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 Aδ- 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 nerves 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 Aδ-fibres transmit noxious stimuli, whereas thinly myelinated Aδ-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 singling 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 (μ1, μ2, μ3), δ (δ1, δ2), k (k1, k2, k3) 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 adaptions 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 inhibiters) 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 inhibiters) 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 inhibiters; 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 inhibiters), intermediate risk (diclofenac, meloxicam, and ketoprofen etc.) and high risk (tenoxicam, naproxen, indomethacin, diflunisal, piroxicam, ketorolac, and azapropazone predominantly COX - inhibiters) 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, Seretogentic and Endocannabinoid systems [136].

Briefly, like NSIADs 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 nerves 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 decrease 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 though 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 (canobinoide 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 suffers 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 that 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 clams.

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 matric, 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 booth 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	↓ Pain (by ~44%), stiffness (by ~28%), physical function (by ~40%), WOMAC score (by ~41%), compared to no improvements in controls ↑ Karnofsky Performance Scale (by ~22%), compared to no improvement in controls ↑ Treadmill walking distance (345% increase from baseline) compared to 89% in controls ↓ 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	
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	↓ NSAID (celecoxib) dependence (p=0.0252) ↓ Pain (by ~55%) vs placebo	[294]
Curcumin	C3 complex, 500 mg curcuminoid capsules including 5 mg Bioperine, 3 times daily for 6 weeks	↓ Naproxen use (by ~73%) vs controls ↓ Pain (by >38%), function (by ~41%) and WOMAC score (by ~41%) vs placebo	[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	↓ Pain (by ~27%), symptoms (by ~27%) No difference in the above between groups	[296]
Ginger	Diclofenac 50 mg orally or Ginger 750 or Ginger 750 mg and Diclofenac 50 mg orally for 12 weeks	↓ 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%) ↓ Use of rescue medication (paracetamol) in Ginger (50%) and Ginger with Diclofenac (87%) compared to Diclofenac alone (not statistically significant)	[297]
Lithothamnion species (Red Algae)	AquaminF, 267 mg Lithothamnion, 3 capsules per day, 3 times a day for 12 weeks	↑ ROM (by 5.2°) and 6MWD (By 136 ft) following 50% forced reduction from all NSAID in AquaminF vs placebo No difference in rescue medication (acetaminophen) consumption between groups ↑ Six meter walking distance (by~92%) following 50% forced reduction from all NSAID in AquaminF vs placebo	[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	↓ Pain (by ~11%), symptoms (by ~7%), no change in Glucosamine ↑ Sport and recreation (by ~9%), no change in Glucosamine ↑ Timed up and go performance (by 7%), no change in Glucosamine ↓ Rescue analgesic use (by 72%) vs Glucosamine	[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 PGE_2 (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 protases 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 there *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 NFκB 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 tree 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 an 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 corallioide, 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 corallioide 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 that 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 reliving 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.

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