Applications in medicine: joint health

Ezequiel R. Coscueta

María Emilia Brassesco

Patrícia Batista

Sandra Borges

Manuela Pintado

Universidade Católica Portuguesa, CBQF—Centro de Biotecnologia e Química Fina—Laboratório Associado, Escola Superior de Biotecnologia, Porto, Portugal

29.1 Introduction

Rheumatic and joint diseases, such as osteoarthritis and rheumatoid arthritis, are among the most widespread painful and disabling pathologies across the globe (Fusco, Skaper, Coaccioli, Varrassi, & Paladini, 2017). Osteoarthritis and joint injury are characterized by remodeling and degradation of cartilage, bone, and other joint tissues. Rheumatoid arthritis is a chronic, inflammatory joint disorder with a worldwide prevalence of nearly 5/1000 adults (Aletaha & Smolen, 2018). The pathophysiology of rheumatoid arthritis is related to chronic inflammation of the synovial membrane, which can destroy articular cartilage (Aletaha, Funovits, Smolen, & Editorial, 2011).

The therapeutic strategies widely used for joint disorders are the administration of analgesics and nonsteroidal antiinflammatory. Nevertheless, these drugs are inept to stop or slow the evolution of structural injury and commonly have gastrointestinal and digestive adverse effects (Puigdellivol et al., 2019). Alternative treatments with dietary supplements have received much attention due to the higher levels of safety and effectiveness.

Natural supplements, such as collagen derivatives, embody bioactive peptides that display physiological activities being beneficial to joint health (Kumar, Sugihara, Suzuki, Inoue, & Venkateswarathirukumara, 2015). Collagen peptides are classified as safe by the European Food Safety Authority (EFSA) (Journal, 2005) and by the Food and Drug Administration (FDA) (Bello & Oesser, 2006). Various studies demonstrated that collagen derivatives are absorbed and allocated to joint tissues. Preclinical studies in the animal model showed that oral administration of collagen derivative was specifically found in cartilage (Oesser, Adam, Babel, & Seifert, 1999). Clinical trials have already been performed to prove the health benefits of dietary supplementation of collagen derivatives in the management of osteoarthritis, reducing the pain, and increasing the mobility of patients (Czajka et al., 2018; Puigdellivol et al., 2019). Prophylaxis and therapy approaches were developed and supported by different kinds of peptides, which will be addressed throughout this chapter.

A better understanding of the action mechanisms in articular tissue may help to identify the more effective targets to counteract the joint pathologies. Understanding the proliferation and regeneration process

of cartilage tissue, clarify the role of antioxidant, antimicrobial, and antiinflammatory agents and relate the neuroactivity with articular and allow to better understand the mechanisms of action and the fundamental role played by peptides. These mechanisms are involved with peptides, and their incorporation in therapies and treatment can be very useful in cartilage regeneration. The interest and research in this area are improving with technological development (purification, mass-spectrometry, peptidomics, and cartilage tissue engineering) and allow the increase of development and performance at the level of prevention, diagnosis by biological markers, treatments, and therapeutics (Hu et al., 2020).

In this chapter, we will critically review the state of the art of the emerging field of application of bioactive peptides in the prevention and control of joint diseases and their mechanisms of action to achieve those benefits.

29.2 Overview of joint diseases

Joint diseases are those disorders or injuries that affect human joints, of which arthritis is the greatest exponent (Sokoloff, 2019). Joint diseases, common in aging, can be short-lived or extremely chronic, very painful or simply bothersome, and uncomfortable; they may be limited to one joint, or they may affect many parts of the skeleton. Inflammation may or may not be an essential feature of joint disease.

Arthritis is a generic term for a set of inflammatory joint diseases. This includes more than 100 rheumatic diseases and conditions, with osteoarthritis being the most common. Other common forms of arthritis are rheumatoid arthritis, lupus, fibromyalgia, and gout. In general, they are characterized by causing pain, stiffness, swelling, and inflammation in and around the joints. The inflammation can be of such a nature and severity that it destroys the articular cartilage and underlying bone and causes irreparable deformities. In such cases, the fusion between the articulated limbs is frequent, with a consequent stiffness and loss of mobility (ankylosis). Some forms of arthritis, such as rheumatoid arthritis and lupus, can affect various organs and cause widespread symptoms (Sokoloff, 2019).

29.2.1 Osteoarthritis

Osteoarthritis is the most common type of arthritis. It mainly affects the common cartilage, which is the tissue that cushions the ends of bones within the joint (D. Horowitz, J. Hanrahan, & R.K, Turley). Once this process begins, the cartilage begins to erode and may eventually suffer severe straining. This leads to joint pain and stiffness. The severity of osteoarthritis symptoms can vary greatly from person to person and between different affected joints. In some cases, the symptoms may be mild and may be recurring. In other

cases, the problems may be more continuous and serious, to the point of making it difficult to carry out daily activities. Almost any joint can be affected by osteoarthritis, but the most common locations involved include the knees, hips, and small joints of the hands.

The exact cause of osteoarthritis remains unknown, but several things are thought to increase the risk of developing this disease. For example, overuse of a joint that has not had enough time to heal after injury or surgery may result in osteoarthritis. Osteoarthritis can also occurs in joints severely damaged by a previous condition (another type of arthritis), such as rheumatoid arthritis or gout. Obesity can also lead to consistent osteoarthritis, since it puts excess stress on the joints, particularly those that support most of the weight, such as the knees and hips. Gender can also be a determining factor since osteoarthritis is more common in women than in men. Also, the risk of developing the condition increases with aging.

29.2.2 Rheumatoid arthritis

Rheumatoid arthritis is an inflammatory disease of the joint lining, generally affecting several joints at the same time (Aletaha & Smolen, 2018). The patients experience pain, stiffness, swelling of the joint lining, and eventually joint damage, leading to deformity and pain, with loss of function of the affected joints. It can affect both hands and both feet. Some people with rheumatoid arthritis also experience problems in other parts of the body or more general symptoms, such as tiredness and weight loss.

Rheumatoid arthritis is an autoimmune disease. This means that your immune system mistakenly attacks the cells that line your joints, causing the joints to be swollen, stiff, and painful. Over time, this can damage joints, cartilage, and nearby bone. It is not clear what triggers this problem with the immune system, although an increased risk has been seen in women, smokers, or with family histories suffering this condition.

29.3 Peptides activity and characterization

Biologically active peptides take an important part in various biological processes of joint health. In recent years, with the technological development of natural peptide identification and their mechanisms of study the peptidome is playing a more and more important role in the study of biological markers (Malmström, Catrina, & Klareskog, 2017) and therapeutic targets (Park et al., 2018) for the development of new molecular tools for the diagnosis, prevention, and therapy of joint diseases based on bioactive peptides.

29.3.1 Natural bioactive peptide sources

Collagen is one of the most abundant proteins in the world that is widely available and inexpensive to recover from animal (Fu, Therkildsen, Aluko, & Lametsch, 2018; Silva et al., 2014)

by-products. Currently, utilization of collagen as high value-added source of ingredients via enzyme technology has been the top trend in the processing industry, leading to a high benefit-to-cost ratio. The resultant collagen peptides have enormous commercial potential as food ingredients or nutraceuticals, because they are recognized as safe components of pharmaceuticals and foods by the FDA Center for Food Safety and Nutrition (Bello & Oesser, 2006) and by the EFSA (Journal, 2005). In this respect, scientific evidence suggests that collagen hydrolysates exert a positive therapeutic effect on osteoarthritis (Bello & Oesser, 2006; Kumar et al., 2015). However, the EFSA panel on dietetic products, nutrition, and allergies recently concluded that so far, no cause-and-effect relationship between the maintenance of joints and the use of collagen hydrolysates has been shown (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011). So, Schadow et al. (Schadow et al., 2013) evaluated for the first time whether different bovine collagen hydrolysate preparations indeed modulate the metabolism of collagen and proteoglycans from human OA cartilage explants and determined the chemical composition of oligopeptides representing collagen fragments. They concluded that collagen hydrolysates from various sources differ significantly with respect to both their chemical composition of oligopeptides representing collagen fragments as well as their effects on human articular cartilage, and metabolized collagen fragments or other collagen hydrolysate preparations might contain therapeutically useful peptides. Thus their biomedical properties must be studied thoroughly both in vitro and in animal as well as clinical trials before being applied as safe and effective nutraceuticals in patients.

