

# ***The Effects of Curcuminoids on Musculoskeletal Pain: A Systematic Review***

Thesis submitted in fulfilment of the Master of Clinical Science

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## Abstract

Musculoskeletal pain creates a serious burden on quality of life across the globe. Its management represents a significant economic cost and monopolizes the time and attention of practitioners involved in medicine and complementary health. Substantial numbers of people use nutraceuticals and traditional remedies to assist in musculoskeletal pain management and improvement of function. Curcuminoids are one group of nutraceuticals which are gaining in popularity and being used for treating musculoskeletal pain. Curcuminoids are extracted from turmeric, which itself is a traditional botanical remedy. The aim of this thesis was to assess the effects of the use of curcuminoids on musculoskeletal pain through a systematic review of the available evidence.

A database search was conducted for studies that assessed the effects of use of curcuminoids by themselves or in combination with other materials on musculoskeletal pain of clinical or experimental origin. It included CINAHL, Embase Cochrane Central, Pubmed, Scopus, Psychinfo and Clinicaltrials.gov. Alternate, traditional medicine and complementary medicine databases including NCCAM and NICM were searched for additional studies.

Locations for the search for unpublished studies included: Mednar, Proquest theses and dissertations, Grey Source, Index to Theses, and Trove (Theses).

The reference lists of all identified reports and articles were searched for additional studies. Studies in English language with human subjects using any form of control including placebo, treatment as usual and before and after measurements were considered for inclusion in the review.

No time limit was imposed on studies for inclusion in the systematic review.



Methodological quality of included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist, and research data was extracted using the JBI Meta-Analysis of Statistics Assessment and Review Instrument (MAStARI) data extraction instruments.

Thirteen randomized controlled trials including 1101 participants were included in this review. The overall quality of included studies was variable. Treatment duration ranged from 10 days to 32 weeks in the studies and included different dosages and presentations of curcuminoids and differing comparators. A high level of heterogeneity between studies and characteristics precluded meta-analysis of findings; therefore, a narrative analysis was presented.

The major finding from the review was that there is currently insufficient evidence to support the effectiveness of the use of curcuminoids in musculoskeletal pain states. Interpretation of this finding needs to be considered in the context of significant limitations imposed by the variable quality of relevant studies, small sample sizes and the small number of relevant studies available for examination. The systematic review found that in the studies examined, the frequency or severity of adverse events relating to the use of curcuminoids was not significantly different from placebo or other study comparators. The findings from the systematic review support the claims of safety in the literature. The absence of long-term follow-up across all studies means that comment on the long-term effect of and safety of the use of curcuminoids in musculoskeletal pain requires further clarifying research.

## Declaration

I, Andrew Gaffey, certify that this work contains no material that has been accepted for the award of any other tertiary institution, and, to the best of my knowledge and belief, contains no material previously published or written by any other person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Andrew Benedict Gaffey

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# Chapter 1: Introduction

## 1.1 Overview

Musculoskeletal pain creates a serious burden and impediment to the enjoyment of life across the globe. The one-year prevalence of experiencing some form of musculoskeletal pain in the previous week appears to range between about 14% and 47% of the general population,<sup>1</sup> with most people experiencing musculoskeletal pain reporting pain from a number of sites.<sup>2, 3</sup> Low back pain and neck pain together, with the category of 'other musculoskeletal disorders', constituted three of the top ten leading causes of global years lived with disability (YLD) in 2013.<sup>4</sup> The category of osteoarthritis (OA), which is itself associated with varying levels of musculoskeletal pain, climbed three places from 16<sup>th</sup> to 13<sup>th</sup> as a leading cause of global YLD from 1990 to 2013.<sup>5</sup>

The management and reduction of musculoskeletal pain represents a significant economic burden and monopolises the time and attention of practitioners involved in medicine and complementary health management. Practitioners face decisions every day concerning which measures at their disposal would be most effective for pain management while at the same time endeavouring to achieve the best health outcomes for their clients. Movement-based treatment approaches such as physiotherapy in the form of joint mobilising, muscle stretching and exercise therapy are successfully used to treat and rehabilitate painful musculoskeletal conditions. These movement-based approaches are often combined with pharmaceutical pain control; however, the most effective pharmaceutical pain control does not necessarily result in the best long-term health outcomes.

At present, paracetamol (acetaminophen)<sup>6</sup> and non-steroidal anti-inflammatory drugs (NSAIDS) are frequently recommended as first-line analgesic treatments for osteoarthritis and

other musculoskeletal pain states.<sup>7</sup> However, there is uncertainty over the safety and/or efficacy of paracetamol<sup>8</sup> and NSAIDs<sup>9</sup> in treating conditions such as osteoarthritis and low back pain. Long term paracetamol use has been associated with abnormal results on liver-function tests<sup>8</sup> and regular/any use of both paracetamol and NSAIDs is associated with an increased risk of kidney cancer.<sup>10</sup> NSAIDs are among the medicines most frequently associated with increased cardiovascular events and hypersensitivity reactions<sup>11</sup> and have been found to increase the risks of upper gastrointestinal bleeding with use.<sup>12-15</sup> Non-selective NSAIDs intake is associated with increases in the risk of post-operative bleeding compared with placebo.<sup>16</sup>

Substantial numbers of people with musculoskeletal pain use other potential sources of pain relief including complementary and alternate medicine (CAM) and traditional remedies.<sup>17, 18</sup> The US National Centre for Complementary Medicine and Alternative Medicine (NCCAM) defines CAM as “the use of products or practices in medical practice that are not considered mainstream”.<sup>19</sup> The percentage of the adult population in western countries using nutraceuticals, CAM or alternative dietary supplements has been variously quoted as close to 40%<sup>20</sup> and as much as 47%.<sup>21</sup> Those numbers appear to be growing. Chronic musculoskeletal pain is the single-most quoted reason (in the UK) for patients to use complementary and alternate medicine.<sup>22</sup>

Curcuminoids are one group of nutraceuticals gaining in popularity and being used as an adjunct to, but also as an alternative, to conventional treatments for musculoskeletal pain. Curcuminoids are extracted from turmeric, which itself is a traditional botanical remedy.<sup>23</sup> Turmeric has a number of traditional uses including pain relief as well as for anti-inflammatory effects.<sup>24</sup> Curcuminoids are considered to constitute the majority of the bioactive fractions of turmeric<sup>25</sup> and to have anti-inflammatory effects.<sup>26, 27</sup>

The focus of this thesis is to assess the effects of the use of curcuminoids on musculoskeletal pain through a systematic review of the available evidence. The aim of the thesis is to advise and inform clinical practice on, and to identify areas of future research in the field of curcuminoid use in musculoskeletal pain states.

## **1.2 Structure of the thesis**

The thesis is structured in four chapters:

The first chapter (introduction) is aimed to introduce the topic by firstly giving an historical context to the use of curcuminoids and their parent plant turmeric, then outlining the curcuminoid fractions of turmeric, their potential bioactive effects and possible mechanism of action through pain modulation. To do this, an understanding of pain mechanisms and musculoskeletal pain is elaborated and given context. The introduction then continues with an explanation of common standardised measurement tools used for pain and function. Pain and function were the primary outcome measures of the systematic review on which the thesis rests.

The introduction concludes with a structured discussion on evidence-based medicine and the place of primary and secondary research. This part holds an explanation of the power and worth of systematic reviews and their methods. It serves to justify the construction of the systematic review, and points to the gap in literature which is filled by the review.

The second and third chapters constitute the methodology and results of the systematic review on the effects of curcuminoids on musculoskeletal pain. This section includes the PRISMA flow diagram, tables elaborating the assessment of methodological quality of the included studies and study characteristics of all included studies, and a narrative summary of the results of the individual studies.

The fourth chapter of the thesis constitutes the discussion of the thesis topic commencing on the broad fronts of musculoskeletal pain control, curcuminoid use and bioavailability, then narrowing to study heterogeneity and sources of bias and pain measurement. The thesis discussion then covers limitations of the systematic review, suggested areas of future research, (both primary and secondary), recommendations for practice and a final conclusion.

