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Exploring the Properties of Deer Antler Velvet (DAV) and its Potential Use in Dentistry: A Narrative Review

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KEYWORDS

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ABSTRACT

For centuries, deer antler velvet (DAV) has been a staple in traditional medicine due to its numerous health benefits, including immune stimulation, anti-ageing, wound healing, and anti-osteoporosis properties. Researchers attribute the therapeutic advantages of DAV to various compounds in its extract, ranging from growth hormones to minerals and amino acids. Recently, there has been renewed interest in these natural products for their potential use in treating chronic diseases such as bone health and development, bacterial infections, and sports supplementation to increase athletic performance. The available literature supports that DAV significantly affects bone development, chondrogenesis, and antimicrobial properties, making it a valuable resource in medical and dental settings. This review aims to provide an in-depth overview of the potential applications of DAV in modern medicine and dentistry.

INTRODUCTION

In dentistry, craniofacial bony defects are ascribed to trauma, periodontal disease, surgical excision, infection or congenital malformations, and oral cancer, with irreversible bone resorption after tooth loss [1]. Deer antler velvet (DAV) describes the entirety of the cartilaginous antler in its pre-calcified growth stage of the *Cervidae* family, such as elk, moose, and caribou, native species found in many parts of the world. Deer species such as sika deer *(Cervus nippon),* sambar deer *(Cervus unicolour)* and rusa timor *(Cervus timorensis)* are among the common species found in Southeast Asia. DAV extract has long been traditionally applied due to its positive pharmacological benefits such as immunomodulatory, anti-cancer, anti-osteoporosis, anti-inflammatory, antioxidant and wound healing [2]. Unlocking DAV's true potential would be monumental in tackling some of the dental concerns mentioned above, as there are researches that show DAV to affect bone strength and bone growth positively [3], facilitate osteoblast [4] and inhibit osteoclast [5] differentiation, have antimicrobial properties against *Candida* species [6], and able to induce stem cell differentiation [7] among others. This natural product holds the potential to offer various benefits in healthcare, including both medical and dental spheres. Our review aims to compile the current research on DAV and provide in-depth understanding of its potential applications for medical and dental health.

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DEER ANTLER VELVET (DAV)

Velvet antlers are valuable cranial appendages that grow on top of the frontal protuberances of the male deer, belonging to the *Cervidae* family [8]. For centuries, traditional Asian medicine has utilised DAV across countries such as China, Taiwan, Korea, Japan, and Mongolia for its supposed health benefits [9]. Various studies have demonstrated that DAV showcases pharmacological activities that enhance bone health (such as anti-osteoporosis and anti-osteoarthritis capabilities), immune-modulatory effects, anti-tumour properties, anti-fatigue benefits, anti-inflammatory properties, and anti-oxidation effects [10]. Additionally, scientists found that DAV extract plays a vital role in bone and cartilage development, growth, and repair [2,10–13]. The numerous compounds present in DAV extracts, such as growth hormones, minerals, and amino acids, support the associated health benefits of this animal-based natural product [2,11,12]. Some of the compounds found in DAV include epidermal growth factor, proteoglycans with a hyaluronic acid core, water-soluble compounds (like carbohydrates, hexosamines, hydroxyproline, mucopolysaccharides, sialic acids, and uronic acids), and water-insoluble fatty acids (for example, prostaglandins, phospholipids, glycolipids, and gangliosides) [13]. The high content of minerals presents in DAV also prompted researchers to incorporate the extract into fabricating scaffolds for tissue regeneration purposes [14].

DAV AND BONE DEVELOPMENT

Restoring functional conditions of bone structures in the craniofacial region involves the installation of endosseous implants, which need adequate bone volume as a prerequisite [15]. To ensure successful implantation, one must increase the bone volume to a sufficient level to support the prosthetic load. Hence, the bone needs to be regenerated, often drawing from the biological principles of osteogenesis, osteoinduction, and osteoconduction, some of which process DAV influences.

Kim et al. (2016) found that DAV extract promotes longitudinal bone growth in an *in vivo* study in adolescent rats with varying efficaciousness for different antler regions [9]. For example, the upper section of the antler has an overall more positive/significant effect on the longitudinal growth rate of the rats and increased level of expressions of bone morphogenic protein-2 (BMP-2) and osteogenic genes (example: collagen, alkaline phosphatase (ALP), osteocalcin) [9]. Adolescent rats treated with DAV showed a 16.4% increase in longitudinal growth rate compared to the control group [9].