Also, collagen peptides are biocompatible and safe due to their unique biological and structural characteristics. Regardless of different collagen types, they all share the nearly identical sequence and structure (Fig. 29.1), which guarantee weak in vivo immunogenicity (Banerjee & Shanthi, 2016). Collagen peptides, especially those with C-terminal Pro or Hyp residue, can be transported across the intestinal epithelial monolayer, enter the bloodstream, and exert their bioactive properties. The unique amino acid composition and structure confer collagen peptides with excellent stability and less protease cleavage sites. The high Pro level existent in collagen peptides (10%–30% abundance) may increase their stability toward digestive enzymes and intestinal peptidases in comparison to other therapeutic peptides (Banerjee & Shanthi, 2016). This is due to the presence of a Pro residue adjacent to the cleavage site that prevents proteases from cleaving the normally susceptible peptide bond (Fu et al., 2018). It is important to highlight that the direct intake of collagen supported by simple digestion may not reach peptides with dimensions for absorption. So, it seems probable that the biological activities of ingested collagen are mediated, at least partly, by collagen-derived oligopeptides such as Pro-Hyp and/or Hyp-Gly. Transportation of an oligopeptide into a cell can be mediated by proton-coupled oligopeptide transporters that support low-molecular weight of peptides.

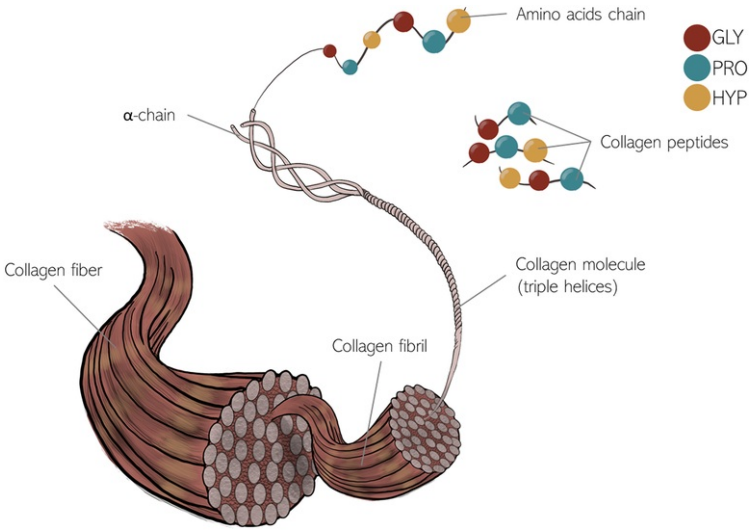

Figure 29.1 Raw collagen molecular structure and collagen peptides.

Several studies indicate that collagen-derived oligopeptides appear in blood at fairly high concentrations and suggest that the beneficial effects of collagen ingestion are mediated by these oligopeptides. Other studies described the mechanism of absorption and distribution

of collagen peptides in the body. It has been demonstrated that C14-labeled collagen peptides can reach the skin, cartilage, bones, and muscles and remain in these tissues up to 14 days after a single ingestion (Kawaguchi, Nanbu, & Kurokawa, 2012; Watanabe-Kamiyama et al., 2010). Iwai and colleagues showed that hydrolyzed collagen from porcine skin, chicken cartilage, and chicken feet, which was ingested by healthy subjects after 12 h of fasting was absorbed and detected in the plasma as small peptides (Iwai et al., 2005). Hydroxyproline-containing peptides detected in the plasma peaked 2 h after oral ingestion and decreased to half of the maximum after 4 h. Several in vivo studies have demonstrated the efficacy of collagen peptides on skin and cartilage health and ageing (Czajka et al., 2018).

29.3.2 Peptidome analysis

Peptidomics is a new branch of proteomics which is based on investigating endogenous protein fragments in tissues or body fluid (Hu et al., 2020). Biologically active peptides are involved in almost all physiological processes, including cell differentiation, immune regulation, and even tumor formation (Ferro, Rioli, Castro, & Fricker, 2014). So, the study of

bioactive peptides as biological markers and therapeutic targets for the diagnosis, prevention, and therapy of joint diseases is a very important research to be performed in the near future.

From a peptidome perspective, the pathophysiology process of joint diseases, as well as the functional mechanism of bioactive peptides, can be disclosed (Hu et al., 2020). For therapeutics targets, there is extensive evidence to support a role for C-type natriuretic peptide (CNP) in maintaining homeostatic function in cartilage and bone. However, the biology of CNP signaling in joint tissues is complex and is influenced by several factors leading to dysfunction

and disease. The differences in the mechanism of natriuretic peptide receptor (NPR) signaling affect the ability of the peptide to function normally. This has widespread impact due to the role of CNP in maintaining joint homeostasis and may crosstalk with other mechanisms linking angiogenesis and osteogenesis with function in vascular systems. The differential effects of NPRs in response to signals that influence their expression will determine the CNP signaling system and their effects on tissue function. Therapeutic application of CNP or interventions targeted to NPR to influence the actions of CNP should therefore be considered to speed up repair mechanisms and stabilize tissue homeostasis. Evidence indicates that enhanced CNP signaling may prevent growth retardation and protect cartilage in patients with inflammatory joint disease (Peake et al., 2014). Another example is the vasoactive intestinal peptide (VIP) that can prevent chronic cartilage damage and joint remodeling. Evidence suggests that VIP is downregulated in synovial fluid of osteoarthritis, and VIP downregulation leads to an increase in the production of proinflammatory cytokines that might contribute to the pathogenesis of osteoarthritis (Jiang, Wang, Li, & Luo, 2016).

29.4 Mechanisms of action

The function of joint involves several processes, and understanding the mechanisms of action (proliferation, degradation, regeneration, and infection) in the joint disease process is important for the diagnostic, prophylaxis, and treatment. Understanding the processes is also important for the development of biomaterials and bioingredients to promote healthy joint. These mechanisms are associated with active peptides that are involved in almost all physiological processes, including cell differentiation, proliferation, inflammatory process, and immune regulation (see Table 29.1).

Table 29.1 Endogenous and exogenous peptides with intervention in the function of joint.