Referencing and appendices follow the conclusion of the thesis.

### **1.3 Historical context- Curcuminoids and Turmeric**

Curcuminoids were isolated and the chemical structures identified by Polish chemists Milobedska and Lampe in 1910.<sup>23, 28</sup> Curcuminoids are polyphenols which come from the turmeric root. *Curcuma longa* (turmeric) from the Ginger family (Zingiberaceae) is a plant native to Southeast India which has been used for centuries in cooking and in medicine.<sup>28-31</sup> In cooking, turmeric's common use is as a spice for flavouring and colouring of foods. The root is the portion of the turmeric plant which is most commonly used. It is grated fresh or dried then grated to form a yellow-orange powder. The leaf is used to wrap foods in the cooking process and also to protect foods in transport.<sup>32</sup>

Freshly grated turmeric root has a characteristic bright yellow-orange colour while the colour of the dried grated root is a duller orange. The majority of the colour of the grated root comes from one of the three bioactive polyphenol curcuminoids of turmeric called curcumin.<sup>33</sup>

Turmeric is coded in the International Numbering System for Food Additives (INS) as E100(ii). Curcumin is coded as E100(i).<sup>34</sup>

It is generally accepted that turmeric intake in South-East Asian and Middle-Eastern countries is higher than in western countries.<sup>35, 36</sup> It is usually consumed in curries and dhals with average daily intakes per person in regions in India being variously quoted as 0.6g<sup>37</sup> and

0.9g<sup>35</sup> to 2-2.5g.<sup>36</sup> Korean daily intake of turmeric per person in the period 2008-2012 was estimated as 0.47g.<sup>38</sup>

Historically, turmeric has been used medicinally to assist in the control of inflammation,<sup>39</sup> and pain.<sup>40, 41</sup> The methods of delivery of the bioactive substances for medicinal use include being eaten, or being applied to the skin, gums<sup>42</sup> or wounds<sup>43</sup> as a paste,<sup>44, 45</sup> poultice, or gel.<sup>46</sup>

Anecdotally, inhalation of burning turmeric smoke has been recorded as a folk-remedy for respiratory illnesses in humans, and recent studies have examined the effectiveness of curcumin inhalation for airway inflammation in horses<sup>47</sup> and inhalation for potential Alzheimer's treatment in mice.<sup>48</sup>

## 1.4 Polyphenols

To understand curcuminoids and their effects, it is useful to appreciate that curcuminoids, isolated from turmeric, belong to a larger group of substances with studied bioactive effects called polyphenols. Polyphenols are naturally occurring compounds found in fruits, vegetables and grains.<sup>49, 50</sup> There is evidence to suggest that polyphenols are produced by plants for protection from damage by ultraviolet radiation and to deter predators.<sup>51, 52</sup> As such, polyphenols as a group are seen to possess antioxidant and anti-inflammatory properties dependent upon their individual chemistry.<sup>53</sup> Foods regularly consumed by humans which have been shown to be high in polyphenols include red wine, green and black tea,<sup>49</sup> cocoa,<sup>50</sup> fruits (such as grapes, cherries and apples<sup>52</sup>), some spices<sup>52</sup> and grains. There are four groups of polyphenols which include flavonoids such as quercetin; phenolic acids; stilbenes, such as resveratrol found in grapes, and lastly; lignans, several of which are phytoestrogens.<sup>49</sup>



### 1.4.1 Polyphenols and inflammation

The intake of polyphenols has been shown to have various effects in tissues including antioxidant and anti-inflammatory effects. Antioxidants in general work to remove free radical intermediates, and inhibit other oxidation reactions by being oxidized themselves.<sup>51</sup>

Polyphenols from turmeric have been shown in vitro to exert free-radical scavenging activity.<sup>54</sup>

A bovine study showed curcumin to have antioxidant activity similar to Vitamin C, and considerably higher antioxidant activity than Vitamin E.<sup>55, 56</sup> Many studies have investigated the potential effects of polyphenols on the inflammatory relationship with increased polyphenol dietary intake associated with decreases in markers of low-grade inflammation.<sup>57</sup>

There appears to be methodologically sound evidence from large studies demonstrating the relationship between the consumption of a polyphenol-rich diet and the reduction of the risk of chronic conditions such as obesity and cardiovascular disease in humans.<sup>58-60</sup> Such chronic diseases have a common link of showing elevated inflammatory markers.<sup>61-63</sup> Polyphenols have well-documented effects on down-regulating inflammatory pathways as discussed above<sup>64, 65</sup> and it is plausible to consider the disease-risk reduction seen with the consumption of polyphenol-rich diets is linked to this reduction of low-grade inflammation.<sup>66</sup> Results from the PREDIMED study showed that specific categories of polyphenols have differing degrees of action in reducing cardiovascular risk,<sup>67, 68</sup> with the intake of nuts,<sup>69-74</sup> olive oil<sup>69, 72, 75</sup> and red wine<sup>76, 77</sup> featuring as significant contributors to the benefits of the Mediterranean diet. McKeown et al.<sup>50</sup> determined that polyphenol-rich foods can effect a significant improvement in endothelium-dependent vasodilation following an 8-week intervention in hypertensive participants. This indicates that a simple change to diet (increasing the intake of polyphenol-rich foods) can have a significant positive effect on markers of cardiovascular risk.

### 1.4.2 Polyphenols, inflammation and pain

The link between pain and inflammation varies, as pain is not influenced by tissue factors alone. Inflammation and the associated inflammatory process is mediated by a number of key chemicals in the body, some of which can sensitise or excite specialised nerve endings called 'nociceptors' on A delta and C sensory nerve fibres.<sup>78-80</sup> These are nerve fibres that transmit information to higher centres, which in turn, may be interpreted by the brain as pain. Kidd and Urban<sup>81</sup> relate the experience of pain to activity in the nociceptive system, with this activity resulting from endogenous (within the body) and exogenous (external to body) sources. They include inflammation as an endogenous stressor which occurs in response to tissue damage and typically this is associated with pain.

There are various studies utilising rat models that investigate the effects on the ingestion of polyphenols as a group on certain types of pain. Yin et al<sup>82</sup> found that the polyphenol resveratrol appeared to facilitate pain attenuation behaviours in a rat model of neuropathic pain, and in an unrelated study, resveratrol was able to reduce levels of pro-inflammatory cytokines in vitro and showed pain-reduction potential in a rat model of radiculopathy.<sup>83</sup>

There is little discussion in the literature directly investigating the effect of polyphenols as a group in modulating pain in humans. A small study (utilising 14 subjects with limited range of motion (ROM); most with OA) investigated the effect of a polyphenol-rich blend of fruit juices and pulp on pain and range of motion.<sup>84</sup> It was found that in people with limited range of motion improvements in serum antioxidant status correlated with improvements in pain and ROM.<sup>84</sup> The authors concluded that the reduction of pain in vivo may have been due to resveratrol reducing pro-inflammatory cytokines.<sup>83</sup>

## 1.5 Curcuminoids- the Polyphenols in Turmeric

Turmeric contains at least three naturally-occurring polyphenols termed curcuminoids; curcumin, demethoxycurcumin and bisdemethoxycurcumin.<sup>28</sup> Various studies describe the total curcuminoids by percentage in the turmeric root as falling between 3% and 6% of dry weight.<sup>85, 86</sup> Curcumin is by far the most prevalent curcuminoid found in turmeric,<sup>39</sup> making up around 77% of the total curcuminoids in the plant. Demethoxycurcumin makes up about 17% of the total curcuminoids and bisdemethoxycurcumin about 5% of the total curcuminoids. Curcuminoids are ascribed antioxidant properties<sup>87</sup> and anti-inflammatory properties.<sup>26, 56</sup>

