

Nutraceutical alternatives to pharmaceutical analgesics in osteoarthritis

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1 Abstract

Chronic pain is a considerable health concern worldwide, effecting almost 30% of all European adults. Osteoarthritis (OA), a progressive pro-inflammatory condition, is one of the leading causes of chronic pain (effecting 13% of all those 50 years, globally) and is the most common cause of joint pain. The prevalence of non-steroidal anti-inflammatory drug (NSAIDs) and analgesic use has been well studied and is abundant throughout the western world, with women being the greatest users and ibuprofen generally being the most reported. In the US, 65% of all OA patients are prescribed NSAIDs for pain management and form part of the current recommended strategy for OA clinical management. While some NSAIDs and analgesics are effective at improving pain and physical function, they come with significant and harmful side effects such as gastrointestinal complications, renal disturbances and severe cardiovascular events. Given these side-effects, any reduction in NSAID and analgesia use (and the resulting potentially harmful side effects) is of particular importance to OA public health. As such, a number of non-pharmaceutical alternatives (bioactive nutraceuticals) have been developed that may reduce NSAID and analgesia use while maintaining pain reduction and improvements in physical function. This chapter will discuss select nutraceuticals that are not currently in mainstream use but may have the potential to aid in the treatment of OA.

Keywords; joint pain, pain medication, non-pharmacological pain management, mechanisms of pain and action, Paracetamol (acetaminophen, N-acetyl-p-aminophenol; APAP), opioids.

2 Introduction

2.1 Chronic Pain

Pain occurs in all demographics, with a higher prevalence in some clusters (such as the elderly) and can be either acute or chronic [1, 2]. Chronic pain is a complex interplay between biology and psychology, where the intensity/magnitude differs depending on personal, sensory, emotional experience and persists more than 3 months beyond “normal” healing time [3, 4]. This type of pain affects more than 1.5 billion people worldwide [5] and has an estimated prevalence ranging between 17-27% [6-9]. Chronic pain represents a significant financial burden that exceeds €300 trillion (approximately 1.5%-3% of the gross domestic product across the European Union) and up to \$635 billion in the United States [10, 11]. According to the International Association for the Study of Pain (IASP), the main overarching categories of chronic pain are primary (such as fibromyalgia) and secondary pain (the focus of this chapter). Secondary chronic pain is further divided into six distinct categories: cancer-related pain, postsurgical or posttraumatic pain, secondary headache/orofacial pain, secondary visceral pain, and secondary musculoskeletal pain [12, 13].

Most chronic pain begins with the occurrence of an acute injury event resulting in pain that if left untreated can develop chronically pathological and will increase the risk of future deleterious health issues such as sleep deficiency, delayed wound healing, immune dysfunction, cardiovascular problems (related to the stress response) and respiratory problems [such as pneumonia; 14, 15]. Furthermore, persistent, unrelieved pain can negatively impact quality of life, daily functioning, sleep quality, work productivity and is associated with a substantial personal economic burden [16].

Pathologic pain is associated with multiple maladaptations in the nervous, endocrine, and immune systems [17-19] that often presents at multiple sites [20] and can be classified into nociceptive (somatic and visceral), neuropathic, nociplastic, or mixed [21]. Nociplastic describes pain of unknown origin that arises from altered nociception, despite no clear evidence of actual or threatened tissue damage that causes activation of peripheral nociceptors, evidence of disease or lesion of the somatosensory system causing the pain, such as early (pre structural damage) osteoarthritis [21]. Similarly, recent suggestions propose that generalised chronic pain is an expression of maladaptive plasticity within the nociceptive system

[22, 23] and relevant to the present chapter as osteoarthritic pain is generally accepted to be mainly of nociceptive origin [24].

2.2 Mechanisms of nociceptive pain

Most painful conditions initially involve the activation of dorsal root ganglion (DRG) neurons, which give rise to high threshold A δ - and C-fibres (nociceptors) that innervate peripheral tissues [skin, bone, joints, viscera; 25]. Primary afferent neurons transduce painful stimuli action potentials through to the spinal cord (to ascending spinal neurons). Transmission of input from nociceptors, through the spinal column and to the central nervous system is mediated by monosynaptic contacts and/or through interneurons [19, 26]. In the spinal cord, neurotransmitter inhibition is mediated by the release of endogenous opioids [such as met-enkephalins and endorphins; 27] or gamma-aminobutyric acid (GABA) which activate presynaptic opioid and/or GABA receptors on central nociceptor terminals to reduce excitatory transmitter release (Figure 1). The central integration of signals from excitatory and inhibitory neurotransmitters from cognitive, emotional, and environmental factors results in the perception of “pain”. When the intricate balance between biological (neuronal), psychological (i.e. memory, distraction etc.) and social (i.e. attention, reward etc.) factors becomes disturbed, chronic pain develops [18].

Pain that is induced by an acute injury, initially localized, relatively proportional to the degree of tissue damage and typically increases with movement is referred to as “nociceptive pain.” Specifically, as immune surveillance cells recognize the danger signals unmasked by tissue injury, the innate immune system initiates an inflammatory response to remove cellular debris and begins the healing process. Activated endothelial cells, stromal cells, and infiltrating immune cells release vasoactive and inflammatory mediators, including histamine, bradykinin, substance P, serotonin, nitric oxide, cytokines, chemokines, and prostaglandins, which amplify signal transduction in the peripheral terminals of nociceptors [26, 28]. These inflammatory mediators augment the responsiveness of nociceptors by increasing expression of pain-sensing ion channels and promoting release of pronociceptive mediators [autosensitization; 29]. This peripheral inflammation caused by local injury and continuous inputs from sensitized nociceptors promote ‘central sensitization’, a process that alters pain processing in the spinal dorsal horn, and in subcortical and cortical regions of the brain [30, 31]. Noxious signals associated with the injury are detected by peripheral nociceptor terminals of

primary afferent neurons, transmitted via the spinal cord to the brain, processed and interpreted as highly unpleasant pain experiences [32]. Nociceptor terminals express molecules, such as transient receptor potential ion channels (TRP), voltage-gated sodium channels (Nav), voltage-gated calcium channels (VGCC), or acid-sensing ion channels (ASICs), which respond to heat, cold, acids, or mechanical stress and transduce them into action potentials [26]. The signal is then transmitted through peripheral axons to the cell bodies of the primary neurons, located in the dorsal root ganglia. Unmyelinated C-fibres and myelinated A δ -fibres transmit noxious stimuli, whereas thinly myelinated A δ -fibres transmit innocuous mechanical stimuli, such as touch. The central axons of the primary neurons enter the spinal cord through the dorsal horn and synapse with secondary somatosensory neurons and, to some extent, with motor neurons to form withdrawal reflex circuits. Signal propagation to the secondary neurons is subject to modulation by descending tracts from the brainstem and by interneurons in the dorsal horn. The signal is then transmitted to the thalamus, from where tertiary afferent neurons are projected to multiple areas of the cortex involved in pain processing [33].

2.3 Mechanisms of neuropathic pain

Neuropathic pain (NP) is defined as “pain caused by a lesion or disease of the somatosensory nervous system” [34]. Chronic neuropathic pain is caused by damage to nerve fibres in the nervous system that then respond by misappropriating sensory inputs leading to spontaneous painful sensation, through multiple mechanisms in the nervous system and its associated modulators. Peripheral nerve damage can result in chronic neuropathic pain through multiple routes [35] via peripheral pain-processing unmyelinated C-fibres and thinly-myelinated ad-libbers because of metabolic damage, toxins, medications, cytokines, and inflammation [36]. This can result in morphological and chemical changes such as fibre density and neuronal hyperexcitability [30, 37-40]. Throughout the axon, trauma, compression, hypoxia, inflammation and chemical damage lead to fibre degeneration and alterations in gene expression [41], resulting in ectopic firing, faulty signal transmission [42], detrimental physiological alterations [43-45] and peripheral second-order targets [46-48]. This results in negative impacts on nociceptive pathways causing them to become sensitized [49], leading to maladaptive central sensitization [50] and increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input [51]. At the molecular level, these damaged processes disrupt second-order neuronal transduction, through alterations in receptor expression, calcium

permeability, synapse location and the release of pain-promoting mediators [52-55]. The precise molecular targets of neuropathic pain stem from multiple mechanisms of peripheral nerve fibre excitation and sensitization leading to sustained electrochemical signalling leading to the neuropathic pain stimulus [56, 57].

2.4 Pharmaceutical treatment of chronic pain

Both acute and chronic pain are, in general, treated with a wide group of pharmaceutical medications known as “analgesics.” The most frequently used are opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol also referred to as acetaminophen or N-acetyl-p-aminophenol [58].

2.4.1 Opioids

Opioid drugs (e.g. morphine, codeine, methadone, fentanyl and their derivatives) are the most widely used analgesic medications globally, so much so that an estimated 26.8 million people were living with ‘opioid use disorder’ globally in 2016, resulting in >100,000 opioid overdose deaths annually [59]. Opioids are a group of pharmaceutical formulations that interact with endogenous opioid receptors to distort neurotransmitter signaling pathways through localized peripheral sensory neurons [60, 61] with the goal to reducing pain sensation. Opioid receptors are a large superfamily of seven-transmembrane G protein-coupled receptors and are classified as μ (μ_1 , μ_2 , μ_3), δ (δ_1 , δ_2), κ (κ_1 , κ_2 , κ_3) and ORL1 [62, 63], of which almost all opioid drugs in use today interact with μ receptors. These receptors are inhibitory and prevent the presynaptic release of a number of neurotransmitters to inhibit the release of glutamate, calcitonin gene related protein (CGRP), and substance P. This is an important action considering the established roles of these molecules in pain signalling and nociceptive transmission [Figure 1; 64]. For example, morphine, extracted from opium, is by far the most commonly known opioid [59], which is thought to be in use since the third century B.C. [22], but identified at the molecular level to have a high binding affinity to sites in the intestine and brain [65]. These receptors mediate an inhibitory signal of neural transmission induced by opioid drugs to produce an analgesic action (Figure 1). Pain stimuli are detected by nociceptors at the spinal cord dorsal horn [66] where they act on the substantia gelatinosa, (inhibitory interneurons rich with opioid receptors) and are activated by the antinociceptive descending system, to control the transmission of painful stimuli from primary nerve fibres to spino-thalamic neurons [22]. Opioid receptors have an intricate relationship with inflammatory status. Early

studies showed that the systemic or local application of receptor agonists elicited greater analgesic effects in inflamed compared to non-inflamed tissue [reviewed in; 67]. Furthermore, opioid receptor trafficking (movement within the neuron) is augmented, expression on DRG membranes is enhanced [68, 69] and axonal transport stimulated by cytokines and nerve growth factor that are produced within inflamed tissues [70, 71]. This enhanced/altered state resulted in increased antinociceptive function of opioid receptors on peripheral nerves [60, 72].

The major limiting factors of opioid therapy are the variety of side effects such as constipation, vomiting, myosis, cough reflex suppression, modulation of the immune system and one of the most dangerous, respiratory rhythm and respiratory depression [73, 74]. Interestingly, studies have shown their long-term use in chronic non-malignant (e.g. musculoskeletal) pain has not been proven effective [75], rather, abuse of prescription opioids have reached epidemic proportions leading to addiction, overdoses and increased death rates [76-78]. Importantly, these side effects may be drug specific and affect immune function differently [79, 80]. Nonetheless, chronic use of opioid medication can cause cellular adaptations that lead to modulation of cellular growth, inflammation, wound healing [81, 82] For a more detailed overview of the potential side effects and opioid tolerance see, [83-86].

Regardless of the potential impact that opioid agonists could have on pain relief, meta-analyses show no improvement in clinically significant pain reduction scores, and epidemiologic data suggest that quality of life and functional capacity are only minimally changed [75, 78]. Nonetheless, more data is required from larger studies (specifically in OA), however the aforementioned adverse effects and lack of analgesic efficacy has led to significant dropout rates in long-term studies [75, 78, 87-89].

2.4.2 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs (particular enzyme inhibitors) are among most widely used medications globally [90, 91] because of the lower potential for addiction [as shown by the US opioid epidemic; 92], robust efficacy, and long history of clinical use [93].

The prevalence of 'non-aspirin' NSAID use has been well studied and is dynamic across age, body mass index and geographical ancestry, ranging between ~15-45%, women being the greatest users and ibuprofen generally being the most reported [94-96]. Short-term use of NSAIDs is particularly prevalent (perhaps 50–80% per

year) in athletes and soldiers [individuals that may be at risk for acute and chronic musculoskeletal injuries; 97, 98, 99]. Extended periods of NSAID treatment (e.g., more than 3 times per week for more than 3 months per year) have been reported by 10% of adults in the United States [100] a rate that can be expected to increase with age [101].

NSAIDs act primarily by mediating peripheral pain sensitization driven by inflammatory stimuli, such as acute or sport injuries, (osteo)arthritis etc. and are less effective in treating pain due to nerve damage (neuropathic pain). At the point of inflammatory pain, initiated by nociceptive stimuli, NSAIDs augment the experienced nociceptive excitability [peripheral and central sensitization; 102]. NSAIDs work differently to opioids in that they do not block central pathways of nociception, but inhibit the formation of prostanoids via competitive inhibition of arachidonic acid binding to cyclooxygenase enzyme (COX) isoform active sites [103] which sensitise nociceptive pain. There are two cyclooxygenase isoforms that are the targets of NSAIDs; COX-1 that are expressed in most tissues (including the endothelium, monocytes, gastrointestinal epithelial cells, and platelets) and controls the basal production of prostanoids (Figure 1) and COX-2 that are not regularly expressed in most tissues but are upregulated in response to and during the inflammatory process (in tissues such as vascular endothelium, rheumatoid synovial endothelial cells, monocytes, and macrophages) through the actions of various inflammatory mediators such as bacterial endotoxins, tumour necrosis factor-alpha and interleukins [104]. The increase in COX-2 protein levels are the primary driving force for enhanced production of prostanoids at inflammatory sites [105, 106]. The resulting COX-2 products, particularly prostaglandin (PG) E₂, potentiate this response, where PGE₂ and prostacyclin (PGI₂), produced during local inflammation, augment pain signalling by peripheral and central neurons [15]. PGE₂ and PGI₂ increase the sensitivity of pain receptors (or nociceptors) in the periphery and enhance the activity of various pain mediators [104, 107]. This mechanism propagates via brain derived PGE₂ traveling through the blood-brain barrier, via venules, during systemic inflammation and lessens the inhibition of neurons in the hypothalamus [108]. Drugs that inhibit both COX isoforms with comparable potency (i.e. nonselective NSAIDs such as ibuprofen and ketoprofen) tend to preferentially activate the COX-1 pathway, while drugs with intermediate or selective target COX-2 inhibition (such as nimesulide, meloxicam, diclofenac, celecoxib, rofecoxib, etoricoxib, lumiracoxib etc.) have lesser potential for COX-1

activation [109]. This pathway selectivity is of significant importance as both COX isoform elicit different potentially harmful adverse effects.