Protein/peptides	Function/impact	References
TGF-β	Improve cartilage proliferation/repair	Varela-Eirin et al. (2018)
BMPs		Tuan et al. (2013)
NF-Kβ (RANKL)		Deng et al. (2018)
SASP		Parmar et al. (2015)
CNP		Peake et al. (2014)
Cytomodulins		Haque Bhuyan et al. (2017)
NLS-TAT		Faust et al. (2018)
E7, L7		Liu et al. (2018)
HA-binding peptide		Dar et al. (2017)
Chondroitin sulfate-binding peptide		
RADA 16-1		
KLD-12		
RGD peptide		
Collagen		
Fish gelatine peptides	Antioxidant peptides and antiinflammatory function	Kim & Mendis (2006)
Resveratrol impact in PI3K/AKT signaling pathway		Yu et al. (2018)
KAFAK		Lin et al. (2016)

		McMasters et al. (2017)
TNF-α IL-1β, IL-6, IL-10, IL-17A 5-LOX, 15-LOX FPR2	Antiinflammatory and immune responses	Al-Madol et al. (2017) Janakiraman et al. (2018)
Antimicrobial peptides (AMPs) Lysozyme Lactoferrin Secretory phospholipase A2 RNase 7 CAP37 Cathelicidin LL37 HBD-2/-3	Antimicrobial peptides	Pinto et al. (2019) Elezagic et al. (2019) Varoga et al. (2005)
VIP SP CGRP	Neuroactivity	Jiang et al. (2016) Kanemitsu et al. (2020) Zhang et al. (2018) Courties et al. (2017)

29.4.1 Cartilage proliferation

Cartilage is a connective tissue composed by a low density of cells, chondrocytes, embedded within an extracellular matrix (ECM). The cartilage ECM is responsible for biomechanical functions, structural support, and resistance to deformation. To ensure these mechanisms of action, various proteins and peptides are present, such as proteoglycans

tangled in a collagen network, noncollagenous proteins, and glycoproteins (Hu et al., 2020). The abundance and distribution of these molecules are different in each cartilage type (hyaline, fibrous, and elastic), according to their function.

The cartilage tissue has a vascular nature and a limited capacity for self-repair, and its repair remains a challenge (Lam, Reuveny, & Oh, 2020; Liu et al., 2018; Tuan, Chen, & Klatt, 2013). Therefore cartilage loss and degeneration are often associated with

pathologies, which consequently triggers the appearance of joint pathologies. To fill this gap, researchers have been studying therapies and new techniques for cartilage repair. So, it is important to understand the role of peptides in this process, because it can be promising in the proliferation and/or inhibition of cartilage degeneration.

Currently, there is an interest in using human mesenchymal stem cells (MSC) as cell therapy of cartilage, because they have an extensive proliferation potential and can undergo chondrogenesis (Lam et al., 2020). These cells (MSC) have emerged as a promising cell source, and it can be functionalized with different coating materials, such as ECM proteins and peptides. For example, ECM molecule affinity peptides are frequently used in biomaterials development, because they can help mimic the native environment of chondrocytes and influencing the biological functions of these molecules (Liu et al., 2018).

The articular cartilage degradation, synovial inflammation, and joint degeneration are typical processes implicit in joint pathologies. During these processes, chondrocytes can undergo phenotypic changes that increase cell proliferation and cluster formation and enhance the production of matrix-remodeling enzymes. Recent investigations suggest that alterations in different proteins, such as transforming growth factor-β (TGF-β)/bone morphogenetic proteins (BMPs), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kß), or senescence-associated secretory phenotype factors involved in signaling pathways in wound healing response, could be directly implicated in these pathologies (Liu et al., 2018; Varela-Eirin et al., 2018). Understand these mechanisms are advantageous in identifying novel targets and designing therapies to promote effective cartilage repair and successful joint ageing by preventing functional limitations and disability (Varela-Eirin et al., 2018).

Studies report that BMPs (the most widely studied are BMP-2, BMP-3, BMP-4, BMP-6, BMP-7, and BMP-9) play an important role in the protection of cartilage degradation (by inflammation or trauma), bind to different receptor combinations and therefore may be active in different intracellular signaling pathways (Deng, Li, Gao, Lei, & Huard, 2018; Tuan et al., 2013). This loss of function of BMP-related receptors contributes to the decrease in intrinsic repair capacity of damaged cartilage, and so, the multifunctional effects make them attractive. So, the use of BMPs and their combination with stem cells and biomaterials can be a promising new therapeutic modality for cartilage repair. Bhuyan and colleagues (Haque Bhuyan et al., 2017) found that the receptor activator of NF-κB ligand (RANKL)-binding peptide, OP3–4 stimulated the differentiation of both chondrocytes and inhibited cartilage degeneration. Their data suggest that the stimulation of mesenchymal cell proliferation by the RANKL-binding peptides might lead to the inhibition of cartilage degeneration. Therefore the introduction of peptides in cartilage tissue engineering has proven to be advantageous and is increasingly a solution in cartilage repair.

Other therapies/treatments have been developed with the aid of peptides, for example, the use of CNP has shown evidence for its ability to regulate cartilage and bone homeostasis.

Data results by in vitro studies reported that exogenous CNP influenced chondrocyte differentiation, proliferation, and matrix synthesis. However, the CNP signaling systems are complex and influenced by multiple factors, but the evidence showed that enhanced CNP signaling may prevent growth retardation and protect cartilage in the presence of inflammatory disease (Peake et al., 2014). In addition to the examples presented, other peptides, such as cytomodulins, NLS-TAT, E7, L7, TGFBP, and HA-binding peptide, chondroitin sulfate-binding peptide, RADA 16-1, KLD-12, and RGD peptide may also improve cartilage proliferation/repair (Liu et al., 2018).

29.4.2 Antioxidant, antimicrobial, and antiinflammatory activities

The future of cartilage tissue engineering not only lies in cartilage matrix production, preventing matrix and cellular degradation, promoting appropriate cartilage integration but also in the delivery of antimicrobial, antioxidant, and antiinflammatory factors to provide durable cartilage constructs. The antimicrobial, antioxidant, antiinflammatory, and immunomodulatory effects of biologically active peptides in cartilage repair have been reported (see Table 29.1).

The biological potential of antioxidant peptides in human clinics has been scarcely reported. One example is the fish gelatine, which showed the potential to maintain normal tendon and bone integrity, treat brittle nails, and improve joint health (Kim & Mendis, 2006).

In addition, some natural plant extracts or compounds have been used in combination or isolated. For example, the polyphenol curcumin has shown a promising potential in terms of antiinflammatory and antioxidant effects, being beneficial for joint pathologies and in delaying cell death in the joint tissue (Kim, In Kim, Sim, & Khang, 2017). Kim and collaborators (Kim et al., 2017) developed a scaffold for cartilage regeneration using curcumin/silk composite scaffold, and the results may provide clinical support for the patients with various cartilage diseases.

Yu and colleagues (Yu et al., 2018) designed a bioactive resveratrol–PLA–gelatin porous nano-scaffold to repair articular cartilage defects. Resveratrol is a poly-phenolic compound with antiaging, antiinflammatory, and antioxidant functions. This bioactive molecule can alleviate damage to cartilage, as it can regulate inflammation signaling (PI3K/AKT signaling pathway) in human chondrocytes.

Other agents involved in the inflammatory process are proinflammatory (TNF-α, IL-1β, and 5-LOX) and antiinflammatory (15-LOX, FPR2, and IL-10) mediators. Al-Madol and colleagues (Al-Madol et al., 2017) suggested that the inflammatory mediators such as TNF-α, IL-1β, and 5-LOX play a key role in driving the inflammation and synovial cell proliferation in rheumatoid arthritis-associated joint destruction. On the other hand, other results showed that the

antiinflammatory cytokines IL-10 is a potent immunoregulatory cytokine and plays a role in preventing exaggerated inflammatory and immune responses and protect the patient from immune-mediated damage (Al-Madol et al., 2017). Cytokines control a wide variety of inflammatory processes in joints, which provide the rationale for current treatments with the use of monoclonal antibodies against TNF-α, IL-1β, IL-6, and IL-17A (Janakiraman, Krishnaswami, Rajendran, Natesan, & Kandasamy, 2018; Krishnan & Grodzinsky, 2018). There is no treatment to recover cartilage, and the antiinflammatory therapies used for joint diseases provide short-term relief but can have adverse side effects. Lin and colleagues (Lin, Poh, & Panitch, 2016) developed a nanoparticle system that delivers therapeutics (in this case an antiinflammatory peptide KAFAK) intracellularly with improved efficacy by triggering degradation and suppressing inflammation in multiple cell types within an inflamed joint. Further, a study by McMasters and collaborators (McMasters, Poh, Lin, & Panitch, 2017), showed that hollow, sulfated poly(N-isopropylacrylamide) nanoparticles are an effective platform for the loading and delivery of antiinflammatory cell-penetrating peptides (KAFAK), with higher loading capacity, and prolonged-release profiles compared to other delivery systems.