Ahmed and Gilani<sup>88</sup> acknowledge that scientists in some studies use the name of curcumin and curcuminoid mixture (also known as commercial curcumin) interchangeably. They go on to examine in their Alzheimer's Disease review the pharmacodynamic properties of curcumin and curcuminoid mixtures used in various studies and include comment on the respective purities of the compounds. Note that curcuminoids can be isolated from ground turmeric powder in various ways. A common method is an industrial process of steam separation and/or distillation using isopropyl alcohol.<sup>89, 90</sup> This processing serves to concentrate the curcuminoids into a crystalline form. This is not a simple process, and the purity of compounds used in studies with respect to particular amounts of the three fractions of curcuminoids finding their way into the mixture is often not stated.<sup>88</sup> For this thesis, a decision has been made respecting the variability of descriptors used in literature. The decision is that unless the study refers specifically to curcumin or another curcuminoid by name as being the only curcuminoid present in the sample used in the study, the term 'curcuminoids' will be used when commenting on that study. In studies where the authors have made it clear that a specific curcuminoid has been used, then the specific descriptor of that particular curcuminoid will be used in the thesis. Conversely, in studies where the authors have used the descriptor

“curcumin” but have clearly stated that a mixture of curcuminoids was used, then references in this thesis to that study’s active treatment material will be ‘curcuminoids’.

## 1.6 Postulated Bioactive effects of Curcuminoids

Curcuminoids are postulated to have various bioactive effects, with various animal studies showing effectiveness in the treatment of joint inflammation,<sup>91, 92</sup> experimentally-induced rheumatoid arthritis,<sup>93</sup> depression,<sup>94</sup> burn pain,<sup>95</sup> the reduction of serum triglycerides,<sup>96</sup> peripheral neuropathy<sup>97</sup>, diabetic neuropathic pain<sup>98-100</sup>, sciatic nerve chronic constrictive injury resulting in neuropathic pain<sup>101</sup>, experimental acute pancreatitis<sup>102-104</sup> and enhancing wound-healing.<sup>95, 105</sup>

The effects of curcuminoids have also been assessed in insect studies. Fruit-flies (*Drosophila*) fed curcumin-supplemented diets showed increased mean life-span compared with *Drosophila* fed curcumin-free diets.<sup>106, 107</sup> In an interesting vector-control study, curcuminoids showed significant larvicidal activity against the mosquito.<sup>108</sup> In a study assessing termite control, non-curcuminoid fractions of turmeric were found to have termiticidal properties.<sup>109</sup>

Other than musculoskeletal pain, human studies investigating the effects of curcuminoid polyphenols identify significant bioactive effects of curcuminoids on inflammation by reducing mastitis,<sup>110</sup> spermatic cord inflammation,<sup>111</sup> dermatitis due to radiation exposure<sup>112</sup> and large bowel inflammation.<sup>113</sup>

Active metabolites of curcuminoids are produced after oral doses of curcuminoids have been ingested.<sup>114, 115</sup> These include tetrahydracurcumin and hexahydrocurcumin. There is some debate in the literature concerning whether one or all of the curcuminoids, or a specific

metabolite of one or all of them, may be responsible for the bioactive effects seen with the use of turmeric and curcuminoids.<sup>114</sup>

## 1.7 Bioavailability of Curcuminoids

For curcuminoids to have an effect in the body they need to be absorbed. Curcuminoids are relatively hydrophobic and poorly absorbed.<sup>86, 115, 116</sup> Compounding these difficulties is the fact that curcuminoids are swiftly eliminated from the body.<sup>117, 118</sup> The resultant effect is that curcuminoids have a low bioavailability in the body after ingesting or exposure by other means.

However, bioavailability of curcuminoids can be enhanced in various ways. One method is to reduce their hydrophobic nature and enhance their solubility in water. A 12-fold increase in solubility was claimed after heating a curcumin solution in water to boiling for 10 minutes.<sup>119, 120</sup> Another method to increase bio-availability is by combining the curcuminoids with or co-administering them with adjuvants.<sup>121, 122</sup> Curcuminoids can be rendered into nano-particles, bio-optimised by complexation, or used as liposomal curcumin.

### 1.7.1 Adjuvants

An adjuvant is a substance that augments the action of a medication or other agent.<sup>123</sup>

Adjuvants are sometimes termed bio-enhancers.<sup>124</sup> In the case of curcuminoids, adjuvants are believed to be important as they can interfere with the enzymes that catalyse the metabolising of curcuminoids, thereby increasing bioavailability.<sup>125-127</sup>

Piperine (1-piperoylpiperidine) is an adjuvant commonly used with curcuminoids. Piperine is itself a plant extract from Black Pepper (*Piper Nigrum* Linn.) or Long Pepper (*Piper Longum* Linn.).<sup>125, 127</sup> Piperine preparations inhibit glucuronidation,<sup>86</sup> and have been shown to increase bioavailability of curcumin by up to 20-fold.<sup>86</sup>

### 1.7.2 Nanoparticle preparations

Nanoparticle preparations of curcumin (where the particle size has been maintained below 100nm and held in a suspension or gel)<sup>116</sup> have been found to increase bioavailability 9-fold compared with curcumin-piperine combinations<sup>121</sup>. They appear to do this by providing more penetration to membrane barriers due to their reduced size.<sup>25</sup> A way of producing nanoparticle preparations is by dissolving curcumin and polymer in ethyl acetate and stirring, adding the mixture to an aqueous solution containing a stabiliser to form an emulsion, and then homogenising the emulsion followed by further dilution with the final result of nano-precipitation.<sup>128</sup>

### 1.7.3 Complexation

Complexation is the combination of individual atom, ion or molecule groups to form one big molecule. Phytosomes are the combination of a natural active ingredient (for example, curcumin or other curcuminoids) with a phospholipid.<sup>123</sup> The complexation of curcuminoids into phytosomes has been shown to improve bioavailability of curcuminoids by increasing their absorption.<sup>129, 130</sup> As a result, commercial preparations of curcuminoids are often combined with a surfactant such as polysorbate and then termed “bio-optimised”.<sup>131, 132</sup>

Another material apart from polysorbate used to produce a phytosome with curcumin is phosphatidylcholine. Rat studies show that curcumin formulated with phosphatidylcholine furnishes higher systemic levels of curcumin than unformulated curcumin.<sup>133</sup> Uncontrolled human studies claim that such phytosomes are safe to use and increase the absorption of curcumin.<sup>134</sup>

### 1.7.4 Non-Curcuminoid portion of turmeric extract

There is evidence that suggests that the non-curcuminoid portion of turmeric increases or potentiates the effects of curcumin.<sup>121, 135, 136</sup> Some emerging evidence suggests that the non-

curcuminoid portion of turmeric extract can deliver an anti-inflammatory effect of its own; distinct from the effect noted from curcuminoids.<sup>137-139</sup>

## 1.8 Pain and Definitions

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage by the International Association for the Study of Pain (IASP) Task Force on Taxonomy 1994.<sup>140, 141</sup> The human experience of pain is multidimensional and comprises sensory, affective, and cognitive dimensions.<sup>142</sup> Acute pain is pain which is recent in onset, typically but not always, proportional to cause<sup>143</sup> and disappears with the resolution of the pathological process.<sup>144</sup> Chronic pain is defined as pain that has lasted longer than 3 months or beyond the expected time for tissue healing.<sup>145</sup> Pain can be experienced in the absence of tissue damage.<sup>146</sup> Pain is always subjective and as such is difficult to quantify.<sup>146</sup>

Tissue damage results in a myriad of physical and chemical effects in the body. Amongst these effects, if tissue injury is sufficient in magnitude and duration nerve terminals called nociceptors depolarize. At the site of tissue injury various neuropeptides are released which can sensitize/excite nociceptors and increase the rate of neuronal firing.<sup>80</sup> Inflammatory mediators such as bradykinin, prostaglandins and pro-inflammatory cytokines released in the area, augment the transmission of nociceptive impulses along sensory afferent fibers<sup>147</sup> to the spinal cord (second order neurones) and up to higher brain centres. Whether the sensory impulses are registered by the brain as pain depends on many factors, as nociception and pain are not synonymous: pain can exist with or without nociceptive input and nociception can exist without pain.<sup>80, 146</sup>