In a recent meta-analysis (n=220,000 patients) of placebo-controlled trials, NSAIDs (coxibs, diclofenac, ibuprofen, and naproxen, predominantly COX-1 inhibitors) significantly increased the risk of upper gastrointestinal complications [eg, ulcer perforations, bleeding, obstructions; 110]. The authors also showed an increased risk of major vascular and major coronary events with high doses of coxibs and diclofenac while ibuprofen was associated with an increase in major coronary (but not vascular) events comparable with that of coxibs and diclofenac [predominantly COX-2 inhibitors; 110]. These data are corroborated with findings from meta-analysis of observational studies showing low risk of upper gastrointestinal complications (aceclofenac, celecoxib, and ibuprofen predominantly COX-2 inhibitors), intermediate risk (diclofenac, meloxicam, and ketoprofen etc.) and high risk (tenoxicam, naproxen, indomethacin, diflunisal, piroxicam, ketorolac, and azapropazone predominantly COX - inhibitors) depending on the NSAID, likely in a dose dependent fashion [111]. Similarly, total daily oral diclofenac had a linear dose dependent relationship cardiovascular event risk [112]. These dose dependencies are likely a product of the relative effectiveness on either COX-1 or COX-2 inhibition [113-116]. As both (non-inhabited) COX-1 and COX-2 produce cytoprotective prostanoids, inhibition of both COX isozymes (induced by NSAIDs) suppress these prostanoids and promotes damage to the gastrointestinal tract and cardiovascular tissues [109, 117]. Based on these and other safety findings, the American Heart Association recommends patients take the lowest effective dose of NSAIDs for the shortest duration of time [118].

2.4.3 Paracetamol (acetaminophen, N-acetyl-p-aminophenol; APAP)

APAP are likely to be the most commonly used pharmaceutical worldwide [119, 120], are expected to reach a global market value of USD 999.4 million in 2020 [121] and is included in the 21st World Health Organization Model List of Essential Medicines as updated in March 2017 [122]. However, recently there have been debates from the National Institute for Health and Care Excellence, about the relevance APAP for some conditions [123]. The efficacy of paracetamol to treat chronic pain has been questioned with systematic reviews showing limited (sometimes null) effects on chronic pain in some conditions [120, 124, 125]. Nonetheless, APAP can be beneficial for acute pain, [126-128], similar to NSAIDs and opioids [129-131]. The precise mechanism of action remains unknown, however

this is most likely due to the interwoven interactions that APAP have in multiple pain pathways. Our current knowledge suggests that APAPs are metabolised by the liver into p-aminophenol, then bound with arachidonic acid, primarily in the brain, to form AM404 (N-(4-hydroxyphenyl)-5Z,8Z,11Z,14Z-eicosatetraenamide) through fatty acid amide hydrolase (FAAH) activity [132-134]. Like NSAIDs, APAP are analgesic and antipyretic, however APAP lacks peripheral anti-inflammatory properties, therefore act through the central nervous system and not peripheral tissues [135]. Current evidence suggests that there are four metabolic systems that interact to elicit the analgesic and antipyretic properties of APAP, the Eicosanoid, Opioidergic, Serotonergic and Endocannabinoid systems [136].

Briefly, like NSAIDs APAP can inhibit central cyclo-oxygenases (COX-1, COX-2) including a proposed third isoform COX-3 [137-142]. Although the results are controversial [143] it is thought that they are involved in prostaglandin (PGs) production thus the analgesic mechanism of action. Furthermore, APAP are more effective in environments with low peroxide tone and low arachidonic acid levels, such as in the central nervous system, mainly through local depletion of glutathione leading to decreased production of PGE2 [139]. Considering the antinociceptive effects of APAP, one of the main brain derived metabolites AM404 (N-arachidonoyl-phenolamine) is decreased in the presence of opioid receptor antagonist. AM404 inhibits the nociceptive activity of particular APAPs in part by modulating many neurotransmitters, including 5-HT, glutamate, and γ -aminobutyric acid [143-145]. Although the precise receptors have not been identified [146-149], serotonin antagonists block the analgesic effect of APAP through mainly indirect non-binding mechanisms [146, 150]. One possible interaction with the serotonergic pathway maybe through altering CNS monoamine neuron types in the brain that contain a major receptor for PGE2 (EP3 receptor [139]). Further to the above, AM404 can inhibit anandamide [151], with stimulation of (cannabinoid 1) CB1 receptor activity (without binding) via FAAH [133], suggesting a reliance of APAP antinociceptive activity on interaction with the endocannabinoid system [134, 152]. Interestingly, AM404 is not identifiable in the blood after APAP administration [133] which might explain, to some degree, the absence of peripheral anti-inflammatory action [134]. This could help to explain why APAP may not have significant clinical effect on conditions such as osteoarthritis [further details below; 153, 154]. A recent study confirmed that APAPs act mainly on central analgesic pathways, showing that APAP modifies the activity and connectivity of analgesia via FAAH, activating a signalling cascade involving TRPV1 channels, mGlu5 receptors, PLC, DAGL and CB1

receptors, associated with the release of glutamate and GABA – through the endocannabinoid systems [155]. Though the molecular mechanisms that provide analgesia are beginning to come to light, there is also potential substantial detrimental side effects of APAPs.

APAPs are generally considered safe if administered at appropriate doses for short periods [156]. However, they remain one of the leading causes of liver disease in high-income countries [157, 158] which has led to legislative restrictions in many countries [see, 159]. It is well accepted that APAPs cause liver injury, hepatotoxicity, mitochondrial toxicity [160, 161] and that this toxicity can be effected by interindividual variation [162]. Nonetheless, consuming APAP can increase the risks of hospitalisation for perforation, peptic ulceration and bleeding [163], relative rates of adverse cardiovascular events such as myocardial infarction, stroke, coronary heart disease and upper gastrointestinal disease such as gastroduodenal ulcers and haemorrhages [164], often in a dose response manor. However, observational studies show a favourable side effect profile for APAPs compared with NSAIDs used in older people with chronic pain conditions [165]. Data from the most recent meta-analysis shows that APAPs are nearly four times more likely to have abnormal results on liver function tests than placebo [166].

3 Osteoarthritis

Osteoarthritis (OA) is a complex musculoskeletal condition that effects people of all ages but particularly those over 55 years [167-171]. According to the Osteoarthritis Research Society International (OARSI) OA can be defined as;

“...a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodelling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness” [172]

OA is a pro-inflammatory branch of rheumatic disease that effects synovial joints progressively and is caused by the failure of joint tissues to repair following damage. This damage may have been caused by stresses due to an abnormality in the

articular cartilage, subchondral bone, ligaments, menisci, periarticular muscles, peripheral nerves or synovium [173, 174]. While cartilage degradation is the traditionally structural trademark of OA, it is generally considered a whole joint disease with many other morphological features [175-178]. For example, an osteoarthritic joint may exhibit sclerosis in the subchondral bone, osteophytes [179], local inflammation such as synovitis [177, 178, 180, 181] and bone marrow lesions [182]. Failure of normal biological repair processes that leads to breakdown of cartilage and bone [183] is characterised by symptoms of pain, stiffness, functional disability [184] that can lead to negative impacts on fatigue, mood, sleep, overall quality of life [185, 186].

OA confers a number of modifiable and non-modifiable risk factors [174, 187]. Non-modifiable risk factors include previous joint injury [188, 189], malalignment and other mechanical factors [175, 176, 190-193], age [189], sex [194], ethnicity [195] and genetic predisposition [196-198]. Modifiable risk factors include obesity [181, 189, 199-202], metabolic syndrome [181, 203-206], in particular diabetes mellitus [207-209] and habitual diet [187, 210].

The condition is one of the most common causes of chronic pain and the most common cause of joint pain [211] with conservative estimates suggesting that there are approximately 500 million sufferers worldwide [167, 212]. OA affects ~13% of all over 50's [~7% in all ages; 213] and has no cure [214-218] while being the 11th highest contributor to years lived with disability [159].

3.1 Pain and osteoarthritis

Chronic inflammatory-associated pain can have multiple mechanisms [219-223] and can stem from mechanical stress or central sensitization either concurrently and/or vary in their influences over time [224]. Pain derived from OA can generally be characterised into two common clinical forms of pain, intermittent but severe/intense and persistent pain or aching [225]. These pain experiences can come from neuropathic and nociceptive process, as discussed above. The prevalence of neuropathic pain features at the knee in OA patients ranges from 19% to 29% [221, 226, 227]. However, recent studies of peripheral and central nerve sensitization [228], as well as nerve ending damage and regrowth [229, 230] have shown that neuropathic pain contributes substantially to the condition. This central sensitization is prominent in those that experience a high level of pain that is not proportional to radiographic evidence of structural damage [219] and contributes

more to the pain experienced in women with symptomatic OA, compared to men [231]. Generally, a higher degree of central sensitization or neuropathic pain is associated with high pain intensity and a greater chance of developing chronic pain following joint replacement [232, 233]. The remaining 70-80% of knee OA pain appears to be nociceptive in nature, thus OA can be described as a chronic mild to moderate nociceptive dominant pain condition [24, 234] and should be considered as such with regards to initial treatment [24].

The diversity of pathophysiological maladaptation in OA effected joints and the low associations of these changes with pain, suggests doubt over the link between joint structural condition and the experience of pain. This is evident from the poor relationship between radiographic images and reported pain. A recent systematic review showed that the prevalence of knee pain in patients with radiographic knee OA ranged from 15% to 81% [235]. However, some studies reported associations between the structural damage of the joint (cartilage and bone) and pain [236] but at higher levels of X-ray derived pathology [Kellgren/Lawrence grade; 237]. Nonetheless, pain may still indicate a level of disease activity. In a number of studies looking more specifically at joint morphological characterises, OA pain has been associated with the rate of medial cartilage loss [also after adjustment for radiographic OA stage; 238], osteophytes [239], more erosive OA compared to non-erosive OA [240] and changes of bone marrow lesions and synovitis [182]. These data show the complexity of the disease-pain nexus and suggests that the disease should, in the first instance (i.e. mild OA), be treated generally with lifestyle and nutritional intervention rather than pharmaceuticals that target specific pathological pathways (figure 1). [241]. Regardless, pharmaceutical therapies remain the main treatment for such conditions [242].

3.2 Pharmaceutical analgesics in Osteoarthritis

OA is a progressive condition with no cure where opioids, acetaminophen and non-steroidal anti-inflammatory drugs (NSAID) are the traditional, non-lifestyle, approach for early management. However, as eluded to earlier, these pharmaceutical treatments are often accompanied with significant side effects. For example, NSAIDs are the traditional approach for early clinical management of mild-to-moderate OA [241] and in the US 65% of all OA patients are prescribed NSAID for pain management - this is the current recommended strategy for OA clinical management by the leading authorities [243]. While some NSAIDs are effective at improving pain and physical function, they come with significant and

potentially harmful side effects such as gastrointestinal complications, renal disturbances and severe cardiovascular events [244]. Although some of these risks may be reduced using topical administration such as Diclofenac gel/cream [245, 246]. Two recent large-scale studies have shown that, depending on the particular medication, the risk of hospital admissions (due to heart failure) can be nearly two times greater [Ketorolac; 247] in OA/rheumatoid arthritis (n=24,081). ibuprofen (generally speaking, the most used NSAID) had the highest rates of NSAID toxicity [248].

Approximately 34% of OA patients use Paracetamol [249], in isolation or in combination with NSAIDs. In fact, the effectiveness of Paracetamol to improve pain management has recently been called into question [124], as it has been shown to be ineffective for treating OA pain [125, 250] and may have similar side effects as ibuprofen [251] particularly when consumed at higher doses [164]. Specifically, in knee or hip OA, a recent Cochrane review concluded that Paracetamol provides no clinically important improvements in pain in the immediate and short term [up to 12 weeks; 16]. In addition, a recent network meta-analysis (56 randomised controlled trials, 22 128 participants) suggests that paracetamol was least effective for the treatment of knee and or hip OA compared with celecoxib (NSAID) or the combination of glucosamine and chondroitin [117] – confirming other reports [252]. In contrast, some authors have concluded that paracetamol had similar efficacy to NSAIDs for the treatment of OA [253]. It is also important to remember that overuse of APAPs can cause liver injury, hepatotoxicity, mitochondrial toxicity [160, 161] which is relevant to a chronic condition with no known cure. These data led to confusion in earlier guidelines that consistently recommended the prescription of paracetamol (acetaminophen) as the first line analgesic for these conditions.[90, 91, 241, 254, 255]. However, the data are now relatively clear that there is little clinically meaningful effect of Paracetamol on OA pain [153, 154].

The potential negative effects such as addiction and the physiological side effects of opioid use are well documented, as discussed above, however they remain highly prescribed for OA and are expected to triple in the coming years [256, 257]. More than half of those prescribed opioids in the first year of OA have been shown to be inappropriately dispensed [257]. The prevalence of opioid use for OA ranges from 8-26% and in Australia, the use for knee/hip OA has been described “alarmingly high” [257]. A number of systematic reviews and meta-analysis have been performed in recent years and have unanimously shown that the tolerability is low,

efficacy for pain relief in OA is not clinically relevant and the potential harms are high [258-260]. Despite calls for guidelines to be changes on the use of opioids and the above-mentioned pharmaceuticals, their use is increasing (likely with the prevalence of the disease) and by proxy the negative consequences will rise in tandem. Therefore, non-pharmaceutical food-based alternatives (termed nutraceuticals;) have been developed and are beginning to be recommended as early intervention treatment [261-263] to improve OA symptoms including pain [241, 264-266].

4 Nutraceutical alternatives and reduction in pharmacological analgesics in osteoarthritis

Given the possible side-effects of pharmaceutical treatments, any reduction in their use is of particular importance to OA public health. As such, a number of non-pharmaceutical alternatives have been developed that may reduce the use/required dose of pharmaceuticals while maintaining or improving the impacts on OA pain and physical function. The majority of these alternatives are termed “nutraceuticals” (a portmanteau of the words “nutrition” and “pharmaceutical”), coined in 1989 by Dr Stephen DeFelice [267], founder and chairman of the Foundation for Innovation in Medicine.

While it is unlikely that Hippocrates (traditionally regarded as the father of modern medicine; died in 375 BCE) actually said: “Let food be your medicine and medicine your food” [268], this is often cited in the context of nutraceuticals. A more apt and legitimate quote defines the position of nutraceuticals in health and disease as “beyond diet, before drug”, coined by Ettore Novellino in 2012 [269].

There is currently no universally accepted definition of a nutraceutical [270], with the main confusion being the differences between nutraceuticals and functional foods, and the lack of regulatory definition between them [Table 1; 270, 271, 272, 273]. In fact, current European regulations do not distinguish between nutraceuticals and food supplements (see the EC Regulation n. 1924/2006 of the European Parliament and Council, recently updated by the UE regulation 2015/2283), therefore neither does the European Food Safety Authority [274, 275]. However, a number of proposed definitions exist (Table 1) and from these definitions, for the purposes of this chapter, a nutraceutical will be defined as; a naturally derived biological substance, not synthetically created, that preserve their

original active properties without chemical manipulation, can enhance health in dosages that exceed those that could be obtained from normal food digestion and has peer-reviewed scientific evidenced to base health claims.