To enhance cartilage regeneration, various strategies have been developed with protective agents, such as antioxidants, antimicrobial, and antiinflammatory factors. The development of nutraceuticals composed by cartilage matrix elements has been studied in supporting joint health. Food supplements with chondroitin and glucosamine have been tested and presented several positive results. Recently, Dar and colleagues (Dar et al., 2017) reported that the oral consumption of a hydrolyzed type 1 collagen preparation, showed chondroprotective and antiapoptotic effects in articular chondrocytes, promoting antiinflammatory effect, and could represent a strategy for supporting joint health.

On the other hand, in addition to the antioxidant and antiinflammatory agents, it is also important to know the potential of antimicrobial agents. The factors controlling the production of joint-associated antimicrobial peptides (AMPs) are unknown; however, it is known that AMPs may act by altering the cellular membrane permeability, protein synthesis inhibition, nucleic acid binding, or inactivation of the toxins that enable microbial infection (Pinto et al., 2019). So, several AMPs mechanisms action may be more advantageous in decreasing the ability of bacteria to acquire resistance and inducing the antiinflammatory response (by T cells stimulation and other cells with immunomodulatory properties) (Pinto et al., 2019). The AMPs may induce the expression of chemokines such as CXCL8 (IL-8), CCL2, and proinflammatory cytokines, and act directly through the binding-receptor interaction between LL37 and formyl peptide receptor-like 1 (FPRL1) (Pinto et al., 2019). So, the bioinspired AMPs have become a promising alternative, namely for cartilage tissue regeneration

application. Varoga and colleagues (Varoga et al., 2005) showed a systematic analysis of in vitro and in vivo antimicrobial active proteins in healthy articular joints and disease states such as pyogenic arthritis, rheumatoid arthritis, and osteoarthritis. The review identified the most prominent antimicrobial proteins in articular joints (Table 29.1), as lysozyme, lactoferrin, secretory phospholipase A2, RNase 7, CAP37, the cathelicidin LL37, and especially the human beta-defensin-2 and -3 (HBD-2/-3). For example, during arthroplasty (in arthroplasty-associated septic arthritis) bacteria can adhere to implant surfaces and therefore be introduced into the patient’s joint, as well as when

adhesion of bacteria contributes to biofilm formation in surfaces of implants. So, theses AMPs prevent bacterial adhesion to the substrates, exhibit an antimicrobial effect, and coating joint prostheses with CLEC3A-derived AMPs could be an application in cartilage tissue engineering (Elezagic et al., 2019).

29.4.3 Neuroactivity

Joint diseases are associated with pain and despite therapeutics to pain control and the use of effective disease-modifying antirheumatic drugs, sometimes the pain persists.

Several studies reported the interaction between the nervous and immune systems, by neuropeptides and cytokines. The nervous system can modulate immunological and inflammatory responses, and several neuropeptides show potent ability to induce vasodilatation, edema and pain. Some neuropeptides, such as vasoactive intestinal polypeptide (VIP), substance P, and calcitonin-related peptide have been detected in the synovial fluid from patients with rheumatic disease.

Recent studies reported the role of the VIP that is a neuropeptide acting as a neurotransmitter or neuromodulator in many organs and tissues (Jiang et al., 2016). This peptide operates in the stimulation of contractility in the heart, vasodilation, promoting neuroendocrine-immune communication, lowering arterial blood pressure, and possesses antiinflammatory, and immune-modulatory activity. Kanemitsu and colleagues (Kanemitsu et al., 2020) concluded that the inhibition of VIP signaling has the potential to be a therapeutic target to prevent osteoarthritis progression.

On the other hand, according to Zhang & Lee (2018), persistent pain in join may not be associated with inflammatory processes but to the dysregulation of central nervous system pain regulatory pathways. Many cells of osteoarticular tissue have receptors for sympathetic and parasympathetic neurotransmitters and thus may respond to their stimuli (Courties, Sellam, & Berenbaum, 2017). Sympathetic nerves also innervate the synovium and maybe induce joint diseases. However, scarce dataare available on parasympathetic innervation of the joint tissue and more research is needed to understand the relation by pain—neuroactive peptides—joint diseases.

29.5 Evidence in joint health benefits

Research studies about compounds that modify the progress of joint diseases have received increasing attention. Collagen derivatives have been studied to prevent or decrease the deterioration of joint tissue. The collagen derivatives are shown in different forms, as undenatured collagen (300 kDa), gelatine (20–90 kDa) and, as mentioned before, collagen hydrolysates (1–10 kDa) (Van Vijven et al., 2012). Collagen and gelatine hydrolysates studies proposed that peptides can be used as building blocks for the cartilage. Collagen hydrolysates showed a stimulatory effect on type II collagen biosynthesis in a cell culture model of chondrocytes, observing a collagen turnover in cartilage tissue (Oesser & Seifert, 2003). In preclinical studies in mice, gelatine hydrolysates demonstrated a cartilage tissue accumulation and intestinal absorption, where 95% of compounds were absorbed in the first 12 h, observing its clinical benefit on degenerative diseases by oral administration (Oesser et al., 1999).

Animal trials have proposed that oral ingestion of collagen derivatives might have positive effects on joint health such as osteoarthritis, showing that collagen peptide decreases the morphological alteration related to osteoarthritic cartilage destruction in knee joints (Ohara, Iida, Ito, Takeuchi, & Nomura, 2010). Therefore the potential function of collagen derivatives in repairing damaged cartilage might relate to the accumulation of orally administered collagen derivatives.

The connective tissues modify with the natural process of ageing. The cartilage ageing can be associated with the softening of the articular surface, reduction of proteoglycan amount, injury of matrix biomechanical properties, and the decrease of chondrocytes. The aged cartilage is more exposed to deformation throughout joint activities and to produce osteoarthritic alterations. To slow down the evolution of the signs of ageing and to improve the cartilage tissues, collagen hydrolysates have been used as a nutraceutical supplement (Czajka et al., 2018). Collagen peptides can reach and remain in several tissues (cartilage, skin, bones, and muscles) after 14 days of ingestion. Gelatine hydrolysates from porcine skin, chicken cartilage, and chicken feet have demonstrated to be absorbed and detected in the plasma of healthy subjects after oral ingestion (Iwai et al., 2005). The oral supplementation of collagen hydrolysates has also proved that can improve the quality of life of patients with osteoarthritis. It has been already reported that the ingestion of 10 g of hydrolyzed collagen during 6 months by patients with osteoarthritis, reduced the pain, and improved the knee joint comfort (Benito-Ruiz et al., 2009; McAlindon et al., 2011). Moreover, it is suggested that the intake of collagen peptides have a potential protective role and might delay osteoarthritis progression (McAlindon et al., 2011). The collagen peptides were also used to reduce knee joint pain in young athletes during physical activity (Zdzieblik, Oesser, Gollhofer, & König, 2017). Table 29.2 summarizes some of the randomized

controlled trials that establish the effectiveness of the ingestion of collagen derivatives for the joint disorders' prevention/treatment and symptoms relief.