Pain associated with tissue damage and inflammation is frequently termed nociceptive inflammatory pain. It is caused by activation of the immune system<sup>148</sup> and characterised by the presence of various chemicals including inflammatory cytokines.<sup>149</sup> Resveratrol,<sup>49</sup> and mangiferin<sup>150</sup> have been shown to modulate the production of inflammatory cytokines. Evidence in tumour studies demonstrates that the anti-inflammatory effect of curcuminoids is likely to occur through markedly inhibiting the mRNA and protein expression of cyclooxygenase-2 (COX-2)<sup>151</sup>, and by inhibiting lipogenase (LOX) and inducible nitric oxide synthase (iNOS).<sup>56, 152</sup> Additionally, murine studies have demonstrated a reduction of inflammatory cytokine expression in adipose tissue with the administration of nutritional doses of curcumin and piperine.<sup>127</sup>

In summary, various studies show curcuminoids can have an anti-inflammatory effect and therefore the potential exists to ameliorate pain which arises from inflammation. No studies were found which hypothesized on any potential mechanism by which curcuminoids could ameliorate chronic pain occurring in the absence of tissue inflammation.

Musculoskeletal pain is the clinical description of non-cancer pain associated with bone, joint and muscular tissues<sup>123</sup> including joint sprains and soft tissue strains, pain associated with joint degeneration and osteoarthritic conditions, as well as pain associated with inflammatory conditions such as rheumatoid arthritis (RA). Neuropathic pain (defined as pain caused by a lesion or disease of the somatosensory system<sup>153</sup>) has clinical examples that in the strictest sense can fit the definition of musculoskeletal pain. However, as it is considered a “stand-alone” type of pain condition, for this study it has been excluded from consideration.



## 1.9 The Effects of Curcuminoids on Inflammation

The effects of curcuminoids on inflammation have been well investigated in animal studies.

Rat studies show curcumin has an anti-inflammatory effect on sciatic-nerve constrictive injuries,<sup>101</sup> has anti-nociceptive effects by probable inhibitory effects on c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK),<sup>154</sup> as well as decreasing neuro-inflammation in diabetic neuropathy.<sup>155</sup> Murine studies show reduction of neuro-inflammation due to intervertebral disc herniation with the administration of elastin-like polypeptide-curcumin conjugates delivered into the perineural space.<sup>156</sup> A hamster study showed curcuma oil attenuates arterial injury-induced accelerated atherosclerosis, inflammation and macrophage foam-cell formation.<sup>157</sup>

Human in-vitro studies show curcuminoids can reduce inflammation in human intervertebral disc cells.<sup>158</sup> A recent review by Shezhad, Rehman and Lee<sup>40</sup> discussed the use of curcumin in inflammatory diseases, and acknowledged its effects while citing numerous studies.

## 1.10 Outcome measures relevant to musculoskeletal pain

The systematic review protocol stipulated that the systematic review would consider studies which assessed the effects of curcuminoids on musculoskeletal pain. The protocol stated the primary outcome measures of visual analogue scales (VASs) and/or questionnaires would be considered. The protocol was constructed thus for two reasons. Firstly, studies of effect of a treatment on musculoskeletal pain require reliable, valid tools for standardising measurement of pain to produce data, and secondly, VAS, numerical rating scales (NRS) and questionnaires are the tools commonly used clinically and are the tools commonly represented in studies dealing with musculoskeletal pain.<sup>159</sup>

The experience of pain, (as discussed in Chapter 1.8) is subjective and complex<sup>160</sup> and not easy to quantify. VAS and NRS have been developed to allow measurement of subjective conditions such as the experience of pain and therefore allow comparisons to be made between discrete time frames and differing treatments.<sup>161</sup> VAS are considered valid and reliable in the measurement of parameters of such diverse conditions as chronic<sup>162</sup> and acute pain,<sup>163, 164</sup> mountain sickness<sup>165</sup>, cervical radiculopathy<sup>166</sup>, Botulinum A toxicity in the treatment of cerebral palsy,<sup>167</sup> nasal obstruction,<sup>168, 169</sup> anxiety<sup>170</sup> and acute abdominal pain.<sup>164</sup>

Visual analogue scales are typically, horizontal or vertical lines 10cm (100mm) long with identified start and finish anchors.<sup>171</sup> Standard descriptors of the anchors are used to guide the user. These descriptors are typically “no pain at all” and “pain as worse as it could be” on the left and right line extremes respectively.<sup>172</sup> NRS have also been validated for measurement of pain in a variety of circumstances and conditions similar to VAS. NRS are usually scales of numbers ranging from 0-10 with a descriptor at either end similar to descriptors used in VAS. One study included in the systematic review used a 12-point numerical scale 1-12.<sup>173</sup> Studies comparing accuracy and interchangeability of VAS and NRS are not consistent in their recommendations for use for one in preference to another in all cases. Both seem reasonably valid and useful for pain assessment, with a recent review by Hjermstad et al.<sup>161</sup> stating that NRS is applicable for the unidimensional assessment of pain intensity in most settings.

Various questionnaires are used in the musculoskeletal setting, with those most frequently encountered being involved with the assessment of disability as opposed to the assessment of the pain experience or levels of pain. Many are validated and considered reliable; focussing on a range of applications including low back disability; such as the Oswestry Disability Index (ODI), and the Roland-Morris Disability Questionnaire (RDQ).<sup>174</sup>

In summary, the quantifying of musculoskeletal pain states is complex and difficult. Various assessment tools are in common use, with VAS and NRS not only the most common, but considered the one of the most reliable for the assessment of pain intensity or severity in numerous different settings and conditions.

## 1.11 Validated measures of function

Numerous different evaluation systems exist to assess function. Some are specific to certain disabilities, others to upper or lower limb function or to age groups. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) was developed at the Western Ontario and McMaster Universities as a standardised and functional assessment questionnaire tool for use primarily in hip and knee OA trials.<sup>175, 176</sup> This tool is used to assess function on four arms and has been seen to be repeatable and accurate across populations and age groups.<sup>177</sup> It is simple and quick to administer, and using individual scores for each subscale rather than an aggregate score enhances interpretation.<sup>178</sup> The WOMAC is a commonly-used assessment tool<sup>178</sup> and four of the studies<sup>173, 179-181</sup> included in the systematic review used WOMAC to assess function.

The Japanese Knee Osteoarthritis Measure (JKOM) is an evaluation score for OA that is patient-based with four subcategories: pain and stiffness (JKOM-pain; total of eight questions, 0-32 points), activities of daily living (ADL) score (total of 10 questions, 0-40 points), participation in social activities score (total of five questions, 0-20 points), and general health conditions (total of two questions, 0-8 points) with 100 points as the maximum score. The higher the JKOM score; the more pain and physical disability is experienced by the patient.<sup>182</sup> This evaluation modality has been shown to have reliability and validity through statistical evaluations and comparison with the Western Ontario and McMaster Universities Arthritis

Index (WOMAC) and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).<sup>182, 183</sup> JKOM was used to measure function in one study<sup>184</sup> included in the systematic review.