Author(s)	Definition
[DeFelice, 267; coined in 1989]	“A nutraceutical is any substance that is a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease.”
[Zeisel, 271]	“.....as those diet supplements that deliver a concentrated form of a presumed bioactive agent from a food, presented in a non-food matrix, and used to enhance health in dosages that exceed those that could be obtained from normal food”
[U.S. Nutraceutical Research and Education 276]	“a dietary supplement, food or medical food that has a benefit, which prevents or reduces the risk of a disease or health condition, including the management of a disease or health condition or the improvement of health; and is safe for human consumption in the quantity, and with the frequency required to realize such properties”
[The European Nutraceutical Association, 277]	“are nutritional products that provide health and medical benefits, including the prevention and treatment of disease. In contrast to pharmaceuticals however, these are not synthetic substances or chemical compounds formulated for specific indications. These are products that contain nutrients (partly in concentrated form) and mostly are assigned to the category of food. Dietary supplements are a typical example for nutraceuticals, but also dietetic and functional foods may be counted among these products.”
[Health Canada, 278]	“A nutraceutical is a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with food. A nutraceutical is demonstrated to have a physiological benefit or provide protection against chronic disease”
[Corzo et al., 279]	“Nutraceuticals are biological substances extracted from natural sources by non-denaturing processes to preserve their original properties without any chemical manipulation.”

Table 1. Currently used definitions to describe nutraceuticals.

As such the following sections will discuss those nutraceuticals that are currently not in mainstream use but may have the potential to aid in treatment of OA (i.e. the well discussed Glucosamine and Chondroitin will not feature in this article) but are in regular use worldwide [280]. The identified nutraceuticals that have been directly compared to NSAID/analgesics with OA can be divided into three categories, defined by their origin, and are presented in Table 2;

- 1) Terrestrial Botanicals, compounds derived from 'land' plant sources (avocado/soybean, pine bark extract and turmeric/curcumin)
- 2) Marine Botanicals compounds derived from 'marine' plant sources (Lithothamnion species)
- 3) Marine Fauna, derived from marine animals (fish oil and green lipped mussel)

Proposed main active compound	Treatment regime	Effect on OA Analgesia and NSAID	Reference
Avocado/soybean unsaponifiables	Avocado/soybean unsaponifiables 300 mg or 600 mg ASU for 3 months	↓ NSAIDs and analgesics use by 50% vs placebo ↓ pain (~50%) in both 300 mg and 600 mg vs placebo	[281]
Avocado/soybean unsaponifiables	Piascledine/ASU (300 mg daily) for 6 months	↓ Participants using analgesics and NSAIDs (from 58.8% to 24.9%) ↓ Median pain (by ~50%) and pain intensity, pain at rest (by 100%) and pain during walking (by ~60%) ↓ Mobility score (by ~50%)	[282]
Avocado/soybean unsaponifiables	Avocado/soybean mixture, 300 mg daily orally versus celecoxib, 200 mg/day orally for 8 weeks	↓ Cartilage oligomeric matrix protein (COMP) in both groups (by ~37%, Avocado/soybean and ~27%, celecoxib), with no differences between groups	[283]
Fish oil/Urtica dioica	Phytalgic (fish-oil, vitamin E, Urtica dioica) 3 capsules daily for 12 weeks	↓ NSAIDs use vs the placebo (by ~60%) ↓ Analgesic use vs the placebo (BY ~40%) ↓ Pain (by ~37%), stiffness (by ~43%) and function (by ~40%) vs placebo	[284]
Green lipped mussel	600 mg of BioLex(R)-GLM extract daily or placebo for 12 weeks	↓ Paracetamol use (by ~30% post-trial) vs placebo ↓ Stiffness (by ~19%) vs placebo, no difference pain	[285]
Pine bark extract	Pycnogenol (pine bark extract) 100 mg for 3 months	↓ Use of drugs (by ~57%) vs placebo ↓ Gastrointestinal complications (by ~60%) vs placebo ↓ WOMAC score (by ~40%) vs placebo ↑ Walking distance (by ~34%), compared to no improvement in placebo	[286]
Turmeric	Turmeric extracts (2 g extracts/day) or ibuprofen (800 mg) for 0, 2, 4 and 6 weeks	↓ Pain on walking stairs vs ibuprofen (however, ibuprofen was greater at baseline thus throughout) No difference in pain on level walking, 100 m walking time or stair climb	[287]
Turmeric	Turmeric extracts (1500 mg extracts/day) or ibuprofen (1200 mg/day) for 4 weeks	↓ WOMAC score, pain and function compared to baseline scores at all time points, and was non-inferior to ibuprofen. ↓ Rate of abdominal pain/distention vs ibuprofen (by ~60%)	[288]
Curcumin	BCM-95® Curcumin: 500 mg/capsule twice daily, Curcumin 500 mg + diclofenac sodium 50 mg/capsule twice daily, diclofenac 50 mg/ capsule twice daily, all for 8 weeks	↓ Disease Activity Score (by ~45%), CRP (by ~52%), American College of Rheumatology score, improved pain (by ~60%), erythrocyte sedimentation rate (by ~11%), greater in Curcumin and Curcumin+ diclofenac vs diclofenac alone	[289]
Curcumin	BCM-95® (curcumin, demethoxycurcumin, bisdemethoxycurcumin, and volatile oils from turmeric rhizome), 500-mg three times daily versus diclofenac 50-mg tablet two times daily for 28 days	↓ Pain similar in both groups (by ~78% for both), no difference between groups ↑ KOOS variables (n=5) similar in both groups, no difference between groups ↑ Flatulence in diclofenac vs curcumin (by ~79%) ↓ Requirement for H2 blockers in curcumin vs diclofenac (by 100%, i.e. zero in curcumin) ↓ Incidence of adverse effects in curcumin vs diclofenac (by ~76%)	[290]
Curcumin	Longvida®, 800 mg patented lipophilic matrix delivering 160 mg curcumin versus Ibuprofen (400 mg) orally and daily for 12 weeks	↓ Pain in both (by ~60%), no difference between groups	[291]
Curcumin	Herbal formulation of curcumin (300mg), gingerols (7.5 mg), and piperine (3.75 mg; Mixodin) versus Naproxen 250 mg capsules, both twice a day for 4 weeks	↓ prostaglandin E2 (PGE2) in both groups with no difference between the two (~27 pg/mL)	[292]
Curcumin	Meriva tablets, a curcumin-phosphatidylcholine phytosome complex, 200 mg equivalent curcumin	↓ NSAIDs use (by ~80%) vs control ↓ Gastrointestinal complaints (by ~40%) vs control	[293]

	daily with best available care (BCA) compared to BCA only as control for 8 months	<p>↓ Pain (by ~44%), stiffness (by ~28%), physical function (by ~40%), WOMAC score (by ~41%), compared to no improvements in controls</p> <p>↑ Karnofsky Performance Scale (by ~22%), compared to no improvement in controls</p> <p>↑ Treadmill walking distance (345% increase from baseline) compared to 89% in controls</p> <p>↓ inflammatory markers sCD40L (by ~56%), IL-1β (by ~35%), IL-6 (by ~27%), sVCAM-1 (by ~30%), ESR (by ~25%), compared to no change in controls</p>	
Curcumin	Theracurmin® (10% of curcumin, 2% other curcuminoids such as demethoxycurcumin and isdemethoxycurcumin, 46% glycerin, 4% gum ghatti, and 38% of water; 180 mg of curcumin) for 8 weeks	<p>↓ NSAID (celecoxib) dependence (p=0.0252)</p> <p>↓ Pain (by ~55%) vs placebo</p>	[294]
Curcumin	C3 complex, 500 mg curcuminoid capsules including 5 mg Bioperine, 3 times daily for 6 weeks	<p>↓ Naproxen use (by ~73%) vs controls</p> <p>↓ Pain (by >38%), function (by ~41%) and WOMAC score (by ~41%) vs placebo</p>	[295]
Ginger	Topical ginger extract gel (4% gel Plygersic) versus sodium diclofenac gel applied 1 mL of solution 4 times a day for 6 weeks	<p>↓ Pain (by ~27%), symptoms (by ~27%)</p> <p>No difference in the above between groups</p>	[296]
Ginger	Diclofenac 50 mg orally or Ginger 750 or Ginger 750 mg and Diclofenac 50 mg orally for 12 weeks	<p>↓ Pain and WOMAC score in all three groups, greatest improvement with Ginger (60%; 75%) the addition of ginger to Diclofenac (67%; 79%), compared to Diclofenac alone (59%; 64%)</p> <p>↓ Use of rescue medication (paracetamol) in Ginger (50%) and Ginger with Diclofenac (87%) compared to Diclofenac alone (not statistically significant)</p>	[297]
Lithothamnion species (Red Algae)	AquaminF, 267 mg Lithothamnion, 3 capsules per day, 3 times a day for 12 weeks	<p>↑ ROM (by 5.2°) and 6MWD (By 136 ft) following 50% forced reduction from all NSAID in AquaminF vs placebo</p> <p>No difference in rescue medication (acetaminophen) consumption between groups</p> <p>↑ Six meter walking distance (by~92%) following 50% forced reduction from all NSAID in AquaminF vs placebo</p>	[298]
Lithothamnion species combination	Aquamin+, 2668 mg Lithothamnion, 268 mg seawater-derived Mg(OH) ₂ and pine bark extract 120 mg versus 2000 mg Glucosamine Sulphate Daily dose for 12 weeks	<p>↓ Pain (by ~11%), symptoms (by ~7%), no change in Glucosamine</p> <p>↑ Sport and recreation (by ~9%), no change in Glucosamine</p> <p>↑ Timed up and go performance (by 7%), no change in Glucosamine</p> <p>↓ Rescue analgesic use (by 72%) vs Glucosamine</p>	[299]

Table 1 Nutraceuticals shown to reduce analgesic and NSAID use.

4.1 Terrestrial Botanicals

Turmeric/curcumin extracts (spices used mainly in South Asian cooking) or nutraceuticals combinations where turmeric/curcumin extracts are the main active ingredient, have the greatest amount evidence for improving OA symptoms, with some recent data on NSAID and analgesics use [Table 2; 300]. Two studies have directly compared raw turmeric/curcumin extracts to NSAIDs and their effectiveness for OA symptoms [287, 288]. These data show that turmeric extracts either improved or were shown to be non-inferior for knee osteoarthritis (KOA) pain, pain during stair walking and resulted in less side effects (particularly the rate of abdominal pain/distention) compared to oral ibuprofen [287-289]. Furthermore, patented/propriety formulations of turmeric/curcumin extracts have been developed around the world and show some promising effects on OA (Table 2). Interestingly, Chandran et al demonstrated that curcumin formulated as BCM-95® or BCM-95® + diclofenac sodium showed superior ‘Disease Activity Scores’, American College of Rheumatology score, pain, CRP levels and erythrocyte sedimentation rate, compared to diclofenac alone [Indian population; 289]. The same formulation showed similar improvements of KOOS variables, but BCM-95® resulted in less adverse events (including flatulence) and a lower requirements for H2 blockers (0% vs 28%; a group of medicines that reduce the amount of acid produced by the cells in the lining of the stomach), compared to diclofenac [290]. In the longest of these studies (8 months in a European cohort), the addition of Meriva® (curcuminoids 20%, phosphatidylcholine 40%, and microcrystalline cellulose 40%) to the “best available treatment”, reduced NSAID and analgesia use by 63% compared to the control group (“best available treatment” only). This reduction resulted in less side-effects between 45-67%, depending on the specific adverse advent, compared to control group [2-12%; 293]. Similarly, an alternative preparation (C3 complex®; Curcuminoids 500-mg capsules with 5-mg Bioperine®) reduced the use of naproxen by 84% (compared to 19% in placebo) in Iranian KOA patients and a further alternative (Theracurmin®; 10% of curcumin, 2% other curcuminoids such as demethoxycurcumin and isdemethoxycurcumin, 46% glycerin, 4% gum ghatti, and 38% of water; 180 mg of curcumin) reduced dependence on celecoxib in Japanese KOA patients [from ~70% to ~30% versus ~80 to ~60% in placebo; 294]. Recently, Heidari-Beni et al. [301] presented findings from a herbal formulation containing curcumin (300 mg), gingerols (7.5 mg) and piperine (3.75 mg), taken twice a day for 4 weeks. This formulation reduced PGE₂ (see above text and Figure 1) of KOA patients to the same extent as Naproxen (250

mg capsules daily). There is significant mechanistic evidence to support these *in vivo* therapeutic effects. Turmeric/curcumin extracts have been shown to reduce proinflammatory cytokines such as tumour necrosis factor alpha, interleukin (IL)-1 beta, IL-8, IL-6 and structural degradation proteases such as matrix metalloproteinases, collagenase, induce positive cell behavioural characteristics (induces apoptosis and growth arrest) and anti-oxidative properties (through stimulation of nuclear factor-erythroid-2-related factor 2 (Nrf2) [292, 302-311]. Of particular interest to the present chapter, turmeric/curcumin extracts inhibit the NFkB pathway and other proinflammatory signalling pathways including COX-2, AP-1, Egr-1, STAT (signal transducers and activators of transcription) and mitogen-activated protein (MAP) kinases [309, 310, 312]. Considering these molecular targets, turmeric/curcumin extracts appear to enact their *in vivo* effects via similar mechanisms of action as commonly used pharmaceutical agents (Figure 1). These data clearly point to the positive impact that turmeric/curcumin extracts, including propriety formulations, can have on NSAID and analgesia use in the short term (best effects from study durations generally ≤ 12 weeks). While the long-term benefits are still being investigated the current data suggests that turmeric/curcumin extracts could be recommended as an early stage treatment adjunct.

Alternative terrestrial botanicals have shown some advantages for OA. Three studies have investigated avocado/soybean extracts and their potential in reducing NSAID and analgesics use. One large randomised control trial (n=260) showed that after 30 days (and continued to day 90) of supplementation, the extracts (300 or 600mg) reduced the daily intake of NSAID and analgesics compared to placebo. Furthermore, 71% (compared to 36% in placebo) of avocado/soybean extract participants reduced their daily intake by greater than 50%, [281]. Although it must be noted that the treatment was stopped in nine participants due to adverse events from the extract, however the authors did not statistically analyse incidence of adverse events of the remaining participants, but they were generally similar to placebo. These results were somewhat supported by a smaller (n=31; part of a large cohort receiving a number of nutraceutical compounds) observational study showing that the proportion of OA patients using analgesics and NSAIDs dropped by 34% over 6 months consuming avocado/soybean extracts [282]. Although, in this large scale “real-world” (PEGASus) study cohort where analgesic and NSAID use was assessed by phone interview bi-monthly over 2 years, avocado/soybean extracts showed no effect on reducing medication use [313]. Recently, a 2-month supplementation of avocado/soybean unsaponifiables (n=30; 300 mg daily) was

compared to celecoxib (n=30; 200 mg/day) for changes in a biomarker of cartilage breakdown (Cartilage oligomeric matrix protein; COMP). The results showed that both interventions reduced serum COMP levels with a tendency for greater improvements with avocado/soybean unsaponifiables [33.8% vs. 30.3%; p=0.06; 283]. These data in addition to other mechanistic work show that avocado/soybean unsaponifiables can affect both inflammatory and structural protein biomarkers of OA pathology. Specifically they can inhibit IL-1, reduce production of stromelysin, IL-6, IL-8 and PGE-2, increase the expression of TGF- β and activate collagen synthesis [283, 314-316]. There is some debate over the efficacy of avocado/soybean extracts to alleviate analgesics and NSAID use but there is developing molecular evidence that they may elicit similar reductions on *in vivo* cartilage breakdown which requires further investigation.