Table 29.2 Randomized controlled clinical trials of oral supplementation of collagen derivatives towards joint disorders.

Intervention	Participants	Follow-up	Outcomes	Reference
Daily consumption of 50 mL of a test product with 8% of hydrolyzed collagen from fish combined with vitamins and other compounds	122 volunteer subjects between 21 and 70 years old	90 days	Improvement of clinical parameters related to joint health, such as reduction of joint pain by 43% and improvement of joint mobility by 39%	Czajka et al. (2018)
Daily consumption of 720 mg of promerim for the first 15 days and then 360 mg for the second 15 days. Promerim is a dietary supplement that contains hydrolyzed fish collagen	92 subjects between 40 and 69 years old with knee pain	1 month	Rapidly reduction of pain and stiffness in the knee osteoarthritis	Kilinc et al. (2018)
Daily consumption of eight tablets containing shark cartilage extract (45 mg of type II collagen peptides and 60 mg chondroitin sulfate), glucosamine hydrochloride, among other ingredients	100 subjects between 40 and 74 years old with knee pain	16 weeks	Improvement of locomotor functions and relieve knee pain	Kanzaki, Ono, Shibata, & Moritani (2015)
Twice a day consumption of 5 g of test product dissolved in 250 mL water or milk containing collagen peptides isolated from pork skin or bovine bone	30 subjects between 30 and 65 years old diagnosed with knee osteoarthritis	91 days	Improvement of the overall physical discomforts resulting from the osteoarthritis, such as pain, stiffness, and physical functions	Kumar et al. (2015)
Consumption of a daily dose of 40 mg of undenatured type II collagen derived from chicken sternum	191 subjects between 40 and 75 years old with moderate-to-severe osteoarthritis	180 days	Amelioration of knee joint symptoms, namely pain, stiffness and physical functions. Undenatured type II collagen presented better clinical outcomes than glucosamine hydrochloride plus chondroitin sulfate (widely available supplement used for reducing joint pain)	Lugo, Saiyed, & Lane (2016)
Oral administration of one tablet three times per day, that comprises mainly hydrolyzed gelatine (500 mg/tablet), chondroitin sulfate, glucosamine sulfate, and devil's claw and bamboo extracts	130 subjects aged ≥18 years with osteoarthritis	180 days	Nutritional supplement reduced articular pain and improved locomotor function of the knee and/or hip	Puigdellivol et al. (2019)
A daily dose of 5 g of collagen peptides	160 athletic subjects between 18 and 30 years old	12 weeks	Supplementation of collagen derivative led to an improvement of activity-related joint pain in a young adult with functional knee problems	Zdzieblik et al. (2017)

29.6 Potential applications, production, and commercialization

29.6.1 Diagnostic

Patients with rheumatoid arthritis have a decreased quality of life triggered by the pain, fatigue, and damage of some body-functions related with disease evolution. Patients have also an improved risk of lung and cardiovascular disorders and premature mortality. Therefore the early diagnosis of rheumatoid arthritis is imperative to ensure effective treatment, because it has been revealed that the patients who receive early an antirheumatics drug have an improvement of health outcomes (Alm et al., 2018). The clinical criteria to identify this disease is generally based on history and physical exam discoveries, laboratory, and radiographic results. Several laboratory tests are already used, including the detection of rheumatoid factor (RF), antibodies directed against the Fc portion of immunoglobulin G, and also antibodies against peptides containing citrulline (Aggarwal, Liao, Nair, Ringold, & Costenbader, 2009). The anticyclic citrullinated peptide ELISA has been an ideal rheumatoid arthritis indicator because it showed a high specificity (98%) and sensitivity (79%) (Vallbracht & Helmke, 2005). The cyclic citrullinated peptide (CCP) test is based on purified synthetic peptides comprising modified arginine residues (citrulline) acting as antigen. The CCP ELISA can anticipate the clinical manifestation of rheumatoid arthritis and is suitable to evaluate the disease

development. Besides, the combination of anti-CCP and RF positive results has been proven to enhance the possibility of a true positive result compared to either of the antibody tests in separated. The high evidence of the value of CCP assays for the diagnosis of rheumatoid arthritis led to the integration of this test in the American College of Rheumatology guidelines (Alm et al., 2018).

The biochemical markers have the potential to identify the different joint diseases and measure the pathology progression. So, some research studies focus on the development of strategies addressed to the detection of protein fragments that are generated in joint

diseases, such as the degradation products of collagen. Additionally, biomarkers can be essential to appraise the individual patients responses to the administered treatment (Saberi Hosnijeh, Bierma-Zeinstra, & Bay-Jensen, 2019).

Rheumatoid arthritis and osteoarthritis have a similar clinical manifestation of abnormal and degraded cartilage in joints. These alterations occur in an early stage of the diseases long before noteworthy damage can be perceived in the radiographic analysis. Herein, it is crucial to recognize the biomarkers of cartilage degradation. The degradation of type II collagen via different enzymatic processes is a very early sign of injury in rheumatoid arthritis and osteoarthritis; so, the detection of type II collagen-derived fragments in biological samples has been an area of interesting research. In this context, an ELISA using the 622–632 peptide derived from the sequence of the α1 chain of type II collagen (HELIX-II) as immunogen was developed to measure that fragment in the urine. The urinary levels of HELIX-II in 89 patients with rheumatoid arthritis and 90 patients with osteoarthritis and 162 healthy persons were measured. The HELIX-II ELISA showed to be a useful noninvasive assay to distinguish patients with rheumatoid arthritis or osteoarthritis from healthy people (Charni, Juillet, & Garnero, 2005).

The diagnosis of prosthetic joint infections (PJI) is also a challenge because a positive synovial fluid culture can detect a PJI; but, a negative culture does not exclude the hypothesis of PJI. Besides that, the skin commensal bacteria (*Staphylococcus* spp., *Propionibacterium acnes*, among others) can confuse the diagnose of PJI; so, other criteria are required to support the diagnosis (Vaishya, Sardana, Butta, & Mendiratta, 2019). A range of new laboratory methods for PJI includes molecular biology tests, antigen and antibody assays, and immune markers in a biological fluid. When the first-line investigations fail to supply a decisive diagnosis, a multidisciplinary discussion for complex PJI is better to define the following diagnostic strategy (Arvieux & Common, 2019). An array of biomarkers has been proposed for PTFI diagnoses, such as inflammatory proteins and AMPs. The AMPs that have been studied comprise alpha-defensins and lactoferrin. Alpha-defensins are released by the neutrophils as a defense mechanism against microorganisms. Alpha-defensin has been the best synovial fluid biomarker for the advance of immunodiagnostic assays (Vaishya et al., 2019). This test is not affected by antibiotherapy or inflammatory conditions. The alpha-defensin PJI assay revealed high specificity (100%) and sensitivity (92.1%) (Hosny & Keenan, 2020).

29.6.2 Prophylaxis/therapeutic

The joint diseases are currently considered to be diseases without a cure. For this reason, the available treatments are aimed at reducing the risk of joint damage or reducing the pain caused by the established disease. These disorders are mostly treated through exercise

combined with the administration of analgesics or nonsteroidal antiinflammatory drugs. These drugs are for symptoms relief but do not alter the disease and still cause adverse effects.