Lequesne's pain functional index (LPFI) is a validated ten-question survey scored on a 0-24 scale, used to assess function in OA of the knee.<sup>185, 186</sup> It was used in one study included in the systematic review as an outcome measure for the assessment of function.<sup>180</sup> The LPFI has been rated against the WOMAC and VAS for sensitivity to change<sup>187</sup> and also shown to have convergent validity against the Thai-modified WOMAC index.<sup>188</sup>

The KOOS (Knee injury and Osteoarthritis Outcome Score) is a score obtained from a questionnaire that was developed in Swedish and English to be used for short- and long-term follow-up of knee OA and knee injury.<sup>189</sup> The KOOS is made up of five separately scored subdomains, based on 42 individual items. The subdomains are symptoms (seven items), pain (nine items), activities of daily living (ADL) (17 items), function in sport and recreation (five items) and knee-related quality-of-life (QoL) (four items). Each item is scored from 0 (least severe) to 4 (most severe).<sup>178, 189, 190</sup> The KOOS has been validated against the WOMAC in total knee replacement<sup>189</sup> and as an instrument to measure the clinical outcome after the treatment of a focal, symptomatic cartilage defect in the knee.<sup>191</sup> It has been validated as an instrument to measure clinical outcome after arthroscopy of the knee.<sup>192, 193</sup> Translations have been validated for use in knee injury and osteoarthritis for speakers of many languages including Polish,<sup>194</sup> Singaporean English and Chinese,<sup>195</sup> Swedish,<sup>192</sup> Greek<sup>196</sup> and Spanish<sup>193</sup>. The KOOS was used in one study included in the systematic review as an outcome measure for the assessment of function.<sup>197</sup>

The DAS28 is an index used to assess RA that combines information from swollen joints, tender joints, acute phase response and general health.<sup>198</sup> It is one of the most commonly used composite scores in clinical practice.<sup>199</sup> It can be used to assess changes in a patient's condition compared with a baseline. Higher scores indicate higher disease activity.<sup>200</sup> The DAS28 index was developed from the DAS and has been validated<sup>201</sup> but at least one study expresses caution as to its reliability.<sup>202</sup> The DAS28 was used in one study<sup>203</sup> in the systematic review as an outcome measure to assist in assessing changes in function.

The HAQ (Health Assessment Questionnaire) is a functional measure designed to help assess RA in both clinical and research circumstances.<sup>204</sup> It is a questionnaire first developed at Stanford University in 1978 by James Fries and colleagues with the initial paper published in 1980.<sup>205</sup> The HAQ is available in over 60 languages and is typically used in two formats.<sup>206</sup> The full version of the HAQ collects data over 5 generic patient-centered health dimensions.<sup>207</sup> These dimensions include functional disability, pain and discomfort, adverse effects of treatment, costs and premature death.<sup>206, 208, 209</sup> The short (2 page version) HAQ is most commonly used and includes the HAQ Disability Index, the HAQ pain scale (VAS), and the VAS global health scale.<sup>206</sup> The short version HAQ has been validated and culturally adapted for use in many languages apart from English,<sup>209</sup> including Bengali,<sup>210</sup> Thai<sup>208</sup> and Chinese.<sup>211</sup> The HAQ Disability Index was used by one study<sup>203</sup> included in the systematic review as an outcome measure to assist in assessing changes in function.

In summary, there are numerous validated scales used to assess function in literature. The six outcome measures of function used in the studies included in the systematic review are discussed above. They all have been validated and are considered to have reliability and repeatability.

## 1.12 Evidence-based medicine and systematic reviews

Medical and allied health practice is guided by consideration of evidence to support or disprove a particular management or treatment method. Evidence-based medicine is defined as the explicit, conscientious and judicious attempt to find the best possible available research evidence to assist the health professionals to make the best decision for their individual clients.<sup>212</sup> Such evidence is accumulated from research studies designed to test hypotheses of treatment; examine result data before and after treatment, or studies aimed to gather observations of relevant treatment methods and cases.

Previously, the collection of evidence for the support or clarification of a particular treatment or procedure was an ad-hoc process. Individuals would gather studies from publications and journals available to them at the time and collate information from those studies based on their own specific needs and biases. This information would be allied to knowledge based on experience and anecdote, as well as received wisdom from tradition and folklore. Decisions to favour a particular treatment or procedure as such were not necessarily reliable or consistent and fraught with the potential for numerous forms of bias.<sup>213</sup>

More recently, secondary research in the form of reviews of literature have added to the body of evidence. Reviews of literature endeavour to collate in one publication narrative, summaries of studies relevant to one area of investigation. They have assisted decision-making by clinicians through the localisation and synthesis of information and results data. These reviews do not involve a systematic search of the literature and can often include an element of selection bias.<sup>214</sup>

Systematic reviews take secondary research one step further. The method of what now constitutes a systematic review (see below in 1.12.1 The Principles of the Systematic Review)

was formally advocated by the Cochrane collaboration after the establishment of the Cochrane Centre in Oxford in October 1992.<sup>215</sup> This centre continues to carry out systematic reviews to the present day which are published in the Cochrane Library. In addition to Cochrane there are organisations that contribute to the development of systematic review methodology, the Joanna Briggs Institute (JBI) being one of them. The JBI, is a not-for-profit research and development organisation within the Faculty of Health Sciences at the University of Adelaide and has been active in the field of global translation of research evidence into practice since 1996 and publishing systematic review reports in various formats since 1998.<sup>216</sup> JBI works closely with Cochrane and the Campbell collaboration and utilises similar methodology in systematic reviews. JBI systematic reviews are commonly published in the JBI database of systematic reviews and implementation reports.<sup>216</sup> The systematic review discussed in this thesis utilised the recommended methodology of JBI for reviews of effectiveness.(see Principles below 1.12.1)

### **1.12.1 The Principles of systematic review**

Aromataris and Pearson<sup>217</sup> remind the scientific community that a systematic review will influence health care decisions and as such should be conducted with the same rigor expected of all research. These researchers outline the generally-accepted defining features of the systematic review.

The defining features of the systematic review are:

- A clearly articulated question or objective
- Inclusion/exclusion criteria stipulated a priori in the systematic review protocol
- A comprehensive pre-planned search

- Appraisal method of the quality of included studies
- Analysis of data
- Presentation and synthesis of findings
- Transparent reporting.<sup>217</sup>

A clearly articulated question or objective assists researchers in conducting a review but also assists readers to decide whether to read the review. The question puts the review in motion and helps the databases in the task of indexing the review.<sup>218</sup>

Specified, predetermined inclusion/exclusion criteria remove one potential source of reviewer bias and the predetermination improves transparency of the review.<sup>218</sup> The reviewer uses predetermined inclusion and exclusion criteria to sort the studies.<sup>216</sup> The JBI systematic review guidelines; similar to the Cochrane, require this predetermination and extend it to the data extraction method.<sup>219, 220</sup> Publication of this predetermined systematic review protocol is now common practice and the protocol for the systematic review on which this thesis was based was published accordingly in the JBI database of systematic reviews and Implementation reports.<sup>221</sup> The process of publishing the protocol assists in alerting the scientific world of a forthcoming systematic review on a specific question and avoiding duplication.<sup>222</sup> Prospero is an international registry developed in 2013 to record prospective systematic reviews in Health and social care, welfare, public health, education, crime, justice, and international development, where there is a health related outcome.<sup>223</sup> Publication of the systematic review protocol in a registry such as Prospero allows a clear comparison of the predetermined protocol with the completed review; reducing the opportunity of reporting bias in the completed systematic review.<sup>223</sup>



In a systematic review, the search terms are predetermined and are systematically applied across all included databases to identify all relevant studies to the pre-established question. Strong efforts should also be made to identify any relevant unpublished studies which will assist in minimising the potential for publication bias in the review.<sup>224</sup> Carrying out a comprehensive database search reduces the potential for assessor bias to influence the selection of studies as all studies which meet the predetermined criteria should be identified and selected. This approach allows the search to be repeated and tested.<sup>222</sup>

Critical appraisal of the selected studies allows sorting and grading of the studies for inclusion.<sup>224, 225</sup> The use of the same critical appraisal checklist or tool across the studies reduces the potential for reviewer bias and assists the systematic review to present a transparent and repeatable method.<sup>214, 226</sup> The Cochrane tool has become the standard approach to assess risk of bias in randomized clinical trials but is frequently implemented in a non-recommended way.<sup>227</sup> Any assessment tool or checklist used in a systematic review needs to be implemented in a consistent and transparent fashion.<sup>227, 228</sup>

Analysis of data extracted from the included studies follows critical appraisal and sorting of the studies.<sup>213</sup> The extracted data will include details of the participants, interventions, comparators and outcomes (i.e. the PICO) with the outcomes those predetermined and published in the protocol.