Two studies investigated Ginger root extract formulations in OA NSAID use. Compared to 1% diclofenac gel, topical ginger extract (Plygersic gel) reduce KOOS variables (pain symptoms etc.) equally after a six week intervention in mild radiographic KOA [296]. Further, oral consumption of a Ginger root extract formulation, compared 1) 50 mg of oral Diclofenac with Ginger 750, 2) Ginger 750 mg and 3) Diclofenac 50 mg for 12 weeks [297]. All interventions decreased pain and WOMAC variables but there was a reduction in rescue medication in the ginger groups, although this was not statically significant [297]. While these results are interesting, significantly more research is needed with larger more well controlled studies but there is molecular evidence to support these reported effects. Ginger root species has can block the formation of inflammatory mediators such as thromboxane, leukotrienes and prostaglandins and inhibit COX and lipoxygenase in arachidonic acid metabolism [317-325] i.e. similar mechanisms to those presented in Figure 1.

Finally, the trade marked Pycnogenol® (pine bark extract; 100mg) has been shown to reduces NSAID use by 58%, compared to only 1% in the placebo group in early-KOA patients over a 12 week [286]. This resulted in reduced hospital admissions and days spent in hospital by 50% compared to placebo [n=156; 286]. As with the above, Pycnogenol inhibits activation of NF κ B pathway mediators, particularly, COX and pain-producing prostaglandins and also active metabolomic compounds with anti-inflammatory bio-efficacy [326-328]. Again, these data are interesting and demonstrate good potential but require further *in vivo* replication in relation to NSAID and analgesic.

4.2 Marine Fauna

New Zealand Green Lipped Mussel (*Perna canaliculus*) lipid extracts have recently been investigated for their potentially benefits for OA symptoms. Moderate-to-severe hip and knee OA patients received 600 mg of Biolex®-GLM for 12 weeks or a placebo and were allowed to consume paracetamol for additional pain relief [285]. Participants consuming the placebo took more paracetamol each week of the 12 weeks resulting in a statically significant change at the final week ($p=0.001$), however did not differ in NSAID equivalence score. This suggests that there may be some potential for Green Lipped Mussel to reduce analgesic medication, although less so than others mentioned herein. Again, Green Lipped Mussel appears to inhibit COX enzymes, competitive inhibition of arachidonic acid metabolism and reduce chronic inflammation [329].

A fish oil and *Urtica dioica* preparation has also been shown to reduce medication use in OA. A proprietary combination of omega-3 and omega-6 fatty acids, *Urtica dioica* (the common nettle), zinc and vitamin E (Phytalgic®) progressively reduced NSAID and analgesia use over a three month period [$n=81$; 6.5 Paracetamol 500 mg-Equivalent per week, compared to 16.5 in the placebo group; 284]. The authors ascribed this adaptation to the anti-inflammatory potential of the mineral composition, mainly from *Urtica dioica* within the formulation rather than the fish oil component [284]. This was most likely the case as a previous study showed no effect of cod liver oil on OA [330] and articles referenced to show a mechanistic potential for fish oil components (n-3 and n-6 polyunsaturated fatty acids) have recently been retracted [331, 332].

4.3 Marine Botanicals

The marine red Algae species *Lithothamnion corallioides*, rich in sea water derived minerals including Calcium and Magnesium (AquaminF®), have recently been investigated for a potential impact on NSAID usage. In a randomised control trial of moderate-to-severe KOA patients that were regularly consuming NSAIDs, AquaminF (534 mg daily) was an effective agent for improving physical performance (six minuet walking distance), when NSAID use was intentionally reduced to 50% of previous consumption, but not when NSAID consumption was reduced to zero [298]. Furthermore, *Lithothamnion* (2668 mg) combined with seawater-derived $Mg(OH)_2$ (268 mg) and pine bark extract (120 mg) reduced analgesic and NSAID use by 72% compared to Glucosamine Sulphate (2000 mg

Daily dose)[299]. Mechanistically, Lithothamnion corallioides species appear to have the ability to inhibit the NFκB pathway, reduce inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) and COX2, along with reduced serum TNF-α [333-336]. This suggested there is potential for Lithothamnion species to reduce the KOA-related drug dependency *in vivo* with mechanistic rationale similar to that of pharmaceuticals (Figure 1). It appears as though Lithothamnion species have the ability to improve physical function and analgesia with reduced NSAID use with reduce further reduction in drug use when combined with other nutraceuticals previously shown to reduce NSAID use. With larger scale replication and confirmation, Lithothamnion species could develop into a recommended early stage treatment adjunct.

5 Discussion and conclusions

These data are of considerable interest to those suffering from OA and medical practitioners concerned with the broader health impacts of pharmaceuticals use in OA patients. There appears to be a growing body of evidence suggesting that a variety of nutraceutical compounds, many in preparatory formulations, could provide some relief from the burden of NSAID and analgesic dependence, thus their associated short-term side-effects. However, currently the data is limited with respect to replication, sample size and duration, making conclusions about long term effectiveness difficult. The one potential exception is turmeric/curcumin extracts that in a recent meta-analysis was shown that typically 1000 mg/day of curcumin to be effective for improve OA symptoms (potentially better than NSAID) over 8-12 weeks - but the authors still call for significantly more research, specifically with increased sample size and better design quality [300].

While the precise molecular mechanisms of OA progression remain unclear, it appears to be exacerbated by the activation of NFκB signalling pathway, initiated by a host of mechanical and chemical stress stimuli, including excessive mechanical stress brought about by surplus body mass, proinflammatory cytokines and extracellular matrix degradation products [337, 338]. These actions reduce the amount of articular cartilage in the joints and degrade subchondral bone, thus induce pain and difficulty in movements. As a result, OA treatments focus on relieving pain and swelling, improving joint mobility, increasing musculoskeletal strength and minimizing the disabling effects of the disease [339]. The NFκB signalling pathway and inflammatory mechanisms appear to be the molecular

actions of the majority of the above nutraceuticals in combination with the inhibition of COX enzymes. These imply that their mechanism of action for pain relief (and therefore potential reduction in analgesic use) are via peripheral nociceptive action with little interaction through neuropathic mechanisms (unless through local inflammatory assault of nerve fibres).

As discussed throughout, there appears to be even further benefit through the combinations of nutraceuticals that may have an additive effects to reduce NSAID/analgesic use and are recommended [263]. However, additional work needs to be carried out to understand the individual effects of these combinations in addition to the synergistic impact. This requirement is evident through the work by Jacquet et al. [284] where it appears that the proposed benefit of the combination was not attributable to the ingredient that is mentioned and discussed firstly (fish oil), rather the benefit lies with *Urtica dioica* and mineral composition. These combinations are often proprietary formulations where the precise combination will not be shared. However, where this is not the case this can be achieved through *in vitro* experimentation to elucidate the mechanisms of action both individually and combined.

In conclusion, this chapter has described and discussed chronic pain, specifically osteoarthritis, and presented evidence that specific nutraceuticals and combinations have potential to either elicit the same pain relieving effect of NSAIDs and analgesics or reduce the dependency on these drugs. Specifically, the greatest evidence exists for the inclusion of turmeric/curcumin extracts as an mild-OA treatment adjunct to reduce NSAID consumption. Any reduction in the use of harmful pharmaceutical drugs should be a welcome inclusion to any treatment plan with some nutraceuticals, that appear to interact with similar molecular pathways as the discussed analgesics, may be capable of offering such benefit. However, it must be noted that significantly more experimental evidence is required for a number of these formulations before specific recommendations can be made.

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7 Conflict of Interests

The authors declare no conflict of interest.

8 References

1. Del Giorno R, Frumento P, Varrassi G, Paladini A, Coaccioli S. Assessment of chronic pain and access to pain therapy: a cross-sectional population-based study. *Journal of pain research*. 2017;10:2577-84.
2. Rekatsina M, Paladini A, Piroli A, Zis P, Pergolizzi JV, Varrassi G. Pathophysiologic Approach to Pain Therapy for Complex Pain Entities: A Narrative Review. *Pain and therapy*. 2020;9(1):7-21.
3. Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain*. 2019;160(1):19-27.
4. Cáceres-Matos R, Gil-García E, Cabrera-León A, Porcel-Gálvez AM, Barrientos-Trigo S. Factors that influence coping with chronic noncancer pain in European countries: a systematic review of measuring instruments. *Pain Management Nursing*. 2020;21(2):123-33.
5. Analysts GI. Global pain management market to reach US \$60 billion by 2015 <https://www.prweb.com/releases/2011/1/prweb8052240.htm>: Cision; 2011 [Available from: <https://www.prweb.com/releases/2011/1/prweb8052240.htm>].
6. Bushnell MC, Čeko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nature Reviews Neuroscience*. 2013;14(7):502-11.
7. Cabrera-León A, Rueda M, Cantero-Braojos M. Calibrated prevalence of disabling chronic pain according to different approaches: a face-to-face cross-sectional population-based study in Southern Spain. *British Medical Journal Open*. 2017;7(1).
8. Leadley RM, Armstrong N, Lee YC, Allen A, Kleijnen J. Chronic diseases in the European Union: the prevalence and health cost implications of chronic pain. *Journal of Pain and Palliative Care Pharmacotherapy*. 2012;26(4):310-25.
9. Reid KJ, Harker J, Bala MM, Truyers C, Kellen E, Bekkering GE, et al. Epidemiology of chronic non-cancer pain in Europe: narrative review of prevalence, pain treatments and pain impact. *Current medical research and opinion*. 2011;27(2):449-62.
10. Torralba A, Miquel A, Darba J. Situación actual del dolor crónico en España: iniciativa "Pain Proposal". *Revista de la Sociedad Española del Dolor*. 2014;21(1):16-22.
11. Gaskin DJ, Richard P. The economic costs of pain in the United States. *The Journal of Pain*. 2012;13(8):715-24.
12. Nicholas M, Vlaeyen JWS, Rief W, Barke A, Aziz Q, Benoliel R, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain*. 2019;160(1):28-37.
13. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. *Pain*. 2015;156(6):1003-7.
14. Haack M, Simpson N, Sethna N, Kaur S, Mullington J. Sleep deficiency and chronic pain: potential underlying mechanisms and clinical implications. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2020;45(1):205-16.

15. Brune K, Patrignani P. New insights into the use of currently available non-steroidal anti-inflammatory drugs. *Journal of pain research*. 2015;8:105-18.
16. McCarberg BH, Nicholson BD, Todd KH, Palmer T, Penles L. The impact of pain on quality of life and the unmet needs of pain management: results from pain sufferers and physicians participating in an Internet survey. *American journal of therapeutics*. 2008;15(4):312-20.
17. Rittner HL, Brack A, Stein C. Pain and the immune system. *British journal of anaesthesia*. 2008;101(1):40-4.
18. Stein C. Opioids, sensory systems and chronic pain. *European journal of pharmacology*. 2013;716(1-3):179-87.
19. Stein C. Opioid Receptors. *Annual review of medicine*. 2016;67:433-51.
20. Carnes D, Parsons S, Ashby D, Breen A, Foster NE, Pincus T, et al. Chronic musculoskeletal pain rarely presents in a single body site: results from a UK population study. *Rheumatology*. 2007;46(7):1168-70.
21. Kosek E, Cohen M, Baron R, Gebhart GF, Mico JA, Rice AS, et al. Do we need a third mechanistic descriptor for chronic pain states? *Pain*. 2016;157(7):1382-6.
22. Morrone LA, Scuteri D, Rombolà L, Mizoguchi H, Baggotta G. Opioids Resistance in Chronic Pain Management. *Curr Neuropharmacol*. 2017;15(3):444-56.
23. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annual review of neuroscience*. 2009;32:1-32.
24. McAlindon TE, Driban JB, Henrotin Y, Hunter DJ, Jiang GL, Skou ST, et al. OARS Clinical Trials Recommendations: Design, conduct, and reporting of clinical trials for knee osteoarthritis. *Osteoarthritis and cartilage*. 2015;23(5):747-60.
25. Baron R, Hans G, Dickenson AH. Peripheral input and its importance for central sensitization. *Annals of neurology*. 2013;74(5):630-6.
26. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell*. 2009;139(2):267-84.
27. Corder G, Castro DC, Bruchas MR, Scherrer G. Endogenous and Exogenous Opioids in Pain. *Annual review of neuroscience*. 2018;41:453-73.
28. Ji RR, Chamesian A, Zhang YQ. Pain regulation by non-neuronal cells and inflammation. *Science (New York, NY)*. 2016;354(6312):572-7.
29. Chen L, Yang G, Grosser T. Prostanoids and inflammatory pain. *Prostaglandins & other lipid mediators*. 2013;104-105:58-66.
30. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *The Journal of Pain*. 2009;10(9):895-926.
31. Descalzi G, Kim S, Zhuo M. Presynaptic and postsynaptic cortical mechanisms of chronic pain. *Molecular neurobiology*. 2009;40(3):253-9.
32. Peirs C, Seal RP. Neural circuits for pain: Recent advances and current views. *Science (New York, NY)*. 2016;354(6312):578-84.
33. Almeida TF, Roizenblatt S, Tufik S. Afferent pain pathways: a neuroanatomical review. *Brain research*. 2004;1000(1-2):40-56.
34. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice AS, et al. A new definition of neuropathic pain. *Pain*. 2011;152(10):2204-5.

35. Kuner R, Flor H. Structural plasticity and reorganisation in chronic pain. *Nature Reviews Neuroscience*. 2016;18(1):20-30.
36. White FA, Jung H, Miller RJ. Chemokines and the pathophysiology of neuropathic pain. *Proceedings of the National Academy of Sciences of the United States of America*. 2007;104(51):20151-8.
37. Rowbotham MC, Yosipovitch G, Connolly MK, Finlay D, Forde G, Fields HL. Cutaneous innervation density in the allodynic form of postherpetic neuralgia. *Neurobiology of disease*. 1996;3(3):205-14.
38. Ochoa JL, Campero M, Serra J, Bostock H. Hyperexcitable polymodal and insensitive nociceptors in painful human neuropathy. *Muscle and Nerve*. 2005;32(4):459-72.
39. Reichling DB, Levine JD. Critical role of nociceptor plasticity in chronic pain. *Trends in neurosciences*. 2009;32(12):611-8.
40. Ratté S, Prescott SA. Afferent hyperexcitability in neuropathic pain and the inconvenient truth about its degeneracy. *Current opinion in neurobiology*. 2016;36:31-7.
41. Novakovic SD, Tzoumaka E, McGivern JG, Haraguchi M, Sangameswaran L, Gogas KR, et al. Distribution of the tetrodotoxin-resistant sodium channel PN3 in rat sensory neurons in normal and neuropathic conditions. *The Journal of Neuroscience* 1998;18(6):2174-87.
42. Bridges D, Thompson SW, Rice AS. Mechanisms of neuropathic pain. *British journal of anaesthesia*. 2001;87(1):12-26.
43. Gaudet AD, Popovich PG, Ramer MS. Wallerian degeneration: gaining perspective on inflammatory events after peripheral nerve injury. *Journal of neuroinflammation*. 2011;8:110.
44. Huang LY, Gu Y, Chen Y. Communication between neuronal somata and satellite glial cells in sensory ganglia. *Glia*. 2013;61(10):1571-81.
45. McLachlan EM, Jänig W, Devor M, Michaelis M. Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. *Nature*. 1993;363(6429):543-6.
46. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet (London, England)*. 1999;353(9168):1959-64.
47. Sandkühler J. Models and mechanisms of hyperalgesia and allodynia. *Physiological reviews*. 2009;89(2):707-58.
48. Study RE, Kral MG. Spontaneous action potential activity in isolated dorsal root ganglion neurons from rats with a painful neuropathy. *Pain*. 1996;65(2-3):235-42.
49. Gracely RH, Lynch SA, Bennett GJ. Painful neuropathy: altered central processing maintained dynamically by peripheral input. *Pain*. 1992;51(2):175-94.
50. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature*. 1983;306(5944):686-8.
51. Loeser JD, Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. *Pain*. 2008;137(3):473-7.
52. Ji RR, Berta T, Nedergaard M. Glia and pain: is chronic pain a gliopathy? *Pain*. 2013;154 Suppl 1(0 1):S10-28.

53. Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature*. 1992;355(6355):75-8.
54. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis and rheumatism*. 1991;34.
55. Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. *Neurobiology of disease*. 1998;5(4):209-27.
56. Meacham K, Shepherd A, Mohapatra DP, Haroutounian S. Neuropathic Pain: Central vs. Peripheral Mechanisms. *Current Pain and Headache Reports*. 2017;21(6):28.
57. Mickle AD, Shepherd AJ, Mohapatra DP. Sensory TRP channels: the key transducers of nociception and pain. *Progress in molecular biology and translational science*. 2015;131:73-118.
58. Varrassi G, Pergolizzi J, Peppin JF, Paladini A. Analgesic drugs and cardiac safety. *Brain and Heart Dynamics*. 2020:649-70.
59. Strang J, Volkow ND, Degenhardt L, Hickman M, Johnson K, Koob GF, et al. Opioid Use Disorder. *Nature Reviews Disease Primers*. 2020;6(1):3.
60. Stein C, Hassan AH, Przewlocki R, Gramsch C, Peter K, Herz A. Opioids from immunocytes interact with receptors on sensory nerves to inhibit nociception in inflammation. *Proceedings of the National Academy of Sciences of the United States of America*. 1990;87(15):5935-9.
61. Stein C. Peripheral mechanisms of opioid analgesia. *Anesthesia and analgesia*. 1993;76(1):182-91.
62. Snyder SH. Opiate receptors and beyond: 30 years of neural signaling research. *Neuropharmacology*. 2004;47 Suppl 1:274-85.
63. Waldhoer M, Bartlett SE, Whistler JL. Opioid receptors. *Annual review of biochemistry*. 2004;73:953-90.
64. Yaksh TL. Pharmacology and mechanisms of opioid analgesic activity. *Acta anaesthesiologica Scandinavica*. 1997;41(1 Pt 2):94-111.
65. Pert CB, Snyder SH. Opiate receptor: demonstration in nervous tissue. *Science (New York, NY)*. 1973;179(4077):1011-4.
66. Hemmings HC, Hopkins PM. *Foundations of anesthesia: basic sciences for clinical practice*: Elsevier Health Sciences; 2006.
67. Stein C. The control of pain in peripheral tissue by opioids. *The New England journal of medicine*. 1995;332(25):1685-90.
68. Hassan AH, Ableitner A, Stein C, Herz A. Inflammation of the rat paw enhances axonal transport of opioid receptors in the sciatic nerve and increases their density in the inflamed tissue. *Neuroscience*. 1993;55(1):185-95.
69. Zollner C, Shaqura MA, Bopaiah CP, Mousa S, Stein C, Schafer M. Painful inflammation-induced increase in mu-opioid receptor binding and G-protein coupling in primary afferent neurons. *Molecular pharmacology*. 2003;64(2):202-10.
70. Mousa SA, Cheppudira BP, Shaqura M, Fischer O, Hofmann J, Hellweg R, et al. Nerve growth factor governs the enhanced ability of opioids to suppress inflammatory pain. *Brain : a journal of neurology*. 2007;130(Pt 2):502-13.

71. Jeanjean AP, Moussaoui SM, Maloteaux JM, Laduron PM. Interleukin-1 beta induces long-term increase of axonally transported opiate receptors and substance P. *Neuroscience*. 1995;68(1):151-7.
72. Zhou L, Zhang Q, Stein C, Schäfer M. Contribution of opioid receptors on primary afferent versus sympathetic neurons to peripheral opioid analgesia. *The Journal of pharmacology and experimental therapeutics*. 1998;286(2):1000-6.
73. Martin WR. Pharmacology of opioids. *Pharmacological reviews*. 1983;35(4):283-323.
74. Sharp B, Yaksh T. Pain killers of the immune system. *Nature medicine*. 1997;3(8):831-2.
75. Reinecke H, Weber C, Lange K, Simon M, Stein C, Sorgatz H. Analgesic efficacy of opioids in chronic pain: recent meta-analyses. *British journal of pharmacology*. 2015;172(2):324-33.
76. Paulozzi LJ. Prescription drug overdoses: a review. *Journal of safety research*. 2012;43(4):283-9.
77. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*. 2015;156(4):569-76.
78. Chou R, Cruciani RA, Fiellin DA, Compton P, Farrar JT, Haigney MC, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. *The Journal of Pain*. 2014;15(4):321-37.
79. Sacerdote P. Opioid-induced immunosuppression. *Current opinion in supportive and palliative care*. 2008;2(1):14-8.
80. Sacerdote P, Bianchi M, Gaspani L, Manfredi B, Maucione A, Terno G, et al. The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. *Anesthesia and analgesia*. 2000;90(6):1411-4.
81. Wei LN. The RNA superhighway: axonal RNA trafficking of kappa opioid receptor mRNA for neurite growth. *Integr Biol*. 2011;3(1):10-6.
82. Stein C, Küchler S. Non-analgesic effects of opioids: peripheral opioid effects on inflammation and wound healing. *Current pharmaceutical design*. 2012;18(37):6053-69.
83. Schumacher M, Basbaum A, Way W. Opioid analgesics and antagonists. 9th ed. New York: Lange Medical Books/McGraw-Hill; 2004. 497-516 p.
84. Mesgarpour B, Griebler U, Glechner A, Kien C, Strobelberger M, Van Noord MG, et al. Extended-release opioids in the management of cancer pain: a systematic review of efficacy and safety. *European journal of pain (London, England)*. 2014;18(5):605-16.
85. Drewes AM, Jensen RD, Nielsen LM, Droney J, Christrup LL, Arendt-Nielsen L, et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. *British journal of clinical pharmacology*. 2013;75(1):60-78.
86. Nestler EJ, Berhow MT, Brodtkin ES. Molecular mechanisms of drug addiction: adaptations in signal transduction pathways. *Molecular psychiatry*. 1996;1(3):190-9.
87. Galer BS, Lee D, Ma T, Nagle B, Schlagheck TG. Morphidex (morphine sulfate/dextromethorphan hydrobromide combination) in the treatment of

chronic pain: three multicenter, randomized, double-blind, controlled clinical trials fail to demonstrate enhanced opioid analgesia or reduction in tolerance. *Pain*. 2005;115(3):284-95.

88. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. *The Cochrane database of systematic reviews*. 2010;2010(1):Cd006605.

89. Gustavsson A, Bjorkman J, Ljungcrantz C, Rhodin A, Rivano-Fischer M, Sjolund KF, et al. Pharmaceutical treatment patterns for patients with a diagnosis related to chronic pain initiating a slow-release strong opioid treatment in Sweden. *Pain*. 2012;153(12):2325-31.

90. Chou R, Qaseem A, Snow V, Casey D, Cross JT, Jr., Shekelle P, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Annals of internal medicine*. 2007;147(7):478-91.

91. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2012;64(4):465-74.

92. Gellad WF, Good CB, Shulkin DJ. Addressing the Opioid Epidemic in the United States: Lessons From the Department of Veterans Affairs Addressing the Opioid Epidemic in the United States Addressing the Opioid Epidemic in the United States. *Journal of the American Medical Association: Internal Medicine*. 2017;177(5):611.

93. Atchison JW, Herndon CM, Rusie E. NSAIDs for musculoskeletal pain management: current perspectives and novel strategies to improve safety. *Journal of Managed Care Pharmacy*. 2013;19(9 Suppl A):S3-19.

94. Gomez-Acebo I, Dierssen-Sotos T, de Pedro M, Perez-Gomez B, Castano-Vinyals G, Fernandez-Villa T, et al. Epidemiology of non-steroidal anti-inflammatory drugs consumption in Spain. The MCC-Spain study. *BMC Public Health*. 2018;18(1):1134.

95. Davis JS, Lee HY, Kim J, Advani SM, Peng HL, Banfield E, et al. Use of non-steroidal anti-inflammatory drugs in US adults: changes over time and by demographic. *Open Heart*. 2017;4(1):e000550.

96. Nelson DA, Marks ES, Deuster PA, O'Connor FG, Kurina LM. Association of Nonsteroidal Anti-inflammatory Drug Prescriptions With Kidney Disease Among Active Young and Middle-aged Adults. *JAMA Network Open*. 2019;2(2):e187896.

97. Walker LA, Zambraski EJ, Williams RF. Widespread Use of Prescription Nonsteroidal Anti-Inflammatory Drugs Among U.S. Army Active Duty Soldiers. *Military medicine*. 2017;182(3):e1709-e12.

98. Gorski T, Cadore EL, Pinto SS, da Silva EM, Correa CS, Beltrami FG, et al. Use of NSAIDs in triathletes: prevalence, level of awareness and reasons for use. *British journal of sports medicine*. 2011;45(2):85-90.

99. Küster M, Renner B, Oppel P, Niederweis U, Brune K. Consumption of analgesics before a marathon and the incidence of cardiovascular, gastrointestinal and renal problems: a cohort study. *British Medical Journal Open*. 2013;3(4).

100. Zhou Y, Boudreau DM, Freedman AN. Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. population. *Pharmacoepidemiology and drug safety*. 2014;23(1):43-50.
101. Grosser T, Theken KN, FitzGerald GA. Cyclooxygenase Inhibition: Pain, Inflammation, and the Cardiovascular System. *Clinical pharmacology and therapeutics*. 2017;102(4):611-22.
102. Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB Journal* 2008;22(2):383-90.
103. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. *Arteriosclerosis, thrombosis, and vascular biology*. 2011;31(5):986-1000.
104. Smyth EM, Grosser T, Wang M, Yu Y, FitzGerald GA. Prostanoids in health and disease. *Journal of lipid research*. 2009;50 Suppl(Suppl):S423-8.
105. Rao P, Knaus EE. Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond. *Journal of Pharmacy and Pharmaceutical Sciences*. 2008;11(2):81s-110s.
106. Simmons DL, Botting RM, Hla T. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. *Pharmacological reviews*. 2004;56(3):387-437.
107. Murata T, Ushikubi F, Matsuoka T, Hirata M, Yamasaki A, Sugimoto Y, et al. Altered pain perception and inflammatory response in mice lacking prostacyclin receptor. *Nature*. 1997;388(6643):678-82.
108. Lazarus M, Yoshida K, Coppari R, Bass CE, Mochizuki T, Lowell BB, et al. EP3 prostaglandin receptors in the median preoptic nucleus are critical for fever responses. *Nature neuroscience*. 2007;10(9):1131-3.
109. Patrignani P, Tacconelli S, Bruno A, Sostres C, Lanas A. Managing the adverse effects of nonsteroidal anti-inflammatory drugs. *Expert review of clinical pharmacology*. 2011;4(5):605-21.
110. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet (London, England)*. 2013;382(9894):769-79.
111. Castellsague J, Riera-Guardia N, Calingaert B, Varas-Lorenzo C, Fourrier-Reglat A, Nicotra F, et al. Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). *Drug safety*. 2012;35(12):1127-46.
112. Odom DM, Mladsi DM, Saag KG, Sherif BN, Miles L, Ronquest N, et al. Relationship between diclofenac dose and risk of gastrointestinal and cardiovascular events: meta-regression based on two systematic literature reviews. *Clinical therapeutics*. 2014;36(6):906-17.
113. Van Hecken A, Schwartz JI, Depré M, De Lepeleire I, Dallob A, Tanaka W, et al. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on COX-2 versus COX-1 in healthy volunteers. *Journal of clinical pharmacology*. 2000;40(10):1109-20.
114. Hinz B, Brune K. Can drug removals involving cyclooxygenase-2 inhibitors be avoided? A plea for human pharmacology. *Trends in pharmacological sciences*. 2008;29(8):391-7.

115. García Rodríguez LA, Tacconelli S, Patrignani P. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. *Journal of the American College of Cardiology*. 2008;52(20):1628-36.
116. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS medicine*. 2011;8(9):e1001098.
117. Massó González EL, Patrignani P, Tacconelli S, García Rodríguez LA. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. *Arthritis and rheumatism*. 2010;62(6):1592-601.
118. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation*. 2007;115(12):1634-42.
119. Bunchorntavakul C, Reddy KR. Acetaminophen-related hepatotoxicity. *Clinics in liver disease*. 2013;17(4):587-607, viii.
120. Ennis ZN, Dideriksen D, Vaegter HB, Handberg G, Pottegård A. Acetaminophen for Chronic Pain: A Systematic Review on Efficacy. *Basic and Clinical Pharmacology and Toxicology*. 2016;118(3):184-9.
121. Market Research Store. Acetaminophen (Paracetamol) Market for Pharmaceuticals, Dye Industry and Chemical Industry - Global Industry Perspective, Comprehensive Analysis, Size, Share, Growth, Segment, Trends and Forecast, 2014 – 2020 2016 [Available from: <https://www.marketresearchstore.com/news/global-acetaminophen-paracetamol-market-148>].
122. World Health Organization. WHO Model Lists of Essential Medicines 2017 [Available from: <https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists>].
123. Wise J. NICE keeps paracetamol in UK guidelines on osteoarthritis. *British Medical Journal*. 2014;348:g1545.
124. Machado GC, Maher CG, Ferreira PH, Pinheiro MB, Lin CW, Day RO, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *British Medical Journal*. 2015;350:h1225.
125. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Juni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet (London, England)*. 2017;390(10090):e21-e33.
126. Rabbie R, Derry S, Moore RA. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. *The Cochrane database of systematic reviews*. 2013;2013(4):Cd008039.
127. Moore RA, Derry S, Aldington D, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. *The Cochrane database of systematic reviews*. 2015;2015(9):Cd008659.
128. Chou D, Abalos E, Gyte GM, Gülmezoglu AM. Drugs for perineal pain in the early postpartum period: generic protocol. *Cochrane Database of Systematic Reviews*. 2009(3).