However, as we already mentioned, there is increasing evidence of the beneficial effects of bioactive peptides, given their high potential for the development of new treatments. For example, daily oral supplementation with a liquid nutraceutical containing hydrolyzed fish collagen, vitamins, antioxidants, and other active ingredients may improve the quality of life of subjects suffering from osteoarthritis (Czajka et al., 2018). Intake of collagen peptides (5 g/day for 12 weeks) may lead to the relief of joint pain and stimulate regeneration of type II collagen and the biosynthesis of proteoglycans in cartilage tissue osteoarthritis patients, improving joint mobility (Czajka et al., 2018; McAlindon et al., 2011; Zdzieblik et al., 2017).

As for rheumatoid arthritis, a promising way to reduce the autoimmune response is to use peptides target anticitrullinated protein/peptide antibodies (Benham et al., 2015). Besides, one of the putative functional peptides

derived from the domain of galectin-1 showed a significant therapeutic effect in TNF-α induced MH7A rheumatoid arthritis model in vitro (Hu et al., 2020). Another rheumatoid arthritis therapy is targeted on the delivery of cytokine therapy to rheumatoid tissue by a synovial targeting peptide (Wythe et al., 2013).

Parmar and colleagues (Parmar et al., 2015) developed a biodegradable hydrogel, by modified a streptococcal collagen-like 2 protein with hyaluronic acid (HA) or chondroitin sulfate-binding peptides and then cross-linked with a matrix metalloproteinase 7-sensitive peptide. Subsequently, human MSCs were incorporated into hydrogels improving viability and significantly enhancing chondrogenic differentiation. This novel biomaterial showed the potential to act in cell-mediated processes and improve the cartilage repair.

Other therapies/treatments have been developed with the aid of peptides, for example, the use of CNP has shown evidence for its ability to regulate cartilage and bone homeostasis. Data results by in vitro studies reported that exogenous CNP influenced chondrocyte differentiation, proliferation, and matrix synthesis. However, the CNP signaling systems are complex and influenced by multiple factors; but, the evidence showed that enhanced CNP signaling may prevent growth retardation and protect cartilage in the presence of inflammatory disease (Peake et al., 2014).

Faust and colleges (Faust et al., 2018) developed a peptide-polymer composed of an HA-binding peptide conjugated to a heterobifunctional poly(ethylene glycol) chain and a collagen-binding peptide as a technology that can be implemented after a cartilage defect to slow further degeneration of the cartilage tissue without additional HA supplementation. The results were promising, and this platform could be conjugated to other active molecules or drugs for targeted delivery to damaged areas of cartilage in vivo. However, more studies are needed to validate their therapeutic efficacy.

Even some studies have been performed, it is considered that the evidence is not enough and that a larger critical mass of human studies is necessary to get a correct validation of all the findings.

29.6.3 Production and commercialization

Biomaterials and ingredients based on collagen and its peptides are very important for biomedical applications, mainly for tissue engineering and regenerative medicine. This is due to its superior biocompatibility and low immunogenicity, always depending on the sources from which the collagen is taken (Silva et al., 2014).

In that sense, researchers are focusing on different sources to avoid the use of bovine collagen due to protein misfolding and allergenicity. For example, marine collagen (type I) is considered an excellent alternative of functional ingredients, also because its source is cheap and prevents bovine spongiform encephalopathy, making it an attractive option for product developers (Avila Rodríguez, Rodríguez Barroso, & Sánchez, 2018). Beyond this, many more types of this protein have yet to be discovered, as well as other alternative sources to prevent outbreaks of communicable disease and immune problems. Because of this, research is still underway to identify the various unexplored sources of collagen that may be used in the future.

In the last decade, the size of the world market for collagen and its derivatives (hydrolyzed) has grown and is expected to witness significant growth in the coming years, reaching USD 6.63 billion by 2025 (Avila Rodríguez et al., 2018). This is mainly due to the growing demand for food and beverages, cosmetics and healthcare. The global market for collagen-based biomaterials and bioingredients for tissue repair and care applications is likely to progress to a solid compound annual growth rate of 10.4% over the next 5 years (Avila Rodríguez et al., 2018).

It is important to say that due to all the forms of collagen currently on the market (intact, hydrolyzed, gelatine, hydrolyzed gelatine), all cosmetic and pharmaceutical products must indicate what type they are using in their formula and why. Not only to know the role it will have in the body, but also because of the sources from which the used collagen was taken that could interfere with the patient’s homeostasis. In the case of peptides, it is also important to know if the hydrolysis was chemical or enzymatic, as well as the size profile of the peptides since their bioactivity depends on it (Coscueta, Campos, Osório, Nerli, & Pintado, 2019).

All the natural sources of collagen that have been found, as well as the development of synthetic sources, had a major impact on the collagen derivatives industry. It is expected to expand more and more in the coming years, thus opening new strong and interesting opportunities in the field of research applicable to the biomedical industry whose main application is in the prophylaxis and treatment of joints.

29.7 Summary

A growing body of evidence provides a rationale for the use of collagen hydrolysate/peptides from different natural sources in patients with joint diseases. The joint function involves several mechanisms of action, such as cartilage proliferation, degradation, regeneration; and positive impact through the action by antimicrobial, antioxidant, and antiinflammatory agents; and neuroactivity. Understanding these mechanisms is important to develop new molecules or biomaterials for diagnosis, prophylaxis, treatments, and therapies for joint diseases. In that sense, peptidomics is playing a vital role in the study of biological markers and therapeutic targets. So, research studies are crucial for the advancement and validation of clinically applicable biomarkers. It is also imperative to evaluate their specificity and sensitivity for a suitable and early diagnosis. Furthermore, it is hoped that ongoing and future research will develop tools and methodologies for the prevention and therapy of joint diseases based on bioactive peptides.

There is evidence that, for example, collagen derivatives are resorbed in the small intestine and are directly transported from the gastrointestinal tract into the bloodstream. In preclinical trials, it has been revealed a significant quantity of biopeptides accumulated in the articular cartilage. In clinical trials, the effectiveness of oral supplementation of collagen derivatives was demonstrated in osteoarthritic patients, and an improvement of clinical parameters related to joint health was reported, that is, reduction of pain and improvement of joint mobility. This therapy was also effective in athletic subjects suffering from joint pain related to excessive physical activity.

Therefore although the application of bioactive peptides in joint pathologies has a promising future, there is still a long way to go. Mainly, the critical mass of clinical work should be increased, adopting the new strategies developed in real cases.

Acknowledgments

This work was supported by National Funds from FCT—Fundação para a Ciência e a Tecnologia through project UID/Multi/50016/2019.

References

Aggarwal R., Liao K., Nair R., Ringold S. and Costenbader K.H., Anti-citrullinated peptide antibody assays and their role in the diagnosis of rheumatoid arthritis, *Arthritis Care and Research* **61**, 2009, 1472–1483.

Aletaha D., Funovits J., Smolen J.S. and Editorial S., Physical disability in rheumatoid arthritis is associated with cartilage damage rather than bone destruction, *Annals of the Rheumatic Diseases* 2011, 733–739. https://doi.org/10.1136/ard.2010.138693.

Aletaha D. and Smolen J.S., Diagnosis and management of rheumatoid arthritis: A review, *JAMA: The Journal of the American Medical Association* **320**, 2018, 1360–1372.

Alm L.M., et al., The performance of anti-cyclic citrullinated peptide assays in diagnosing rheumatoid arthritis: A systematic review and meta-analysis, *Clinical and Experimental Rheumatology* **36**, 2018, 144–152.

Al-Madol M.A., et al., Comparative expression analyses of pro- versus anti-inflammatory mediators within synovium of patients with joint trauma, osteoarthritis, and rheumatoid arthritis, *Mediators of Inflammation* **2017**, 2017.