### **1.12.2 Systematic Reviews assist in establishing evidence-based medicine guidelines**

A major value of systematic reviews is in establishing evidence-based guidelines. Systematic reviews use a specific predetermined format to conscientiously and judiciously assess the value of evidence from all the primary studies which have met the stated inclusion criteria.<sup>222</sup>

Grading the quality of evidence and the strength of recommendations is commonly carried out

utilising the GRADE system<sup>229</sup> which is seen to provide the highest levels of trustworthy comment on strength of evidence.<sup>226</sup> Evidence-based guidelines are able to include data from other non-systematic and systematic reviews to assist in forming recommendations, guidance and conclusions. The construction of evidence-based guidelines is reliant on best-evidence synthesis using methods which minimise the potential for all forms of bias.<sup>216</sup> Systematic reviews provide the strongest and most-defensible sources of evidence on which to base these syntheses.

In the case of the use of turmeric and curcuminoids, there is a long historical record of use in traditional medicine to help achieve various desirable outcomes<sup>31</sup>, but a lack of high quality studies and evidence of effectiveness. Studies such as the systematic review under discussion are aiming to contribute to evidence-based guidelines for the use of turmeric or curcuminoids in musculoskeletal pain states. At present, there are no evidence-based guidelines for the use of turmeric or curcuminoids in the clinical management of musculoskeletal pain states. Many claims of effectiveness are made in the popular media based on animal studies or human studies with high potential for bias and poor or no controls.

### **1.13 Gap in the literature**

The aim of this study is to address a gap in knowledge of the potential for curcuminoids to assist in the management of musculoskeletal pain by systematically reviewing all relevant studies.

A review of the Cochrane Library, JBI Library of Systematic Reviews, CINAHL, and other relevant databases did not find any past, current or planned systematic reviews on this topic.

Related recent non-systematic reviews included Jurenka,<sup>39</sup> Shen et al.<sup>49</sup> and Gupta et al.<sup>230</sup> Recent related systematic reviews by Lakhan et al.<sup>231</sup> and Sahebkar and Henrotin.<sup>232</sup> included heterogeneous meta-analyses and had significant differences in focus.

Jurenka reviewed the anti-inflammatory properties of curcumin; acknowledging its potential as a therapeutic agent for a variety of inflammatory conditions.<sup>39</sup> Shen et al. reviewed the effects of commonly consumed polyphenols on mechanisms of osteoarthritis and identified that the beneficial effects of curcumin can be achieved through dietary supplementation.<sup>49</sup> Gupta et al.<sup>230</sup> reviewed the therapeutic roles of curcumin in specific diseases and conditions through the examination of clinical trials. Their review commented on a variety of topics which included arthritis, alcohol intoxication, Alzheimer's disease, lupus and numerous other conditions but did not include specific investigation on the role of curcuminoids in treating musculoskeletal pain. In their review, Gupta et al.<sup>230</sup> concluded that curcumin's effects may be linked to modulation of numerous signalling molecules considered key to sensitisation processes associated with pain.<sup>230</sup> The systematic review by Lakhan et al.<sup>231</sup> examined the effects of Zingiberaceae (the botanical Ginger family as a whole which includes turmeric) extracts for pain and concluded they are effective hypoalgesic agents (reduce tissue sensitivity) with a better safety profile than NSAIDs drugs.<sup>231</sup> The Lakhan et al.<sup>231</sup> review differed from the Gaffey et al.<sup>221</sup> systematic review upon which this thesis is based as the Gaffey et al.<sup>221</sup> systematic review specifically focussed on examining the effects of curcuminoids on musculoskeletal pain. The Lakhan et al.<sup>231</sup> reviewers drew the strongest conclusions from a meta-analysis of the results from eight studies; only one of which assessed the effects of curcuminoids for pain. Thus, their strongest conclusions had little relationship specifically to curcuminoids. Additionally, type or category of pain in the Lakhan et al.<sup>231</sup> review was not limited to musculoskeletal pain.

Sahebkar and Henrotin<sup>232</sup> reviewed the analgesic efficacy and safety of curcuminoids in clinical practice and carried out a meta-analysis of pain and algofunctional status, using heterogeneous sources of pain (post-operative, visceral and musculoskeletal), differing controls (placebo and non-selective NSAIDs: (nsNSAIDs)) and heterogeneous dosages of curcuminoids and controls. Due to the heterogeneous nature of the controls, pain sources and dosages of active treatments and controls in the studies examined by Sahebkar and Henrotin<sup>232</sup>, their meta-analysis process could have incorporated statistical flaws. This represents a limitation in their systematic review and questions the results gained from their meta-analysis.

## **Chapter 2: Systematic Review Methodology**

### **2.1 Review Objective**

The objective of this review was to investigate the effect of curcuminoids on human musculoskeletal pain.

### **2.2 Criteria for considering studies for this review**

This review considered studies that included any humans (children, adults and older people) experiencing musculoskeletal pain; including experimentally induced pain.

#### **2.2.1 Types of intervention(s)**

This review considered studies that evaluated the use of turmeric, turmeric extract or curcuminoids on subjects experiencing pain of clinical or experimental origin. Where turmeric or curcuminoids were delivered as one component of a combination of bioactive agents and not individually controlled for, the studies were included but considered separately.

#### **2.2.2 Types of comparator**

This review considered studies with any form of comparator including placebo and active controls. Studies using before and after measurements and treatment as usual as comparators were also considered for inclusion in this review.

#### **2.2.3 Types of outcomes**

This review considered studies that included the following outcome measures: pain diaries, visual analogue scales (VASs), or pain questionnaires. Secondary outcome measures of functionality including activities of daily living and range of motion (ROM) were included. Any reports or data in selected studies on adverse events were included.

## 2.2.4 Types of studies

A range of experimental study designs including randomized controlled trials, non-randomized controlled trials, quasi-experimental and before and after studies were eligible for consideration in this review. Studies published in English were considered without date restriction.

## 2.3 Method of the review

This systematic review was carried out in accordance with a published protocol in The JBI Database of Systematic Reviews and Implementation Reports (registration #1684) and Prospero Centre for Reviews and Dissemination (reg.#CRD42015019039).<sup>221</sup>

### 2.3.1 Search strategy

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was utilised in this review. Firstly, an initial limited search of MEDLINE and CINAHL was undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms was then undertaken across all included databases. It searched terms specific and related to *Pain*, *Curcuminoids* and their parent *turmeric* and *Musculoskeletal* terms and descriptors.

Using the database “PubMed” as the example, these terms and their relations were expanded to cover all variations using the data-base specific abbreviations and macros and combined using Boolean logic terminology (see below) with the resultant located studies being searched by title and abstract for relevance by the principal reviewer (ABG). This relevance search was aimed to ensure all studies meeting inclusion criteria proceeded to full-text assessment. Specifically, due to the large numbers of animal studies published in the field, abstract

relevance screening aimed to ensure identification of all human studies in the field potentially meeting inclusion criteria; excluding animal studies. In addition, the relevance screening of title and abstract assisted in removing studies which were specific to non-musculoskeletal pain sources and therefore not meeting inclusion criteria.