Furthermore, DAV also possesses anti-osteoporotic activity, and the upper and middle sections of DAV effectively protect bones from oestrogen deficiency [16], a condition that leads to osteoporosis [17]. DAV also stimulate osteoblastic differentiation and mineralisation, as seen in MC3T3-E1 osteoblast cells derived from mice [4]. In their study, Lee et al., (2011) also conclude that upper portions of the antlers significantly affect the proliferation and mineralisation of MC3T3-E1 [4]. In the same vein, insulin-like growth factor-1 (IGF-1), a protein that promotes longitudinal bone growth by encouraging growth plate chondrocyte proliferation [18], varies in concentration levels along the length of the antler [16], which may affect the antler's efficacy in inducing bone growth.

Bone morphogenetic proteins (BMPs), a multirole growth factor of the transforming growth factor beta (TGFβ) superfamily [19], play a significant role in developing the epiphyseal growth plate, the leading site of longitudinal growth of the long bones like the femur [20]. Bone morphogenetic protein-2 (BMP-2) incites chondrocyte proliferation in the proliferative zones of the growth plate and causes an increase in chondrocyte hypertrophy (i.e., increased growth) [21]. Therefore, the changes in the expression or production of *BMP-2* could regulate the proliferation and activity of bone-forming cells. Kim et al. show that rats treated with DAV exhibit higher *BMP-2* expression levels in their growth and ossification zones than in the control groups [9].

Bone regeneration is regulated by balancing biochemical and cellular events, eventually stimulating osteoblast cells to produce new tissues, specifically, a new extracellular matrix comprised primarily of collagen [9,22]. Soon after, the collagen matrix is mineralised by alkaline phosphatase (ALP) activity, prompting the formation of calcium phosphate crystals [9]. *ALP* is one of the phenotype markers for osteoblasts and an essential mineralisation enzyme [23]. The proliferation rate, *ALP* activity, collagen content and calcium deposition of MG-63 cancer cells (fibroblast morphology cells isolated from an osteosarcoma patient) significantly increased when treated with 100 ug/ml of DAV extract from the upper portions of the antler [9,16].

In 2016, Kim et al. examined the impact of DAV on MG-63 cells by measuring the mRNA expression

levels of critical proteins involved in osteogenesis, including collagen *(COL)*, *ALP*, osteocalcin *(OCN)*, and osteopontin *(OPN)*, after DAV treatment [9]. During bone formation, pre-osteoblastic cells first produce proteins such as COL, then gradually produce ALP, OPN, and OCN during the mineralisation phase [4,22]. Osteoblasts exhibit increased expression of osteogenic genes, which is critical for constructing the extracellular matrix and depositing minerals during bone formation [25].

In the later stages of osteogenesis, osteoblasts produce OCN, a glycoprotein of the bone matrix, and OPN, a non-collagenous protein [26]. In their research, Kim et al. show that DAV treatment upregulates *COL* and *OCN*. Specifically, *COL*, *OCN*, and *ALP* expressions increased 8-, 22-, and 4-fold when treated with DAV, respectively [9]. These results indicate that DAV positively affects the cells and may even accelerate osteogenesis. Lee et al., (2011) conducted a study that further supports this finding, showing that DAV increases mRNA expression of bone sialoprotein (BSP), a protein associated with bone mineralisation [4].

Periodontal disease can lead to the loss of teeth and bone support caused by the disruption of the alveolar bone and can result in crestal defects and even maxillary atrophy. As mentioned earlier, the presence of growth factors in DAV also highlights its involvement in bone development and strength. Previous studies have shown the presence of insulin-like growth factor-I *(Igf-1)* from the DAV [27]. Insulin-like growth factor-1 (IGF-1) is a circulating protein involved in regulating cell growth, survival, and metabolism. In the bone tissue, IGF-1 is one of the most abundant growth factors deposited in the bone matrix, maintains bone mass and stimulates osteoblastic differentiation of mesenchymal stem cells (MSCs) [28]. Hence, this notion allows DAV to be applied in bone augmentation, especially during implant placement. The process of preserving the augmented bone volume depends on the control of bone remodelling through osteoclast bone resorption and osteoblast bone formation, where part of these processes are suggested to be able to be performed by DAV.