Arvieux C. and Common H., New diagnostic tools for prosthetic joint infection, *Orthopaedics and Traumatology: Surgery and Research* **105**, 2019, S23–S30.

Avila Rodríguez M.I., Rodríguez Barroso L.G. and Sánchez M.L., Collagen: A review on its sources and potential cosmetic applications, *Journal of Cosmetic Dermatology* **17**, 2018, 20–26.

Banerjee P. and Shanthi C., Cryptic peptides from collagen: A critical review, *Protein and Peptide Letters* **23**, 2016, 664–672.

Bello A.E. and Oesser S., Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders: A review of the literature, *Current Medical Research and Opinion* **22**, 2006, 2221–2232.

Benham H., et al., Citrullinated peptide dendritic cell immunotherapy in HLA risk genotype—Positive rheumatoid arthritis patients, *Rheumatoid arthritis* **7**, 2015.

Benito-Ruiz P., et al., A randomized controlled trial on the efficacy and safety of a food ingredient, collagen hydrolysate, for improving joint comfort, *International Journal of Food Sciences and Nutrition* **60**, 2009, 99–113.

Charni N., Juillet F. and Garnero P., Urinary type II collagen helical peptide (HELIX-II) as a new biochemical marker of cartilage degradation in patients with osteoarthritis and rheumatoid arthritis, *Arthritis and Rheumatism* **52**, 2005, 1081–1090.

Coscueta E.R., Campos D.A., Osório H., Nerli B.B. and Pintado M., Enzymatic soy protein hydrolysis: A tool for biofunctional food ingredient production, *Food Chemistry: X* **1**, 2019, 100006.

Courties A., Sellam J. and Berenbaum F., Role of the autonomic nervous system in osteoarthritis, *Best Practice and Research: Clinical Rheumatology* **31**, 2017, 661–675.

Czajka A., et al., Daily oral supplementation with collagen peptides combined with vitamins and other bioactive compounds improves skin elasticity and has a beneficial effect on joint and general wellbeing, *Nutrition Research (New York, N.Y.)* **57**, 2018, 97–108.

Dar Q.-A.A., et al., Daily oral consumption of hydrolyzed type 1 collagen is chondroprotective and anti-inflammatory in murine posttraumatic osteoarthritis, *PLoS One* **12**, 2017, e0174705.

Deng Z.H., Li Y.S., Gao X., Lei G.H. and Huard J., Bone morphogenetic proteins for articular cartilage regeneration, *Osteoarthritis and Cartilage* **26**, 2018, 1153–1161.

Elezagic D., et al., Antimicrobial peptides derived from the cartilage-specific C-type lectin domain family 3 member A (CLEC3A)—Potential in the prevention and treatment of septic arthritis, *Osteoarthritis and Cartilage* **27**, 2019, 1564–1573.

Faust H.J., et al., A hyaluronic acid binding peptide-polymer system for treating osteoarthritis, *Biomaterials* **183**, 2018, 93–101.

Ferro E.S., Rioli V., Castro L.M. and Fricker L.D., Intracellular peptides: From discovery to function, *EuPA Open Proteomics* **3**, 2014, 143–151.

Fu Y., Therkildsen M., Aluko R.E. and Lametsch R., Exploration of collagen recovered from animal by-products as a precursor of bioactive peptides: Successes and challenges, *Critical Reviews in Food Science and Nutritio.* **8398**, 2018.

Fusco M., Skaper S.D., Coaccioli S., Varrassi G. and Paladini A., Degenerative Joint diseases and neuroinflammation, *Pain Practice* **17**, 2017, 522–532.

Haque Bhuyan M.Z., et al., The intra-articular injection of RANKL-binding peptides inhibits cartilage degeneration in a murine model of osteoarthritis, *Journal of Pharmacological Sciences* **134**, 2017, 124–130.

Hosny H.A. and Keenan J., Management of prosthetic joint infection, *Surgery (United Kingdom)* **38**, 2020, 114–120.

Hu J., et al., Peptidomic analysis on synovial tissue reveals galectin-1 derived peptide as a potential bioactive molecule against rheumatoid arthritis, *Cytokine* **131**, 2020, 155020.

D. Horowitz, J. Hanrahan & R.K Turley. (n.d.). Osteoarthritis. *Health Encyclopedia—University of Rochester Medical Center* Available at: https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=85&contentid=p00061.

Iwai K., et al., Identification of food-derived collagen peptides in human blood after oral ingestion of gelatin hydrolysates, *Journal of Agricultural and Food Chemistry* **53**, 2005, 6531–6536.

Janakiraman K., Krishnaswami V., Rajendran V., Natesan S. and Kandasamy R., Novel nano therapeutic materials for the effective treatment of rheumatoid arthritis-recent insights, *Materials Today Communications* **17**, 2018, 200–213.

Jiang W., Wang H., Li Y.S. and Luo W., Role of vasoactive intestinal peptide in osteoarthritis, *Journal of Biomedical Science* **23**, 2016, 1–6.

EFSA Journal. (2005). Undefined. Opinion of the Food Safety Authority on safety of collagen and a processing method for the production of collagen.

Kanemitsu M., et al., Role of vasoactive intestinal peptide in the progression of osteoarthritis through bone sclerosis and angiogenesis in subchondral bone, *Journal of Orthopaedic Science: Official Journal of the Japanese Orthopaedic Association* 2020. https://doi.org/10.1016/j.jos.2019.11.010.

Kanzaki N., Ono Y., Shibata H. and Moritani T., Glucosamine-containing supplement improves locomotor functions in subjects with knee pain: A randomized, double-blind, placebo-controlled study, *Clinical Interventions in Aging* **10**, 2015, 1743–1753.

Kawaguchi T., Nanbu P.N. and Kurokawa M., Distribution of prolylhydroxyproline and its metabolites after oral administration in rats, *Biological & Pharmaceutical Bulletin* **35**, 2012, 422–427.

Kilinc B.E., et al., An observational 1-month trial on the efficacy and safety of promerim for improving knee joint, *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders* **11**, 2018.

Kim D.K., In Kim J., Sim B.R. and Khang G., Bioengineered porous composite curcumin/silk scaffolds for cartilage regeneration, *Materials Science and Engineering C* **78**, 2017, 571–578.

Kim S.K. and Mendis E., Bioactive compounds from marine processing byproducts—A review, *Food Research International* **39**, 2006, 383–393.

Krishnan Y. and Grodzinsky A.J., Cartilage diseases, *Matrix Biology* **71–72**, 2018, 51–69.

Kumar S., Sugihara F., Suzuki K., Inoue N. and Venkateswarathirukumara S., A double-blind, placebo-controlled, randomised, clinical study on the effectiveness of collagen peptide on osteoarthritis, *Journal of the Science of Food and Agriculture* **95**, 2015, 702–707.

Lam A.T.L., Reuveny S. and Oh S.K.W., Human mesenchymal stem cell therapy for cartilage repair: Review on isolation, expansion, and constructs, *Stem Cell Research* **44**, 2020, 101738.

Lin J.B., Poh S. and Panitch A., Controlled release of anti-inflammatory peptides from reducible thermosensitive nanoparticles suppresses cartilage inflammation, *Nanomedicine: Nanotechnology, Biology and Medicine* **12**, 2016, 2095–2100.

Liu Q., et al., Functional peptides for cartilage repair and regeneration, *American Journal of Translational Research* **10**, 2018, 501–510.

Lugo J.P., Saiyed Z.M. and Lane N.E., Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: A multicenter randomized, double-blind, placebo-controlled study, *Nutrition Journal* **15**, 2016, 1–15.