## **PubMed**

### **Pain**

("pain"[MeSH Terms] OR "pain"[All Fields]) OR discomfort[All Fields] OR ("nociception"[MeSH Terms] OR "nociception"[All Fields]) OR ("headache"[MeSH Terms] OR "headache"[All Fields]) OR (delayed[All Fields] AND ("age of onset"[MeSH Terms] OR "age"[All Fields] AND "onset"[All Fields]) OR "age of onset"[All Fields] OR "onset"[All Fields]) AND ("myalgia"[MeSH Terms] OR "myalgia"[All Fields] OR ("muscle"[All Fields] AND "soreness"[All Fields]) OR "muscle soreness"[All Fields]))

### **Turmeric and its active polyphenol curcuminoids**

(curcum[All Fields] OR curcuma[All Fields] OR curcumadione[All Fields] OR curcumadionol[All Fields] OR curcumae[All Fields] OR curcumagalactomannoside[All Fields] OR curcumagalactomannosides[All Fields] OR curcumal[All Fields] OR curcumalactone[All Fields] OR curcumalactones[All Fields] OR curcumall[All Fields] OR curcumalonga[All Fields] OR curcumanggoside[All Fields] OR curcumanoid[All Fields] OR curcumanolide[All Fields] OR curcumanolides[All Fields] OR curcumara[All Fields] OR curcumas[All Fields] OR curcumatherapie[All Fields] OR curcumawurzelstock[All Fields] OR curcumazedoaria[All Fields] OR curcumba[All Fields] OR curcume[All Fields] OR curcumen[All Fields] OR curcumenal[All Fields] OR curcumene[All Fields] OR curcumenes[All Fields] OR curcumenoids[All Fields] OR curcumenol[All Fields] OR curcumenolactone[All Fields] OR curcumenolactones[All Fields] OR curcumenone[All Fields] OR curcumeroid[All Fields] OR curcumference[All Fields] OR curcumi[All Fields] OR curcumia[All Fields] OR curcumaticola[All Fields] OR curcumimoids[All Fields] OR curcumin[All Fields] OR curcumin'[All Fields] OR curcumin's[All Fields] OR curcumin1[All Fields] OR curcumina[All Fields] OR curcuminate[All Fields] OR curcuminato[All Fields] OR curcuminbf2[All Fields] OR curcuminc3complex[All Fields] OR curcumine[All Fields] OR curcuminiiii[All Fields] OR curcuminin[All Fields] OR

curcumininduced[All Fields] OR curcumininoids[All Fields] OR curcuminis[All Fields] OR curcuminkinetic[All Fields] OR curcuminmediated[All Fields] OR curcuminn[All Fields] OR curcumino[All Fields] OR curcuminoid[All Fields] OR curcuminoides[All Fields] OR curcuminoidessential[All Fields] OR curcuminoids[All Fields] OR curcuminoids'[All Fields] OR curcuminoids'components[All Fields] OR curcuminol[All Fields] OR curcuminon[All Fields] OR curcumins[All Fields] OR curcumintreated[All Fields] OR curcumintreatment[All Fields] OR curcuminy[All Fields] OR curcuminy[thymidine][All Fields] OR curcuminy[luridine][All Fields] OR curcumisome[All Fields] OR curcumisomes[All Fields] OR curcumnoids[All Fields] OR curcumoid[All Fields] OR curcumol[All Fields] OR curcumol's[All Fields] OR curcumolhas[All Fields] OR curcumolide[All Fields] OR curcumone[All Fields] OR curcumonoids[All Fields] OR curcumorpha[All Fields] OR curcumstances[All Fields] OR curcumurin[All Fields] OR ("curcuma"[MeSH Terms] OR "curcuma"[All Fields] OR "turmeric"[All Fields])

#### **Musculoskeletal terms and descriptors**

("inflammation"[MeSH Terms] OR "inflammation"[All Fields]) OR ("arthritis"[MeSH Terms] OR "arthritis"[All Fields]) OR ("osteoarthritis"[MeSH Terms] OR "osteoarthritis"[All Fields]) OR ("wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields] OR "wound"[All Fields]) OR ("ligaments"[MeSH Terms] OR "ligaments"[All Fields] OR "ligament"[All Fields]) OR (soft[All Fields] AND ("tissues"[MeSH Terms] OR "tissues"[All Fields] OR "tissue"[All Fields])) OR ("joints"[MeSH Terms] OR "joints"[All Fields] OR "joint"[All Fields]) OR ("muscles"[MeSH Terms] OR "muscles"[All Fields] OR "muscle"[All Fields]) OR ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) OR ("wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields] OR "wound"[All Fields]) OR ("ligaments"[MeSH Terms] OR "ligaments"[All Fields] OR "ligament"[All Fields]) OR ("tendons"[MeSH Terms] OR "tendons"[All Fields] OR "tendon"[All Fields]) OR ("fascia"[MeSH Terms] OR "fascia"[All Fields]) OR musculoskeletal[All Fields] OR DOMS[All Fields] OR (delayed[All Fields] AND ("age of onset"[MeSH Terms] OR "age"[All Fields] AND "onset"[All Fields]) OR "age of onset"[All Fields] OR "onset"[All Fields]) AND ("myalgia"[MeSH Terms] OR "myalgia"[All Fields] OR ("muscle"[All Fields] AND "soreness"[All Fields]) OR "muscle soreness"[All Fields]))



Other data bases searched as discussed in the systematic review protocol (including CINAHL and EMBASE) were searched using a similar strategy to that used with PubMed. The CINAHL search is included as a further example below.

### ***CINAHL***

#### **Pain terms**

TX pain OR TX discomfort OR TX sciatica OR TX headache OR TX delayed onset muscle soreness OR SU Pain

#### *Curcuminoid Terms:*

TX Curcuminoid OR TX curcuminoids OR TX curcuma longa OR TX turmeric OR SU turmeric

Study references were obtained from combining the above fields using “AND” with a subsequent hand-search for relevance.

Thirdly, the reference lists of all identified reports and articles were searched for additional studies not already identified.

Full-text screening was then performed by the principle reviewer (ABG) following the completion of the three-stage search and relevance search of titles and abstracts. Full-text screening found any further studies not meeting inclusion criteria and not previously excluded. As examples, full-text screening facilitated the identification of studies using non-curcuminoid extracts of turmeric and no form of controls.

Studies published in English were considered for inclusion in this review. No time limit was imposed on studies for inclusion in this systematic review as traditional usage of turmeric in medicine has not markedly changed over time.

The databases searched included CINAHL, Embase, Cochrane Central, Pubmed, Scopus, Psychinfo and Clinicaltrials.gov. Alternate, traditional medicine and complementary medicine

databases including NCCAM and NICM were searched for additional studies. Locations for the search for unpublished studies included: Mednar, Proquest theses and dissertations, Grey Source, Index to Theses, and Trove (Theses).

Initial keywords used were:

Turmeric, curcumin, Curcuma Longa, curcuminoids, pain

### **2.3.2 Assessment of methodological quality**

After the data sources were searched for relevant studies, papers selected for retrieval were assessed at the study level by two independent reviewers for methodological validity. This was done prior to inclusion in the review, using standardised critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MASARI) (Appendix II).

A threshold of six 'yes' responses to the assessment questions was required for a study to be included in the review. (Appendix II). Specifically, 'Yes' responses were required for questions seven to ten regarding whether the groups were treated identically other than for the named interventions; whether outcomes were measured in the same way for all groups; whether outcomes were measured in a reliable way; and whether appropriate statistical analysis was undertaken. Each study was then given a Global Quality Rating. Studies which blinded the assessors and had 'Yes' scores  $\geq 80\%$  were considered to be strong quality; those that scored 60% to  $< 80\%$  "Yes" scores were graded as moderate and studies that scored  $< 60\%$  were classed as weak quality. Any questions answered 'NA' (non-applicable) were discounted from the calculation. Any disagreements that arose between the reviewers were resolved through discussion between the two reviewers.

### **2.3.3 Data extraction**

Data was extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix III). Data extracted included specific details about the interventions, populations, study methods and outcomes assessed. Additional raw data clarifying VAS start and end-points was requested from the author(s) of four included studies through personal communication (email).