129. Bailey E, Worthington HV, van Wijk A, Yates JM, Coulthard P, Afzal Z. Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth. *The Cochrane database of systematic reviews*. 2013(12):Cd004624.
130. Yoon YJ, Kim JH, Kim SY, Hwang IH, Kim MR. A Comparison of Efficacy and Safety of Non-steroidal Anti-inflammatory Drugs versus Acetaminophen in the Treatment of Episodic Tension-type Headache: A Meta-analysis of Randomized Placebo-controlled Trial Studies. *Korean journal of family medicine*. 2012;33(5):262-71.
131. Pathan SA, Mitra B, Cameron PA. A Systematic Review and Meta-analysis Comparing the Efficacy of Nonsteroidal Anti-inflammatory Drugs, Opioids, and Paracetamol in the Treatment of Acute Renal Colic. *European urology*. 2018;73(4):583-95.
132. Dalmann R, Daulhac L, Antri M, Eschaliere A, Mallet C. Supra-spinal FAAH is required for the analgesic action of paracetamol in an inflammatory context. *Neuropharmacology*. 2015;91:63-70.
133. Högestätt ED, Jönsson BA, Ermund A, Andersson DA, Björk H, Alexander JP, et al. Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. *The Journal of biological chemistry*. 2005;280(36):31405-12.
134. Mallet C, Daulhac L, Bonnefont J, Ledent C, Etienne M, Chapuy E, et al. Endocannabinoid and serotonergic systems are needed for acetaminophen-induced analgesia. *Pain*. 2008;139(1):190-200.
135. Gerriets V, Anderson J, T.M. N. Acetaminophen Treasure Island (FL): StatPearls Publishing; 2020 [Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482369/>].
136. Smith HS. Potential analgesic mechanisms of acetaminophen. *Pain physician*. 2009;12(1):269-80.
137. Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elton TS, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proceedings of the National Academy of Sciences of the United States of America*. 2002;99(21):13926-31.
138. Flower RJ, Vane JR. Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). *Nature*. 1972;240(5381):410-1.
139. Graham GG, Scott KF. Mechanism of action of paracetamol. *American journal of therapeutics*. 2005;12(1):46-55.
140. Kis B, Snipes JA, Busija DW. Acetaminophen and the cyclooxygenase-3 puzzle: sorting out facts, fictions, and uncertainties. *The Journal of pharmacology and experimental therapeutics*. 2005;315(1):1-7.
141. Pickering G, Loriot MA, Libert F, Eschaliere A, Beaune P, Dubray C. Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. *Clinical pharmacology and therapeutics*. 2006;79(4):371-8.

142. Warner TD, Mitchell JA. Cyclooxygenase-3 (COX-3): filling in the gaps toward a COX continuum? Proceedings of the National Academy of Sciences of the United States of America. 2002;99(21):13371-3.
143. Sandrini M, Vitale G, Ruggieri V, Pini LA. Effect of acute and repeated administration of paracetamol on opioidergic and serotonergic systems in rats. *Inflammation Research*. 2007;56(4):139-42.
144. Ruggieri V, Vitale G, Pini LA, Sandrini M. Differential involvement of opioidergic and serotonergic systems in the antinociceptive activity of N-arachidonoyl-phenolamine (AM404) in the rat: comparison with paracetamol. *Naunyn-Schmiedeberg's archives of pharmacology*. 2008;377(3):219-29.
145. Schoffelmeer AN, Hogenboom F, Wardeh G, De Vries TJ. Interactions between CB1 cannabinoid and mu opioid receptors mediating inhibition of neurotransmitter release in rat nucleus accumbens core. *Neuropharmacology*. 2006;51(4):773-81.
146. Pelissier T, Alloui A, Caussade F, Dubray C, Cloarec A, Lavarenne J, et al. Paracetamol exerts a spinal antinociceptive effect involving an indirect interaction with 5-hydroxytryptamine₃ receptors: in vivo and in vitro evidence. *The Journal of pharmacology and experimental therapeutics*. 1996;278(1):8-14.
147. Alloui A, Chassaing C, Schmidt J, Ardid D, Dubray C, Cloarec A, et al. Paracetamol exerts a spinal, tropisetron-reversible, antinociceptive effect in an inflammatory pain model in rats. *European journal of pharmacology*. 2002;443(1-3):71-7.
148. Chen C, Bazan NG. Acetaminophen modifies hippocampal synaptic plasticity via a presynaptic 5-HT₂ receptor. *Neuroreport*. 2003;14(5):743-7.
149. Bardin L, Lavarenne J, Eschalier A. Serotonin receptor subtypes involved in the spinal antinociceptive effect of 5-HT in rats. *Pain*. 2000;86(1-2):11-8.
150. Raffa RB, Codd EE. Lack of binding of acetaminophen to 5-HT receptor or uptake sites (or eleven other binding/uptake assays). *Life sciences*. 1996;59(2):PI37-40.
151. Di Marzo V, Deutsch DG. Biochemistry of the endogenous ligands of cannabinoid receptors. *Neurobiology of disease*. 1998;5(6 Pt B):386-404.
152. Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. *European journal of pharmacology*. 2006;531(1-3):280-1.
153. Negrini F, Negrini S. Is paracetamol better than placebo for knee and hip osteoarthritis? A Cochrane review summary with commentary. *International journal of rheumatic diseases*. 2020;23(4):595-6.
154. Leopoldino AO, Machado GC, Ferreira PH, Pinheiro MB, Day R, McLachlan AJ, et al. Paracetamol versus placebo for knee and hip osteoarthritis. *The Cochrane database of systematic reviews*. 2019;2(2):Cd013273.
155. Barrière DA, Boumezbear F, Dalmann R, Cadeddu R, Richard D, Pinguet J, et al. Paracetamol is a centrally acting analgesic using mechanisms located in the periaqueductal grey. *British journal of pharmacology*. 2020;177(8):1773-92.
156. Józwiak-Bebenista M, Nowak JZ. Paracetamol: mechanism of action, applications and safety concern. *Acta poloniae pharmaceutica*. 2014;71(1):11-23.

157. Wei G, Bergquist A, Broomé U, Lindgren S, Wallerstedt S, Almer S, et al. Acute liver failure in Sweden: etiology and outcome. *Journal of internal medicine*. 2007;262(3):393-401.
158. Tanne J. Paracetamol causes most liver failure in UK and US. *British Medical Journal*. 2006;332(7542):628.
159. Wastesson JW, Martikainen JE, Zoëga H, Schmidt M, Karlstad Ø, Pottegård A. Trends in Use of Paracetamol in the Nordic Countries. *Basic and Clinical Pharmacology and Toxicology*. 2018;123(3):301-7.
160. Moore M, Thor H, Moore G, Nelson S, Moldéus P, Orrenius S. The toxicity of acetaminophen and N-acetyl-p-benzoquinone imine in isolated hepatocytes is associated with thiol depletion and increased cytosolic Ca²⁺. *The Journal of biological chemistry*. 1985;260(24):13035-40.
161. Xie Y, McGill MR, Du K, Dorko K, Kumer SC, Schmitt TM, et al. Mitochondrial protein adducts formation and mitochondrial dysfunction during N-acetyl-m-aminophenol (AMAP)-induced hepatotoxicity in primary human hepatocytes. *Toxicology and applied pharmacology*. 2015;289(2):213-22.
162. Athersuch TJ, Antoine DJ, Boobis AR, Coen M, Daly AK, Possamai L, et al. Paracetamol metabolism, hepatotoxicity, biomarkers and therapeutic interventions: a perspective. *Toxicology research*. 2018;7(3):347-57.
163. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis and cartilage*. 2010;18(4):476-99.
164. Roberts E, Delgado Nunes V, Buckner S, Latchem S, Constanti M, Miller P, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Annals of the rheumatic diseases*. 2016;75(3):552-9.
165. Rahme E, Barkun A, Nedjar H, Gaugris S, Watson D. Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. *The American journal of gastroenterology*. 2008;103(4):872-82.
166. Saragiotto BT, Abdel Shaheed C, Maher CG. Paracetamol for pain in adults. *British Medical Journal*. 2019;367:l6693.
167. GBD. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet (London, England)*. 2016;388(10053):1545-602.
168. GBD. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet (London, England)*. 2017;390(10100):1211-59.
169. Deshpande BR, Katz JN, Solomon DH, Yelin EH, Hunter DJ, Messier SP, et al. Number of Persons With Symptomatic Knee Osteoarthritis in the US: Impact of Race and Ethnicity, Age, Sex, and Obesity. *Arthritis Care Res*. 2016;68(12):1743-50.
170. Losina E, Weinstein AM, Reichmann WM, Burbine SA, Solomon DH, Daigle ME, et al. Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. *Arthritis care & research*. 2013;65(5):703-11.

171. Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press; 2011. 382 p.
172. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthritis and cartilage*. 2015;23(8):1233-41.
173. Lane NE, Brandt K, Hawker G, Peeva E, Schreyer E, Tsuji W, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. *Osteoarthritis and cartilage*. 2011;19(5):478-82.
174. Eitner A, Hofmann GO, Schaible HG. Mechanisms of Osteoarthritic Pain. *Studies in Humans and Experimental Models*. *Frontiers in molecular neuroscience*. 2017;10:349.
175. Felson DT. Developments in the clinical understanding of osteoarthritis. *Arthritis Research and Therapy*. 2009;11(1):203.
176. Hofmann GO, Marticke J, Grossstück R, Hoffmann M, Lange M, Plettenberg HK, et al. Detection and evaluation of initial cartilage pathology in man: A comparison between MRT, arthroscopy and near-infrared spectroscopy (NIR) in their relation to initial knee pain. *Pathophysiology : the official journal of the International Society for Pathophysiology*. 2010;17(1):1-8.
177. Goldring MB, Otero M. Inflammation in osteoarthritis. *Current opinion in rheumatology*. 2011;23(5):471-8.
178. Yusup A, Kaneko H, Liu L, Ning L, Sadatsuki R, Hada S, et al. Bone marrow lesions, subchondral bone cysts and subchondral bone attrition are associated with histological synovitis in patients with end-stage knee osteoarthritis: a cross-sectional study. *Osteoarthritis and cartilage*. 2015;23(11):1858-64.
179. Burr DB, Gallant MA. Bone remodelling in osteoarthritis. *Nature reviews Rheumatology*. 2012;8(11):665-73.
180. Attur M, Krasnokutsky S, Statnikov A, Samuels J, Li Z, Friese O, et al. Low-grade inflammation in symptomatic knee osteoarthritis: prognostic value of inflammatory plasma lipids and peripheral blood leukocyte biomarkers. *Arthritis & rheumatology (Hoboken, NJ)*. 2015;67(11):2905-15.
181. Berenbaum F, van den Berg WB. Inflammation in osteoarthritis: changing views. *Osteoarthritis and cartilage*. 2015;23(11):1823-4.
182. Zhang Y, Nevitt M, Niu J, Lewis C, Torner J, Guermazi A, et al. Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging. *Arthritis and rheumatism*. 2011;63(3):691-9.
183. Eckstein F, Burstein D, Link TM. Quantitative MRI of cartilage and bone: degenerative changes in osteoarthritis. *NMR in Biomedicine*. 2006;19(7):822-54.
184. Link TM, Steinbach LS, Ghosh S, Ries M, Lu Y, Lane N, et al. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology*. 2003;226(2):373-81.
185. Hawker GA, French MR, Waugh EJ, Gignac MA, Cheung C, Murray BJ. The multidimensionality of sleep quality and its relationship to fatigue in older adults with painful osteoarthritis. *Osteoarthritis and cartilage*. 2010;18(11):1365-71.
186. Hawker GA, Gignac MA, Badley E, Davis AM, French MR, Li Y, et al. A longitudinal study to explain the pain-depression link in older adults with osteoarthritis. *Arthritis Care Res*. 2011;63(10):1382-90.

187. Georgiev T, Angelov AK. Modifiable risk factors in knee osteoarthritis: treatment implications. *Rheumatology international*. 2019;39(7):1145-57.
188. Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ. Joint injury in young adults and risk for subsequent knee and hip osteoarthritis. *Annals of internal medicine*. 2000;133(5):321-8.
189. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis and cartilage*. 2010;18(1):24-33.
190. Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ. Body mass index in young men and the risk of subsequent knee and hip osteoarthritis. *The American journal of medicine*. 1999;107(6):542-8.
191. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *Journal of the American Medical Association*. 2001;286(2):188-95.
192. Toivanen AT, Heliövaara M, Impivaara O, Arokoski JP, Knekt P, Lauren H, et al. Obesity, physically demanding work and traumatic knee injury are major risk factors for knee osteoarthritis--a population-based study with a follow-up of 22 years. *Rheumatology*. 2010;49(2):308-14.
193. Felson DT, Niu J, Gross KD, Englund M, Sharma L, Cooke TD, et al. Valgus malalignment is a risk factor for lateral knee osteoarthritis incidence and progression: findings from the Multicenter Osteoarthritis Study and the Osteoarthritis Initiative. *Arthritis and rheumatism*. 2013;65(2):355-62.
194. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis and cartilage*. 2005;13(9):769-81.
195. Vina ER, Ran D, Ashbeck EL, Kwok CK. Natural history of pain and disability among African-Americans and Whites with or at risk for knee osteoarthritis: A longitudinal study. *Osteoarthritis and cartilage*. 2018;26(4):471-9.
196. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. *British Medical Journal*. 1996;312(7036):940-3.
197. MacGregor AJ, Antoniadou L, Matson M, Andrew T, Spector TD. The genetic contribution to radiographic hip osteoarthritis in women: results of a classic twin study. *Arthritis and rheumatism*. 2000;43(11):2410-6.
198. Loughlin J. The genetic epidemiology of human primary osteoarthritis: current status. *Expert reviews in molecular medicine*. 2005;7(9):1-12.
199. Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. *BMC musculoskeletal disorders*. 2008;9:132.
200. Marks R. Obesity profiles with knee osteoarthritis: correlation with pain, disability, disease progression. *Obesity*. 2007;15(7):1867-74.
201. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. *Osteoarthritis and cartilage*. 2015;23(4):507-15.

202. Kulkarni K, Karssiens T, Kumar V, Pandit H. Obesity and osteoarthritis. *Maturitas*. 2016;89:22-8.
203. Yoshimura N, Muraki S, Oka H, Tanaka S, Kawaguchi H, Nakamura K, et al. Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. *Osteoarthritis and cartilage*. 2012;20(11):1217-26.
204. Courties A, Gualillo O, Berenbaum F, Sellam J. Metabolic stress-induced joint inflammation and osteoarthritis. *Osteoarthritis and cartilage*. 2015;23(11):1955-65.
205. Wang X, Hunter D, Xu J, Ding C. Metabolic triggered inflammation in osteoarthritis. *Osteoarthritis and cartilage*. 2015;23(1):22-30.
206. Berenbaum F, Griffin TM, Liu-Bryan R. Review: Metabolic Regulation of Inflammation in Osteoarthritis. *Arthritis and Rheumatology*. 2017;69(1):9-21.
207. Schett G, Kleyer A, Perricone C, Sahinbegovic E, Iagnocco A, Zwerina J, et al. Diabetes is an independent predictor for severe osteoarthritis: results from a longitudinal cohort study. *Diabetes care*. 2013;36(2):403-9.
208. Eymard F, Parsons C, Edwards MH, Petit-Dop F, Reginster JY, Bruyère O, et al. Diabetes is a risk factor for knee osteoarthritis progression. *Osteoarthritis and cartilage*. 2015;23(6):851-9.
209. King KB, Rosenthal AK. The adverse effects of diabetes on osteoarthritis: update on clinical evidence and molecular mechanisms. *Osteoarthritis and cartilage*. 2015;23(6):841-50.
210. Dai Z, Niu J, Zhang Y, Jacques P, Felson DT. Dietary intake of fibre and risk of knee osteoarthritis in two US prospective cohorts. *Annals of the rheumatic diseases*. 2017;76(8):1411-9.
211. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *European Journal of Pain*. 2006;10(4):287-.
212. Hunter DJ, March L, Chew M. Osteoarthritis in 2020 and beyond: a Lancet Commission. *Lancet (London, England)*. 2020;396(10264):1711-2.
213. Global Burden of Disease Network Collaborative. Global Burden of Disease Study 2019 (GBD 2019) Results 2019 [Available from: <http://ghdx.healthdata.org/gbd-results-tool>].
214. French HP, Galvin R, Horgan NF, Kenny RA. Prevalence and burden of osteoarthritis amongst older people in Ireland: findings from The Irish Longitudinal Study on Ageing (TILDA). *European Journal of Public Health*. 2016;26(1):192-8.
215. Murray CJ, Lopez AD, Organization WH. The Global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Harvard University Press. 1996;1:41.
216. Kopec JA, Sayre EC, Schwartz TA, Renner JB, Helmick CG, Badley EM, et al. Occurrence of radiographic osteoarthritis of the knee and hip among African Americans and whites: a population-based prospective cohort study. *Arthritis Care Res*. 2013;65(6):928-35.
217. Wallace IJ, Worthington S, Felson DT, Jurmain RD, Wren KT, Maijanen H, et al. Knee osteoarthritis has doubled in prevalence since the mid-20th century.