DAV AND TISSUE ENGINEERING

The loss of tissue due to trauma, disease, or congenital abnormalities, especially in the craniofacial region, is a major global healthcare issue due to its severe physiological and psychological effects on patients. Consequently, reconstruction of the craniofacial area to restore/repair damages that incur is most desirable to affected patients [29]. It is common in today's dental practice to use dental bone grafts with growth factors, sometimes with barrier membranes, in treatments such as periodontal regeneration therapies and guided bone regeneration procedures before implant placements [30]. Autologous, allogeneic, and xenogeneic bone grafts are the currently available techniques for periodontal and bone regeneration in dentistry. However, they all present certain complications and risks [31], presenting the need for an alternate approach in regeneration therapies. Tissue engineering (TE) is a scientific field that marries engineering ingenuity and bioscience to develop biological substances to restore, conserve and improve tissue function [32]. In TE, three components underpin a successful TE construct: i) a relevant selection of cells, ii) a biomaterial scaffold, and iii) appropriate signal/growth factors, such as biochemical cues and chemical mediators that coordinate to create new tissue. Collectively, these components are known as the tissue engineering triad [33].

Recently, a study has shown that proteins derived from DAV can induce neural stem cells (NSCs) into neurons, highlighting their potential as a signal or growth factor in TE studies. Through 3-(4, 5-dimethyl-hioazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay and following a protocol of neural differentiation of NSCs, the study shows that NSCs treated with 50 ug/ml of DAV polypeptide exhibited increased cell growth and cell differentiation towards neurons [7]. Additionally, a separate study reported on DAV's ability to continuously survive and promote the growth and differentiation of stem cells [34].

The use of DAV in dentistry is still in its early stages. However, a recent study conducted by Sari et al., (2019) has shown promising results for using animal-based natural products for periodontal tissue regeneration [35]. The study examined using bovine teeth as a scaffold to promote osteogenic differentiation of rat adipose-derived mesenchymal stem cells. Briefly, Sari et al. ground the bovine teeth into a powder using a bone miller, sterilised, and dried the bovine powder before using it as a scaffold. Similarly, DAV can be ground into a powder and incorporated into a biocompatible scaffold to work synergistically with stem cells for bone regeneration in dentistry.

The potential of DAV in TE, as illustrated by these findings, opens the question of the effects of DAV on other types of stem cells. In dentistry, viable

osteogenic progenitor cells, such as mesenchymal stem cells (MSC), can be used with materials such as cytokines and growth factors to stimulate new bone formation and enhance bone healing through osteoconduction and osteogenesis [1]. Bone substitute materials and MSC work better in tandem, showing marked improvement in bone healing and reconstruction compared to using either of these materials alone. Using stem cells significantly improves biomechanical performance and, in turn, the success of dental implant placements in general.

Another exciting aspect of the application of DAV in TE is the potential of DAV extract to be incorporated into biomaterials to create a scaffold for tissue regeneration. The presence of minerals in DAV, such as calcium and phosphorus, made it possible to be considered a promising material for bone substitution. The composition of velvet antlers resembles a mineralised bone matrix, as well as being a natural biomaterial. Hence, due to its natural biological origin, the DAV is expected to result in a crystalline structure of hydroxyapatite with a composition like human bone, making it an attractive and promising raw material for biomedical applications, as demonstrated by Abdul Hamid et al. (2022). The researcher managed to fabricate and characterised DAV/PVA scaffold (deer velvet antler/polyvinyl alcohol) and showed that the fabricated scaffold is suitable for bone tissue engineering based on the scaffold's swelling, porosity and degradation study. This study highlights that DAV powder is a promising biomaterial with a high potential for synthesising calcium-enriched implants.

DAV AND CHONDROGENESIS

Deer antlers are considered zoological anomalies due to their extraordinary growth rate and regenerative ability [36]. The growth rate of these antlers can reach up to 2 cm/day, making them the fastest-growing tissues among the mammalian species [37]. In 2021, Guan et al. conducted a study to analyse deer antlers' molecular effects on xiphoid cartilage (XC), whose primary function is an attachment site for soft tissues and helps protect the internal thoracic viscera (example: heart, lungs) [39].

Regenerating cartilage remains one of the significant challenges of the century due to the nature of cartilage being solely composed of cells (i.e., chondrocytes) with poor self-renewal capacities [40]. There are 17 differently expressed genes (DEGs) associated with cartilage growth and regeneration, all significantly upregulated with deer antler treatment. Such DEGs include cellular communication network factor 2 (*Cnn2*), also known as connective tissue growth factor *(Ctgf)*), aggrecan protein (*Acan*) and sestrin 3 (*Sesn3*) (38). *Cnn2* plays a pivotal role in regulating homeostasis, development, and regulation [41]. *Acan*, on the other hand, is a critical proteoglycan component for cartilage structure, essential in cartilage formation during development and maintenance after maturation [42]. Continually, *Sesn3*, a gene downregulated in old age and osteoarthritic cartilage [43], is upregulated in this instance [38]. Rats treated with DAV have increased DEGs involved in cartilage growth and chondrogenesis, while DEGs associated with inflammation decrease [38].

