilage defect by a periosteal graft [49,50]. The main disadvantages of ACI is the requirement for an invasive surgical procedure and the fact that chondrocytes that are expanded in culture gradually undergo differentiation and lose morphological features and specialized functions [51,52].

However, treatment of OA joints with a wide range of growth factors necessary for maintenance of cartilage homeostasis *in vitro* and *in vivo* remain a challenge. One alternative or rather a combination approach to the standard treatment methods will be to test traditional medicinal plants that are likely to stop the progress of OA or at least slow it down to a satisfactory degree. The drug of choice for treating OA should be one that has anti-inflammatory properties with no side effects. The genus *E. autumnalis* has been found to have anti-inflammatory, anti-bacterial, anti-tumor/cancer, anti-oxidative and anti-histaminic characteristics [8,16-19]. Preliminary results from our study on articular cartilage chondrocytes showed that *E. autumnalis* is fast-acting, with maximum cell viability and proliferation noticed within the first 24-48 hours of incubation. The anti-inflammatory property of *E. autumnalis* indicates its potential to exert a chondroprotective effect. Future studies on this plant must focus on exploring the potential effects of *E. autumnalis* plant extracts on stem cells. The experimental procedure must focus on influencing stem cells' transduction pathways; this is crucial for the induction of cell differentiation, improving proliferative capacity, expressing articular cartilage anabolic markers and inhibiting cartilage mineralization.

Eucomis autumnalis in bone regeneration

Bone healing after fracture has been described in four phases. The first phase is the inflammatory phase characterized by hematoma formation and the release of pro-inflammatory cytokines from the surrounding cells. This is followed by the soft callus phase, where chondrocytes begin to form cartilage tissue that creates a bridge at the fracture gap. The next phase is the hard callus phase, where the fragile cartilage is transformed into woven bone, through the deposition of calcium and phosphate into the cartilage [53]. Finally, the bone remodeling phase takes place where bone is restored to its previous form and function. Clinical conditions such as rheumatoid arthritis, osteoporosis, diabetes mellitus, or ageing have been reported to increase the time it takes for a fracture to heal and the possibility of complications such as fracture non-union [54].

E. autumnalis has been found to have anti-inflammatory activity and inhibition of prostaglandin synthesis was investigated by assessing the inhibition of the cyclooxygenase enzymes COX-1 and COX-2 [12, 16 33]. *E. autumnalis* ethanol extract has shown up to 80 % COX-1 inhibition, while the water extract showed 60 % COX-1 inhibition [33]. Gesternfeld and colleagues [55-57] studied the effect of COX inhibitors on fracture healing and reported that COX-2 inhibitors delayed fracture healing while COX-1 inhibitors showed no negative effects on bone healing. Other studies have shown that different medicinal plants, which also have anti-inflammatory effects similar to those of *E. autumnalis,* can stimulate osteoblast function, and inhibit osteoclast and adipocyte functions either alone or in combination [58-60].

Similarly, *E. autumnalis* extract may stimulate bone formation by virtue of its anti-inflammatory properties (Figure 2).

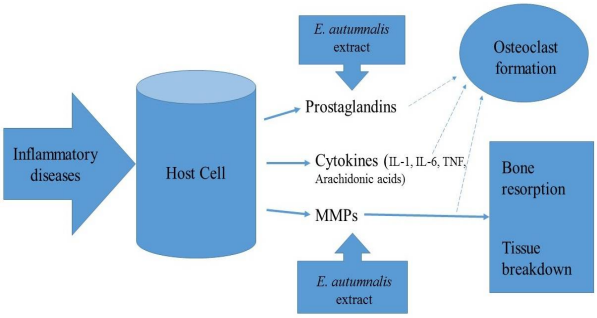


Figure 2: Possible proposed function of *E. autumnalis* plant extract in host modulatory therapy in bone and tissue regeneration. IL, interleukin; TNF, tumor necrosis factor; MMPs, Matrix metalloproteinase; *E. autumnalis, Eucomis autumnalis*

Cytokines, chemokines and prostaglandins have been identified as regulators of immune-inflammatory process in bone and cartilage formation. Cytokines like interleukin-1 and tumor necrosis factor-α are well known factors that can induce bone resorption indirectly in host cells by promoting the differentiation and activation of osteoclast precursors [61, 62]. Since *E. autumnalis* has anti-inflammatory property, it can be employed just like non-steroid anti-inflammatory drugs in host modulatory therapy during intervention for nonsurgical therapy, in other to restore balance between pro-inflammatory mediators, as anti-inflammatory mediator and enzyme inhibitors [Fig 2]. Furthermore, *E. autumnalis* may help reduce the significant unwanted effects of nonsteroidal anti-

inflammatory drugs such as hemorrhage, gastrointestinal problems and rebound effects in patients [63, 64]. The *E. autumnalis* extract may provide a safe and cost-effective alternative treatment for bone fracture and complications such as non-union. Despite the popular use of this medicinal plant for rapid fracture healing, there are currently no reported studies investigating the effect of this plant extract on bone repair and regeneration.

CONCLUSION

Generally, with the extensive screening of plants used in traditional medicine, evidence of their rational use in treating infections, diseases, inflammation and other disorders has been provided. Despite the huge potential of these herbal plants, a definite gap exists in research on them - little information is available on indigenous South African plants like *E. autumnalis*.

In nature, *E. autumnalis* subspecies have a widespread distribution, extending across all of the provinces of South Africa, as well as neighboring countries. A few isolated compounds have been recorded in the literature on these subspecies and the variations in the phytochemical properties of the isolated compounds are yet to be investigated.
The review highlighted some environmental factors capable of affecting the availability of *E. autumnalis* species. The effects of these environmental contaminants should always be considered when reporting on biological activities of crude plant extracts. *E. autumnalis* as a medicinal plant has a highly potential role in bone formation and cartilage regeneration. Its possible role in bone and tissue regeneration is an important factor in OA, obesity, osteoporosis therapeutics and other inflammatory diseases. Further studies should be undertaken highlighting more on *E autumnalis* properties that enhances its performance in regenerative medicine.

DECLARATIONS

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Conflict of interest

No conflict of interest.

Authors' contributions

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Alaribe FN designed, prepared the tables/figures and wrote the manuscript. Maepa JM and Mkhumbeni N made conceptual contribution. Motaung SKM reviewed and proof read the manuscript. All the authors approved the manuscript.

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