Proceedings of the National Academy of Sciences of the United States of America. 2017;114(35):9332-6.

218. van Tunen JAC, Peat G, Bricca A, Larsen LB, Søndergaard J, Thilising T, et al. Association of osteoarthritis risk factors with knee and hip pain in a population-based sample of 29-59 year olds in Denmark: a cross-sectional analysis. *BMC musculoskeletal disorders*. 2018;19(1):300.
219. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. *Arthritis and rheumatism*. 2013;65(2):363-72.
220. Akinci A, Al Shaker M, Chang MH, Cheung CW, Danilov A, José Dueñas H, et al. Predictive factors and clinical biomarkers for treatment in patients with chronic pain caused by osteoarthritis with a central sensitisation component. *International journal of clinical practice*. 2016;70(1):31-44.
221. Lluch E, Torres R, Nijs J, Van Oosterwijck J. Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review. *European Journal of Pain*. 2014;18(10):1367-75.
222. Giesecke T, Gracely RH, Grant MA, Nachemson A, Petzke F, Williams DA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis and rheumatism*. 2004;50(2):613-23.
223. Lee YC, Bingham CO, 3rd, Edwards RR, Marder W, Phillips K, Bolster MB, et al. Association Between Pain Sensitization and Disease Activity in Patients With Rheumatoid Arthritis: A Cross-Sectional Study. *Arthritis Care Res*. 2018;70(2):197-204.
224. Felson DT. The sources of pain in knee osteoarthritis. *Current opinion in rheumatology*. 2005;17(5):624-8.
225. Hawker GA, Stewart L, French MR, Cibere J, Jordan JM, March L, et al. Understanding the pain experience in hip and knee osteoarthritis--an OARSI/OMERACT initiative. *Osteoarthritis and cartilage*. 2008;16(4):415-22.
226. Oteo-Álvaro Á, Ruiz-Ibán MA, Miguens X, Stern A, Villoria J, Sánchez-Magro I. High Prevalence of Neuropathic Pain Features in Patients with Knee Osteoarthritis: A Cross-Sectional Study. *Pain Practice*. 2015;15(7):618-26.
227. Hochman JR, Gagliese L, Davis AM, Hawker GA. Neuropathic pain symptoms in a community knee OA cohort. *Osteoarthritis and cartilage*. 2011;19(6):647-54.
228. Suokas AK, Walsh DA, McWilliams DF, Condon L, Moreton B, Wylde V, et al. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis and cartilage*. 2012;20(10):1075-85.
229. Mapp PI, Walsh DA. Mechanisms and targets of angiogenesis and nerve growth in osteoarthritis. *Nature Reviews Rheumatology*. 2012;8(7):390-8.
230. Schaible HG. Mechanisms of chronic pain in osteoarthritis. *Current Rheumatology Reports*. 2012;14(6):549-56.
231. Bartley EJ, King CD, Sibille KT, Cruz-Almeida Y, Riley JL, 3rd, Glover TL, et al. Enhanced Pain Sensitivity Among Individuals With Symptomatic Knee Osteoarthritis: Potential Sex Differences in Central Sensitization. *Arthritis Care Res*. 2016;68(4):472-80.

232. Petersen KK, Arendt-Nielsen L, Simonsen O, Wilder-Smith O, Laursen MB. Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. *Pain*. 2015;156(1):55-61.
233. Wylde V, Sayers A, Lenguerrand E, Gooberman-Hill R, Pyke M, Beswick AD, et al. Preoperative widespread pain sensitization and chronic pain after hip and knee replacement: a cohort analysis. *Pain*. 2015;156(1):47-54.
234. European Medicines Agency. Guideline on the Clinical Development of Medicinal Products Intended for the Treatment of Pain 2016 [Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-development-medicinal-products-intended-treatment-pain-first-version_en.pdf].
235. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC musculoskeletal disorders*. 2008;9:116.
236. Malfait AM, Schnitzer TJ. Towards a mechanism-based approach to pain management in osteoarthritis. *Nature reviews Rheumatology*. 2013;9(11):654-64.
237. Neogi T, Felson D, Niu J, Nevitt M, Lewis CE, Aliabadi P, et al. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. *British Medical Journal*. 2009;339:b2844.
238. Eckstein F, Cotofana S, Wirth W, Nevitt M, John MR, Dreher D, et al. Greater rates of cartilage loss in painful knees than in pain-free knees after adjustment for radiographic disease stage: data from the osteoarthritis initiative. *Arthritis and rheumatism*. 2011;63(8):2257-67.
239. Kaukinen P, Podlipská J, Guerhazi A, Niinimäki J, Lehenkari P, Roemer FW, et al. Associations between MRI-defined structural pathology and generalized and localized knee pain - the Oulu Knee Osteoarthritis study. *Osteoarthritis and cartilage*. 2016;24(9):1565-76.
240. Wittoek R, Cruyssen BV, Verbruggen G. Predictors of functional impairment and pain in erosive osteoarthritis of the interphalangeal joints: comparison with controlled inflammatory arthritis. *Arthritis and rheumatism*. 2012;64(5):1430-6.
241. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and cartilage*. 2014;22(3):363-88.
242. Bertin P, Becquemont L, Corruble E, Derumeaux G, Falissard B, Hanon O, et al. The therapeutic management of chronic pain in ambulatory care patients aged 65 and over in France: the S.AGES Cohort. Baseline data. *The Journal of Nutrition, Health and Aging*. 2013;17(8):681-6.
243. Pelletier JP, Martel-Pelletier J, Rannou F, Cooper C. Efficacy and safety of oral NSAIDs and analgesics in the management of osteoarthritis: Evidence from real-life setting trials and surveys. *Seminars in Arthritis and Rheumatism*. 2016;45(4 Suppl):S22-7.
244. Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. *Journal of Pharmacy & Pharmaceutical Sciences*. 2013;16(5):821-47.

245. Persson MSM, Stocks J, Walsh DA, Doherty M, Zhang W. The relative efficacy of topical non-steroidal anti-inflammatory drugs and capsaicin in osteoarthritis: a network meta-analysis of randomised controlled trials. *Osteoarthritis and cartilage*. 2018;26(12):1575-82.
246. Adili A, Bhandari M. Cochrane in CORR®: Topical NSAIDs for Chronic Musculoskeletal Pain in Adults. *Clinical Orthopaedics and Related Research*. 2018;476(11):2128-34.
247. Arfe A, Scotti L, Varas-Lorenzo C, Nicotra F, Zambon A, Kollhorst B, et al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. *British Medical Journal*. 2016;354:i4857.
248. Solomon DH, Husni ME, Libby PA, Yeomans ND, Lincoff AM, Lupsilonscher TF, et al. The Risk of Major NSAID Toxicity with Celecoxib, Ibuprofen, or Naproxen: A Secondary Analysis of the PRECISION Trial. *The American journal of medicine*. 2017;130(12):1415-22.
249. van den Driest JJ, Pijnenburg P, Bindels PJE, Bierma-Zeinstra SMA, Schiphof D. Analgesic Use in Dutch Patients With Osteoarthritis: Frequent But Low Doses. *Journal of Clinical Rheumatology*. 2019;Ahead of print.
250. Moore N, Salvo F, Duong M, Gulmez SE. Does paracetamol still have a future in osteoarthritis? *Lancet (London, England)*. 2016;387(10033):2065-6.
251. McCrae JC, Morrison EE, MacIntyre IM, Dear JW, Webb DJ. Long-term adverse effects of paracetamol - a review. *British journal of clinical pharmacology*. 2018;84(10):2218-30.
252. Doherty M, Hawkey C, Goulder M, Gibb I, Hill N, Aspley S, et al. A randomised controlled trial of ibuprofen, paracetamol or a combination tablet of ibuprofen/paracetamol in community-derived people with knee pain. *Annals of the rheumatic diseases*. 2011;70(9):1534-41.
253. Stewart M, Cibere J, Sayre EC, Kopec JA. Efficacy of commonly prescribed analgesics in the management of osteoarthritis: a systematic review and meta-analysis. *Rheumatology international*. 2018;38(11):1985-97.
254. Zhang W, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther KP, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Annals of the rheumatic diseases*. 2005;64.
255. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Annals of the rheumatic diseases*. 2003;62.
256. Ackerman IN, Zomer E, Gilmartin-Thomas JF, Liew D. Forecasting the future burden of opioids for osteoarthritis. *Osteoarthritis and cartilage*. 2018;26(3):350-5.
257. Thorlund JB, Turkiewicz A, Prieto-Alhambra D, Englund M. Inappropriate opioid dispensing in patients with knee and hip osteoarthritis: a population-based cohort study. *Osteoarthritis and cartilage*. 2020;28(2):146-53.
258. Welsch P, Petzke F, Klose P, Häuser W. Opioids for chronic osteoarthritis pain: An updated systematic review and meta-analysis of efficacy, tolerability and

- safety in randomized placebo-controlled studies of at least 4 weeks double-blind duration. *European Journal of Pain*. 2020;24(4):685-703.
259. Osani MC, Lohmander LS, Bannuru RR. Is There Any Role for Opioids in the Management of Knee and Hip Osteoarthritis? A Systematic Review and Meta-Analysis. *Arthritis Care Res*. 2020.
260. Fuggle N, Curtis E, Shaw S, Spooner L, Bruyère O, Ntani G, et al. Safety of Opioids in Osteoarthritis: Outcomes of a Systematic Review and Meta-Analysis. *Drugs and Aging*. 2019;36(Suppl 1):129-43.
261. Liu X, Eyles J, McLachlan AJ, Mobasheri A. Which supplements can I recommend to my osteoarthritis patients? *Rheumatology*. 2018;57(suppl_4):iv75-iv87.
262. Liu X, Machado GC, Eyles JP, Ravi V, Hunter DJ. Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis. *British journal of sports medicine*. 2018;52(3):167-75.
263. Henrotin Y, Mobasheri A. Natural Products for Promoting Joint Health and Managing Osteoarthritis. *Current Rheumatology Reports*. 2018;20(11):72.
264. Kucharz EJ, Kovalenko V, Szántó S, Bruyère O, Cooper C, Reginster J-Y. A review of glucosamine for knee osteoarthritis: why patented crystalline glucosamine sulfate should be differentiated from other glucosamines to maximize clinical outcomes. *Current medical research and opinion*. 2016;32(6):997-1004.
265. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. *British journal of sports medicine*. 2015;49(24):1554-7.
266. Altman R, Lim S, Steen RG, Dasa V. Hyaluronic Acid Injections Are Associated with Delay of Total Knee Replacement Surgery in Patients with Knee Osteoarthritis: Evidence from a Large U.S. Health Claims Database. *PLoS One*. 2015;10(12):e0145776.
267. DeFelice SL. The nutraceutical revolution: its impact on food industry R&D. *Trend Food Science Tech*. 1995;6(2):59-61.
268. Witkamp RF, van Norren K. Let thy food be thy medicine...when possible. *European journal of pharmacology*. 2018;836:102-14.
269. Santini A, Novellino E. Nutraceuticals: Beyond the diet before the drugs. *Current Bioactive Compounds*. 2014;10(1):1-12.
270. Aronson JK. Defining 'nutraceuticals': neither nutritious nor pharmaceutical. *British journal of clinical pharmacology*. 2017;83(1):8-19.
271. Zeisel SH. Regulation of "nutraceuticals". *Science (New York, NY)*. 1999;285(5435):1853-5.
272. Espín JC, García-Conesa MT, Tomás-Barberán FA. Nutraceuticals: facts and fiction. *Phytochemistry*. 2007;68(22-24):2986-3008.
273. Santini A, Tenore GC, Novellino E. Nutraceuticals: A paradigm of proactive medicine. *European Journal of Pharmaceutical Sciences*. 2017;96:53-61.
274. European Food Safety Authority PoDPNA. Scientific opinion on the substantiation of health claims related to monacolin K from red yeast rice and maintenance of normal blood LDL cholesterol concentrations (ID 1648, 1700) pursuant to Article 13 (1) of Regulation (EC) No 1924/2006. *European Food Safety Authority Journal*. 2011;9(7):2304.

275. European Council. EC Regulation n. 1924/2006 2006 [Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02006R1924-20141213>].
276. Act USNRaE. H.R.3001–Nutraceutical Research and Education Act. (106th Congress of 1999–2000): U.S. Congress; 1999 [Available from: <https://www.congress.gov/bill/106th-congress/house-bill/3001?q=%7B%22search%22%3A%5B%22Nutraceutical+Research+and+Education+Act%22%5D%7D&r=13&s=5>].
277. The European Nutraceutical Association. Nutraceutical Definition: The European Nutraceutical Association; 2018 [Available from: <https://www.enaonline.eu>].
278. Health Canada. Policy Paper - Nutraceuticals/Functional Foods and Health Claims On Foods 2002 [Available from: <https://www.canada.ca/en/health-canada/services/food-nutrition/food-labelling/health-claims/nutraceuticals-functional-foods-health-claims-foods-policy-paper.html>].
279. Corzo L, Fernández-Novoa L, Carrera I, Martínez O, Rodríguez S, Alejo R, et al. Nutrition, Health, and Disease: Role of Selected Marine and Vegetal Nutraceuticals. *Nutrients*. 2020;12(3).
280. Vaishya R, Agarwal AK, Shah A, Vijay V, Vaish A. Current status of top 10 nutraceuticals used for Knee Osteoarthritis in India. *J Clin Orthop Trauma*. 2018;9(4):338-48.
281. Appelboom T, Schuermans J, Verbruggen G, Henrotin Y, Reginster JY. Symptoms modifying effect of avocado/soybean unsaponifiables (ASU) in knee osteoarthritis. A double blind, prospective, placebo-controlled study. *Scandinavian Journal of Rheumatology*. 2001;30(4):242-7.
282. Gluszko P, Stasiak M. Symptom-modifying effects of oral avocado/soybean unsaponifiables in routine treatment of knee osteoarthritis in Poland. An open, prospective observational study of patients adherent to a 6-month treatment. *Reumatologia*. 2016;54(5):217-26.
283. Jokar M, Azadeh H, Mirfeizi Z, Shariati Sarabi J, Hashemzadeh K. A Comparison between Avocado-Soybean Unsaponifiables and Celecoxib on Serum Levels of Cartilage Oligomeric Matrix Protein in Patients with Knee Osteoarthritis. *Rheumatology Research*. 2019;4(2):71-5.
284. Jacquet A, Girodet P-O, Pariente A, Forest K, Mallet L, Moore N. Phytalgic, a food supplement, vs placebo in patients with osteoarthritis of the knee or hip: a randomised double-blind placebo-controlled clinical trial. *Arthritis Research and Therapy*. 2009;11(6):R192-R.
285. Stebbings S, Gray A, Schneiders AG, Sansom A. A randomized double-blind placebo-controlled trial to investigate the effectiveness and safety of a novel green-lipped mussel extract -BioLex® -for managing pain in moderate to severe osteoarthritis of the hip and knee. *BMC Complement Altern Med*. 2017;17(1):416.
286. Belcaro G, Cesarone MR, Errichi S, Zulli C, Errichi BM, Vinciguerra G, et al. Treatment of osteoarthritis with Pycnogenol. The SVOS (San Valentino Osteoarthritis Study). Evaluation of signs, symptoms, physical performance and vascular aspects. *Phytotherapy Research*. 2008;22(4):518-23.