Malmström V., Catrina A.I. and Klareskog L., The immunopathogenesis of from triggering to targeting, *Nature Reviews. Immunology* **17**, 2017, 60–75.

McAlindon T.E., et al., Change in knee osteoarthritis cartilage detected by delayed gadolinium enhanced magnetic resonance imaging following treatment with collagen hydrolysate: A pilot randomized controlled trial, *Osteoarthritis and Cartilage* **19**, 2011, 399–405.

McMasters J., Poh S., Lin J.B. and Panitch A., Delivery of anti-inflammatory peptides from hollow PEGylated poly(NIPAM) nanoparticles reduces inflammation in an ex vivo osteoarthritis model, *Journal of Controlled Release: Official Journal of the Controlled Release Society* **258**, 2017, 161–170.

Oesser S., Adam M., Babel W. and Seifert J., Oral administration of 14C labeled gelatin hydrolysate leads to an accumulation of radioactivity in cartilage of mice (C57/BL), *The Journal of Nutrition* **129**, 1999, 1891–1895.

Oesser S. and Seifert J., Stimulation of type II collagen biosynthesis and secretion in bovine chondrocytes cultured with degraded collagen, *Cell and Tissue Research* **311**, 2003, 393–399.

Ohara H., Iida H., Ito K., Takeuchi Y. and Nomura Y., Effects of Pro-Hyp, a collagen hydrolysate-derived peptide, on hyaluronic acid synthesis using in vitro cultured synovium cells and oral ingestion of collagen hydrolysates in a guinea pig model of osteoarthritis, *Bioscience, Biotechnology, and Biochemistry* **74**, 2010, 2096–2099.

Park Y.J., et al., A novel antimicrobial peptide acting via formyl peptide receptor 2 shows therapeutic effects against rheumatoid arthritis, *Scientific Reports* **8**, 2018, 4–13. https://doi.org/10.1038/s41598-018-32963-5

Parmar P.A., et al., Collagen-mimetic peptide-modifiable hydrogels for articular cartilage regeneration, *Biomaterials* **54**, 2015, 213–225.

Peake N.J.J., et al., Role of C-type natriuretic peptide signalling in maintaining cartilage and bone function, *Osteoarthritis and Cartilage* **22**, 2014, 1800–1807.

Pinto I.B., et al., Utilization of antimicrobial peptides, analogues and mimics in creating antimicrobial surfaces and bio-materials, *Biochemical Engineering Journal* **150**, 2019, 107237.

Puigdellivol J., et al., Effectiveness of a dietary Supplement containing hydrolyzed collagen, chondroitin sulfate, and glucosamine in pain reduction and functional capacity in osteoarthritis patients, *Journal of Diet* **16**, 2019, 379–389.

Saberi Hosnijeh F., Bierma-Zeinstra S.M. and Bay-Jensen A.C., Osteoarthritis year in review 2018: Biomarkers (biochemical markers), *Osteoarthritis and Cartilage* **27**, 2019, 412–423.

Schadow S., et al., Collagen metabolism of human osteoarthritic articular cartilage as modulated by bovine collagen hydrolysates, *PLoS One* **8**, 2013.

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Scientific Opinion on the substantiation of a health claim related to collagen hydrolysate and maintenance of joints pursuant to Article 13(5) of Regulation (EC) No 1924/2006, *EFSA Journal* **9**, 2011.

Silva T.H., et al., Marine origin collagens and its potential applications, *Marine Drugs* **12**, 2014, 5881–5901.

Sokoloff L., Joint disease, *Encyclopædia Britannica* 2019, Available at. https://www.britannica.com/science/joint-disease.

Tuan R.S., Chen A.F. and Klatt B.A., Cartilage regeneration, *Journal of the American Academy of Orthopaedic Surgeons* **21**, 2013, 303–311.

Vaishya R., Sardana R., Butta H. and Mendiratta L., Laboratory diagnosis of prosthetic joint infections: Current concepts and present status, *Journal of Clinical Orthopaedics and Trauma* **10**, 2019, 560–565.

Vallbracht I. and Helmke K., Additional diagnostic and clinical value of anti-cyclic citrullinated peptide antibodies compared with rheumatoid factor isotypes in rheumatoid arthritis, *Autoimmunity Reviews* **4**, 2005, 389–394.

Varela-Eirin M., et al., Cartilage regeneration and ageing: Targeting cellular plasticity in osteoarthritis, *Ageing Research Reviews* **42**, 2018, 56–71.

Varoga D., et al., Expression and regulation of antimicrobial peptides in articular joints, *Annals of Anatomy (Anatomischer Anzeiger: Official Organ of the Anatomische Gesellschaft)* **187**, 2005, 499–508.

Van Vijven J.P.J., et al., Symptomatic and chondroprotective treatment with collagen derivatives in osteoarthritis: A systematic review, *Osteoarthritis and Cartilage* **20**, 2012, 809–821.

Watanabe-Kamiyama M., et al., Absorption and effectiveness of orally administered low molecular weight collagen hydrolysate in rats, *Journal of Agricultural and Food Chemistry* **58**, 2010, 835–841.

Wythe S.E., et al., Targeted delivery of cytokine therapy to rheumatoid tissue by a synovial targeting peptide, *Annals of the Rheumatic Diseases* 2013, 129–135. https://doi.org/10.1136/annrheumdis-2012-201457.

Yu F., et al., Mechanism research on a bioactive resveratrol–PLA–gelatin porous nano-scaffold in promoting the repair of cartilage defect, *International Journal of Nanomedicine* **13**, 2018, 7845–7858.

Zdzieblik D., Oesser S., Gollhofer A. and König D., Improvement of activity-related knee joint discomfort following supplementation of specific collagen peptides, *Applied Physiology, Nutrition, and Metabolism (Physiologie Appliquee, Nutrition et Metabolisme)* **42**, 2017, 588–595.

Zhang A. and Lee Y.C., Mechanisms for joint pain in rheumatoid arthritis (RA): From cytokines to central sensitization, *Current Osteoporosis Reports* **16**, 2018, 603–610.

Zhang Y., et al., Soy peptide nanoparticles by ultrasound-induced self-assembly of large peptide aggregates and their role on emulsion stability, *Food Hydrocolloids* **74**, 2018, 62–71.

Abstract

Rheumatic and joint diseases are among the most widespread pathologies associated with pain and cause a great impact in society across the globe. Given the continuing rise in life expectancy, their prevalence i destined to grow. Osteoarthritis, a degenerative joint disease, is on its way to becoming the fourth leading cause of disability worldwide by 2020. Accompanying osteoarthritis is rheumatoid arthritis, which is a chroni systemic disease that often causes pain and deformity. The joint function involves several processes and understanding the mechanism of action of the joint disease process (proliferation, degradation, regeneration, an infection) is important for the diagnostic, prophylaxis, and treatment. These mechanisms are associated with active peptides that are involved in almost all physiological processes, including cell differentiatior

proliferation, inflammatory processes, and immune regulation. Therefore the study of bioactive peptides as biological markers and therapeutic targets for the diagnosis, prevention, and therapy of joint diseases has very important research ahead. In this context, the present chapter will highlight the importance of bioactive peptides in joint health, underline peptides natural sources, their mechanisms of action, and their potential applications on joint diseases.

Keywords: Joint health; osteoarthritis; rheumatoid arthritis; collagen peptides; biological markers; therapeutics targets

Queries and Answers

Query: Please check the chapter title and correct if necessary.

Answer: The title is correct.

Query: Please check the author group and correct if necessary.

Answer: The author group names are correct.