According to Yao et al. (2018), rapidly growing sika deer antlers significantly promote chondrocyte proliferation, which drives the growth of the skeletal elements and forms a scaffold for the mineralisation of osteoblasts. Water-soluble proteins, polypeptides, and free amino acids are some of the more significant components of the sika deer antler. Protein and peptides are DAV's main functional molecules to promote cell proliferation. DAV is also rich in growth factors such as nerve, fibroblast, vascular endothelial and epidermal growth factors [44]. Consequently, due to its many biochemical components, DAV can promote cell proliferation by affecting mitotic cells, thus locking the chondrocyte in a proliferating state. Accordingly, study found that DAV upregulates the expression of chondrocyte proliferation marker genes, which include proliferating cell nuclear antigen (*Pcna)*, marker of proliferation Ki-67 (*Mki67*), SRY-box transcription factor 9 (*Sox9*), SRY-box transcription factor 5 (*Sox5*), and proline and arginine-rich end leucine-rich repeat protein (*Prelp*). Inversely, DAV treatment downregulates the expression of chondrocyte differentiation markers such as collagen type II alpha 1 (*Col2a1*), *Acan*, *Sp7*, parathyroid hormone 1 receptor (*Pth1r*), Indian hedgehog homolog (*Ihh*), collagen type 1 alpha 1 (*Coll0a1*), integrin binding sialoprotein (*Ibsp*), and actin-like protein 1 (*Alp1*) [44].

Regeneration of cartilage is paramount in orthopaedics. However, in the oral and maxillofacial regions, cartilage repair is limited anatomically to the articular disk in the temporomandibular joint (TMJ) and auricular and nasal cartilage. With the data obtained from the fundamental studies done previously, there is also

a possibility to apply DAV for the regeneration of cartilage in dentistry.

DAV AND ITS ANTIMICROBIAL PROPERTIES

Bacterial infection and bacterial diseases are rising due to the ever-growing emergence of drug-resistant bacteria [45]. Efficient, low-toxicity, broad-spectrum antimicrobial peptides are the most promising antibiotic alternatives (45). Antler collagen polypeptide isolated from the sika deer antler significantly inhibits *Escherichia coli* and *Staphylococcus aureus*, with more than 80% and nearly 70% inhibitory effects on the former and latter, respectively [45].

Cerebrosides, groups of complex lipids found in sheaths of nerve fibres, have been proven to have various physiological traits, including anti-tumour/cytotoxic [46–49], antifungal [47] and antifouling properties [50]. A study analysing the cerebroside's antimicrobial activity isolated from the liposoluble constituents of the sika deer antler velvet using petroleum ether showed promising results [51]. Both crude and pure cerebrosides show antimicrobial properties against *E. coli,* with the purified form having a more significant impact (minimum inhibitory concentration (MIC) of 27 ug/ml) versus crude (MIC of 12 ug/ml). Note, however, that antler velvet cerebroside does not inhibit the growth of *S. aureus* [51]. Despite that, there are apparent antimicrobial properties of products derived from deer antlers, thus showing promise towards developing new, natural-based drugs to treat microbial infections and diseases.

In dentistry, dental decay/caries arise due to the irreversible solubilisation of tooth minerals by acidic by-products of certain bacteria that adhere to the tooth surface [52]. Aside from bacteria, fungi are also an unignorable member of the oral microbiota, among which is the *Candida* species, the most frequent commensal for oral cavities [53]. On top of their association with dental caries, the growth of *Candida albicans* is also attributed to 95% of oral candidiasis instances, a fungal infection commonly known as "thrush", which affects the oral mucosa [54,55]. The DAV obtained from the Malayan deer (*Cervus timorensis*) has antimicrobial properties that work against the biofilm activity of the *Candida* species [6]. Seven of the nine species of *Candida* showed a decreased biofilm density when treated with DAV extract as demonstrated by antimicrobial analysis performed by Arzmi et al., highlighting another potential use of DAV in dentistry [6,55].

CONCLUSION

In brief, DAV shows much promise in developing new and innovative ways to treat various problems in the dental and medical field, specifically regarding bone health and development, tissue engineering and antimicrobial research. Additionally, DAV positively influences chondrocyte proliferation, chondrogenesis, osteogenesis, anti-osteoarthritic capabilities, and antimicrobial properties, among others.

Despite this, scientists have barely scratched the surface of this animal-based natural product, and many facets of DAV are yet to be discovered. For example, literature on the relationship between DAV and stem cells and how it could potentially affect the bioactivity of the cells is still scarce. Thus, more studies on DAV are needed to unlock its full potential in medicine, dentistry and beyond.

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DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

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