287. Kuptniratsaikul V, Thanakhumtorn S, Chinswangwatanakul P, Wattanamongkonsil L, Thamlikitkul V. Efficacy and safety of *Curcuma domestica* extracts in patients with knee osteoarthritis. *The Journal of Alternative and Complementary Medicine*. 2009;15(8):891-7.
288. Kuptniratsaikul V, Dajpratham P, Taechaarpornkul W, Buntragulpoontawee M, Lukkanapichonchut P, Chootip C, et al. Efficacy and safety of *Curcuma domestica* extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. *Clinical Interventions in Aging*. 2014;9:451-8.
289. Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phytotherapy Research*. 2012;26(11):1719-25.
290. Shep D, Khanwelkar C, Gade P, Karad S. Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis: a randomized open-label parallel-arm study. *Trials*. 2019;20(1):214.
291. Gupte PA, Giramkar SA, Harke SM, Kulkarni SK, Deshmukh AP, Hingorani LL, et al. Evaluation of the efficacy and safety of Capsule Longvida(®) Optimized Curcumin (solid lipid curcumin particles) in knee osteoarthritis: a pilot clinical study. *Journal of inflammation research*. 2019;12:145-52.
292. Heidari-Beni M, Moravejolahkami AR, Gorgian P, Askari G, Tarrahi MJ, Bahreini-Esfahani N. Herbal formulation "turmeric extract, black pepper, and ginger" versus Naproxen for chronic knee osteoarthritis: A randomized, double-blind, controlled clinical trial. *Phytotherapy Research*. 2020;34(8):2067-73.
293. Belcaro G, Cesarone MR, Dugall M, Pellegrini L, Ledda A, Grossi MG, et al. Efficacy and safety of Meriva [R], a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. *Alternative Medicine Review*. 2010;15(4):337-45.
294. Nakagawa Y, Mukai S, Yamada S, Matsuoka M, Tarumi E, Hashimoto T, et al. Short-term effects of highly-bioavailable curcumin for treating knee osteoarthritis: a randomized, double-blind, placebo-controlled prospective study. *Journal of Orthopaedic Science*. 2014;19(6):933-9.
295. Panahi Y, Rahimnia AR, Sharafi M, Alishiri G, Saburi A, Sahebkar A. Curcuminoid treatment for knee osteoarthritis: A randomized double-blind placebo-controlled trial. *Phytotherapy Research*. 2014;28(11):1625-31.
296. Niempoog S, Siriarchavatana P, Kajsongkram T. The efficacy of Plygersic gel for use in the treatment of osteoarthritis of the knee. *Journal of the Medical Association of Thailand*. 2012;95 Suppl 10:S113-9.
297. Paramdeep G. Efficacy and tolerability of ginger (*Zingiber officinale*) in patients of osteoarthritis of knee. *Indian journal of physiology and pharmacology*. 2013;57(2):177-83.
298. Frestedt JL, Kuskowski MA, Zenk JL. A natural seaweed derived mineral supplement (Aquamin F) for knee osteoarthritis: a randomised, placebo controlled pilot study. *Nutrition Journal*. 2009;8:7.
299. Heffernan SM, McCarthy C, Eustace S, FitzPatrick RE, Delahunty E, De Vito G. Mineral rich algae with pine bark improved pain, physical function and analgesic use in mild-knee joint osteoarthritis, compared to Glucosamine: a

randomized controlled pilot trial. *Complementary Therapies in Medicine*. 2020:In Press.

300. Daily JW, Yang M, Park S. Efficacy of Turmeric Extracts and Curcumin for Alleviating the Symptoms of Joint Arthritis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Journal of Medicinal Food*. 2016;19(8):717-29.

301. Heidari-Beni M, Moravejolahkami AR, Gorgian P, Askari G, Tarrahi MJ, Bahreini-Esfahani N. Herbal formulation "turmeric extract, black pepper, and ginger" versus Naproxen for chronic knee osteoarthritis: A randomized, double-blind, controlled clinical trial. *Phytotherapy Research*. 2020.

302. Bengmark S. Curcumin, an atoxic antioxidant and natural NFkappaB, cyclooxygenase-2, lipooxygenase, and inducible nitric oxide synthase inhibitor: a shield against acute and chronic diseases. *J Parenter Enteral Nutr*. 2006;30(1):45-51.

303. Oyagbemi AA, Saba AB, Ibraheem AO. Curcumin: from food spice to cancer prevention. *Asian Pacific journal of cancer prevention*. 2009;10(6):963-7.

304. Khanna D, Sethi G, Ahn KS, Pandey MK, Kunnumakkara AB, Sung B, et al. Natural products as a gold mine for arthritis treatment. *Current opinion in pharmacology*. 2007;7(3):344-51.

305. Saja K, Babu MS, Karunagaran D, Sudhakaran PR. Anti-inflammatory effect of curcumin involves downregulation of MMP-9 in blood mononuclear cells. *International immunopharmacology*. 2007;7(13):1659-67.

306. Kim KH, Lee EN, Park JK, Lee JR, Kim JH, Choi HJ, et al. Curcumin attenuates TNF- α -induced expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and proinflammatory cytokines in human endometriotic stromal cells. *Phytotherapy Research*. 2012;26(7):1037-47.

307. Yang Q, Wu S, Mao X, Wang W, Tai H. Inhibition effect of curcumin on TNF- α and MMP-13 expression induced by advanced glycation end products in chondrocytes. *Pharmacology*. 2013;91(1-2):77-85.

308. Jackson JK, Higo T, Hunter WL, Burt HM. The antioxidants curcumin and quercetin inhibit inflammatory processes associated with arthritis. *Inflammation Research*. 2006;55(4):168-75.

309. Goel A, Boland CR, Chauhan DP. Specific inhibition of cyclooxygenase-2 (COX-2) expression by dietary curcumin in HT-29 human colon cancer cells. *Cancer Letters*. 2001;172(2):111-8.

310. Goel A, Jhurani S, Aggarwal BB. Multi-targeted therapy by curcumin: how spicy is it? *Mol Nutr Food Res*. 2008;52(9):1010-30.

311. Mathy-Hartert M, Jacquemond-Collet I, Priem F, Sanchez C, Lambert C, Henrotin Y. Curcumin inhibits pro-inflammatory mediators and metalloproteinase-3 production by chondrocytes. *Inflammation Research*. 2009;58(12):899.

312. Reuter S, Gupta SC, Park B, Goel A, Aggarwal BB. Epigenetic changes induced by curcumin and other natural compounds. *Genes and Nutrition*. 2011;6(2):93-108.

313. Rovati LC, Girolami F, D'Amato M, Giacobelli G. Effects of glucosamine sulfate on the use of rescue non-steroidal anti-inflammatory drugs in knee

- osteoarthritis: Results from the Pharmaco-Epidemiology of GonArthroSis (PEGASus) study. *Seminars in Arthritis and Rheumatism*. 2016;45(4 Suppl):S34-41.
314. Henrotin YE, Sanchez C, Deberg MA, Piccardi N, Guillou GB, Msika P, et al. Avocado/soybean unsaponifiables increase aggrecan synthesis and reduce catabolic and proinflammatory mediator production by human osteoarthritic chondrocytes. *The Journal of rheumatology*. 2003;30(8):1825-34.
315. Boumediene K, Felisaz N, Bogdanowicz P, Galera P, Guillou GB, Pujol JP. Avocado/soya unsaponifiables enhance the expression of transforming growth factor beta1 and beta2 in cultured articular chondrocytes. *Arthritis and rheumatism*. 1999;42(1):148-56.
316. Henrotin YE, Labasse AH, Jaspar JM, De Groote DD, Zheng SX, Guillou GB, et al. Effects of three avocado/soybean unsaponifiable mixtures on metalloproteinases, cytokines and prostaglandin E2 production by human articular chondrocytes. *Clinical rheumatology*. 1998;17(1):31-9.
317. Panthong A, Kanjanapothi D, Niwatananant W, Tuntiwachwuttikul P, Reutrakul V. Anti-inflammatory activity of compound D {(E)-4-(3',4'-dimethoxyphenyl)but-3-en-2-ol} isolated from *Zingiber cassumunar* Roxb. *Phytomedicine : international journal of phytotherapy and phytopharmacology*. 1997;4(3):207-12.
318. Jeenapongsa R, Yoovathaworn K, Sriwatanakul KM, Pongprayoon U, Sriwatanakul K. Anti-inflammatory activity of (E)-1-(3,4-dimethoxyphenyl)butadiene from *Zingiber cassumunar* Roxb. *Journal of ethnopharmacology*. 2003;87(2-3):143-8.
319. Minghetti P, Sosa S, Cilurzo F, Casiraghi A, Alberti E, Tubaro A, et al. Evaluation of the topical anti-inflammatory activity of ginger dry extracts from solutions and plasters. *Planta medica*. 2007;73(15):1525-30.
320. Thomson M, Al-Qattan KK, Al-Sawan SM, Alnaqeeb MA, Khan I, Ali M. The use of ginger (*Zingiber officinale* Rosc.) as a potential anti-inflammatory and antithrombotic agent. *Prostaglandins, leukotrienes, and essential fatty acids*. 2002;67(6):475-8.
321. Nurtjahja-Tjendraputra E, Ammit AJ, Roufogalis BD, Tran VH, Duke CC. Effective anti-platelet and COX-1 enzyme inhibitors from pungent constituents of ginger. *Thrombosis research*. 2003;111(4-5):259-65.
322. Lantz RC, Chen GJ, Sarihan M, Solyom AM, Jolad SD, Timmermann BN. The effect of extracts from ginger rhizome on inflammatory mediator production. *Phytomedicine : international journal of phytotherapy and phytopharmacology*. 2007;14(2-3):123-8.
323. Pongprayoon U, Soontornsaratune P, Jarikasem S, Sematong T, Wasuwat S, Claeson P. Topical antiinflammatory activity of the major lipophilic constituents of the rhizome of *Zingiber cassumunar*. Part I: The essential oil. *Phytomedicine : international journal of phytotherapy and phytopharmacology*. 1997;3(4):319-22.
324. Pongprayoon U, Tuchinda P, Claeson P, Sematong T, Reutrakul V, Soontornsaratune P. Topical antiinflammatory activity of the major lipophilic constituents of the rhizome of *Zingiber cassumunar*. Part II: Hexane extractives. *Phytomedicine : international journal of phytotherapy and phytopharmacology*. 1997;3(4):323-6.

325. Han AR, Kim MS, Jeong YH, Lee SK, Seo EK. Cyclooxygenase-2 inhibitory phenylbutenoids from the rhizomes of *Zingiber cassumunar*. *Chem Pharm Bull.* 2005;53(11):1466-8.
326. Jessberger S, Högger P, Genest F, Salter DM, Seefried L. Cellular pharmacodynamic effects of Pycnogenol® in patients with severe osteoarthritis: a randomized controlled pilot study. *BMC Complement Altern Med.* 2017;17(1):537-.
327. Grimm T, Skrabala R, Chovanová Z, Muchová J, Sumegová K, Liptáková A, et al. Single and multiple dose pharmacokinetics of maritime pine bark extract (pycnogenol) after oral administration to healthy volunteers. *BMC Clin Pharmacol.* 2006;6:4-.
328. Schäfer A, Chovanová Z, Muchová J, Sumegová K, Liptáková A, Duracková Z, et al. Inhibition of COX-1 and COX-2 activity by plasma of human volunteers after ingestion of French maritime pine bark extract (Pycnogenol). *Biomedicine and Pharmacotherapy.* 2006;60(1):5-9.
329. Ulbricht C, Chao W, Costa D, Nguyen Y, Seamon E, Weissner W. An evidence-based systematic review of green-lipped mussel (*Perna canaliculus*) by the natural standard research collaboration. *J Diet Suppl.* 2009;6.
330. Stammers T, Sibbald B, Freeling P. Efficacy of cod liver oil as an adjunct to non-steroidal anti-inflammatory drug treatment in the management of osteoarthritis in general practice. *Annals of the rheumatic diseases.* 1992;51(1):128-9.
331. Curtis CL, Rees SG, Cramp J, Flannery CR, Hughes CE, Little CB, et al. Effects of n-3 fatty acids on cartilage metabolism. *The Proceedings of the Nutrition Society.* 2006;65(4):434.
332. Curtis CL, Rees SG, Little CB, Flannery CR, Hughes CE, Wilson C, et al. Pathologic indicators of degradation and inflammation in human osteoarthritic cartilage are abrogated by exposure to n-3 fatty acids. *Arthritis and rheumatism.* 2002;46(6):1544-53.
333. Murphy CT, Martin C, Doolan AM, Molloy MG, Dinan TG, Gorman D, et al. The Marine-derived, Multi-mineral formula, AquaPT Reduces TNF- α Levels in Osteoarthritis Patients. *Journal of Nutrition Health Food Science.* 2014;2:1-3.
334. Frestedt JL, Walsh M, Kuskowski MA, Zenk JL. A natural mineral supplement provides relief from knee osteoarthritis symptoms: a randomized controlled pilot trial. *Nutrition Journal.* 2008;7:9.
335. Ryan S, O'Gorman DM, Nolan YM. Evidence that the marine-derived multi-mineral Aquamin has anti-inflammatory effects on cortical glial-enriched cultures. *Phytotherapy Research.* 2011;25(5):765-7.
336. O'Gorman DM, O'Carroll C, Carmody RJ. Evidence that marine-derived, multi-mineral, Aquamin inhibits the NF- κ B signaling pathway in vitro. *Phytotherapy research : PTR.* 2012;26(4):630-2.
337. Marcu KB, Otero M, Olivotto E, Borzi RM, Goldring MB. NF-kappaB signaling: multiple angles to target OA. *Current drug targets.* 2010;11(5):599-613.
338. He Y, Yue Y, Zheng X, Zhang K, Chen S, Du Z. Curcumin, inflammation, and chronic diseases: how are they linked? *Molecules (Basel, Switzerland).* 2015;20(5):9183-213.

339. Moyer RF, Ratneswaran A, Beier F, Birmingham TB. Osteoarthritis year in review 2014: mechanics--basic and clinical studies in osteoarthritis. *Osteoarthritis and cartilage*. 2014;22(12):1989-2002.