### **2.3.4 Data synthesis**

Meta-analysis was considered for data synthesis of primary and secondary outcomes. A large degree of heterogeneity between the study populations (including gender balance and age), interventions (curcuminoids, curcuminoids in combination with other herbs, curcuminoids in combination with other herbs and minerals), intervention duration, dosage and outcome assessment tools (VAS, modified VAS, Japanese Knee OA assessment tools, WOMAC, modified ADL scales – non-standardised) precluded any meta-analysis of included studies. Results of all included studies were synthesised in narrative form, with the inclusion of tables to aid in data presentation. The assessment of publication bias was considered, but too few sufficiently homogenous studies were obtained for the creation of an informative funnel plot.

## Chapter 3: Results

### 3.1 Description of studies

A total of 1879 articles were identified from searches of databases and grey literature. After exclusion of duplicates, 1145 articles were screened for inclusion by title and abstract relevance. A further 1122 articles were then removed. Full texts of the remaining 24 publications were assessed and a further eight articles were removed for not meeting the inclusion criteria. One study was removed for using non-matched controls<sup>233</sup> and another for having no controls.<sup>132</sup> One study was removed as its study material was a turmeric extract but contained negligible curcuminoids.<sup>137</sup> One study was removed for having no curcuminoids in the herbomineral mixture.<sup>234</sup> Four studies were removed as the measured pain was from non-musculoskeletal sources.<sup>110, 111, 235, 236</sup>

### 3.2 Methodological quality

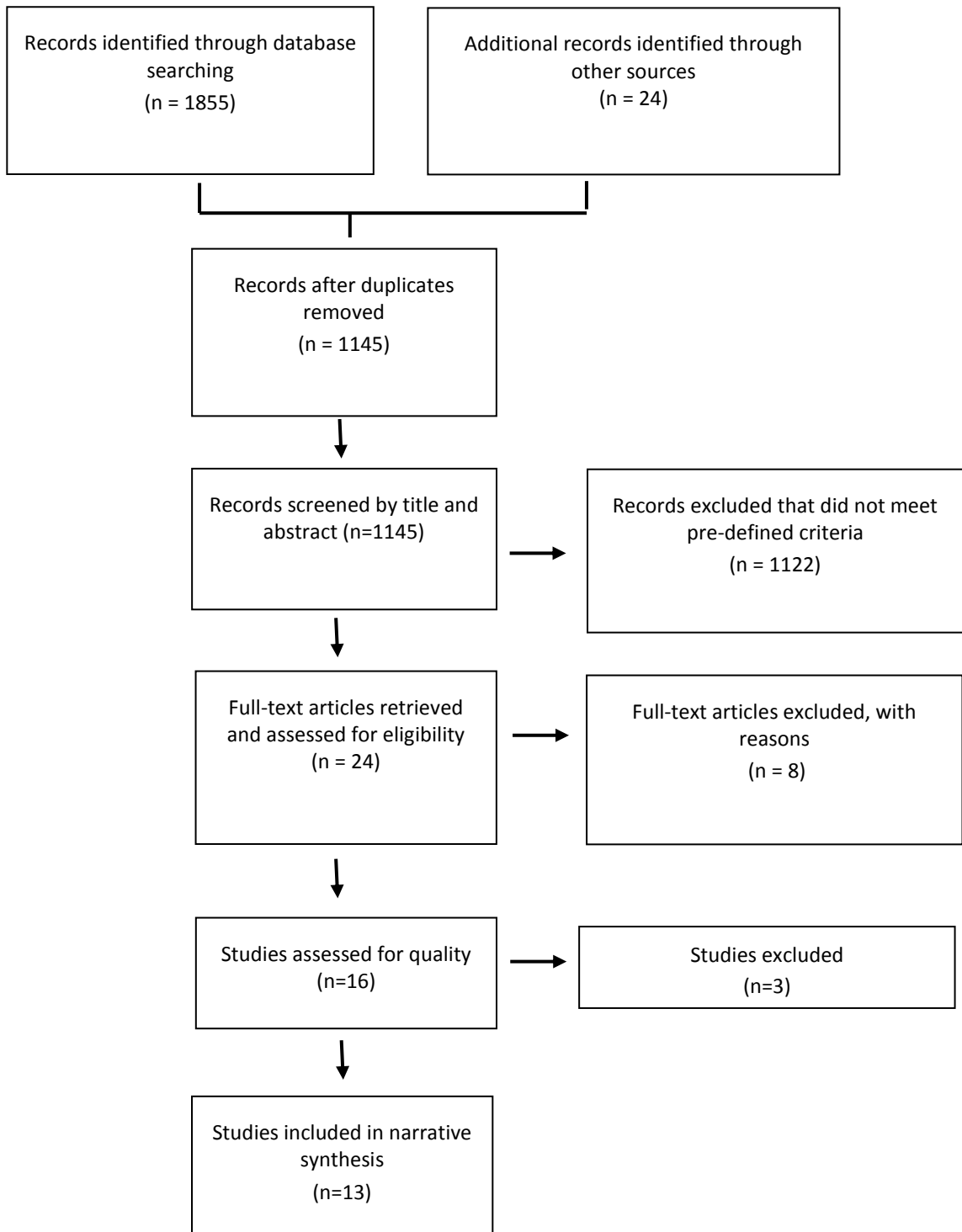
A total of 16 articles were progressed to critical appraisal where a further three studies were excluded. These studies did not achieve minimum quality threshold.<sup>134, 237, 238</sup> Details regarding the study selection process are presented below in Figure 1. Further detail regarding study exclusion is provided in Appendix III. Thirteen articles were included and progressed to the data extraction stage of the systematic review.

All included studies achieved a “Yes” for questions relating to treatment of groups, the measurement of outcomes and statistical analysis (questions 7-10 in the JBI Randomised Controlled Trial (RCT)/experimental study appraisal tool)

Additionally, 12 out of the 13 studies had statistically comparable baseline characteristics (Question 6) for study groups on entry to the studies (92.30%). However, three of the thirteen studies did not blind the assessors (question 5), and three were unclear in their reporting (Table 1).



**FIGURE 1: PRISMA FLOW DIAGRAM**



Flow Diagram of Selection Process : Based on Moher D, Liberati A, Tetzlaff J, Alsmann DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement PLoS Med 6(6): e1000097. Doi: 10. 1371/journal.pmed1000097

**TABLE 1: ASSESSMENT OF METHODOLOGICAL QUALITY OF INCLUDED STUDIES**

| Citation                                  | Q1    | Q2    | Q3    | Q4    | Q5    | Q6    | Q7     | Q8     | Q9     | Q10    | Global Quality Rating |
|---|-------|-------|-------|-------|-------|-------|--------|--------|--------|--------|-----------------------|
| Nakagawa et al. <sup>184</sup>            | U     | Y     | U     | Y     | U     | Y     | Y      | Y      | Y      | Y      | Moderate              |
| Chandran and Goel <sup>203</sup>          | Y     | U     | Y     | Y     | N     | Y     | Y      | Y      | Y      | Y      | Moderate              |
| Kuptniratsaikul et al. <sup>239</sup>     | Y     | U     | Y     | Y     | Y     | Y     | Y      | Y      | Y      | Y      | Strong                |
| Kuptniratsaikul et al. <sup>181</sup>     | Y     | Y     | Y     | U     | Y     | Y     | Y      | Y      | Y      | Y      | Strong                |
| Pinsornsak and Niempoog <sup>197</sup>    | U     | U     | U     | U     | Y     | Y     | Y      | Y      | Y      | Y      | Weak                  |
| Panahi.et al. <sup>180</sup>              | Y     | Y     | Y     | Y     | U     | Y     | Y      | Y      | Y      | Y      | Moderate              |
| Kizhakkedath <sup>240</sup>               | Y     | U     | U     | Y     | N     | Y     | Y      | Y      | Y      | Y      | Moderate              |
| Drobnic.et al. <sup>241</sup>             | Y     | Y     | Y     | Y     | Y     | Y     | Y      | Y      | Y      | Y      | Strong                |
| Kizhakkedath <sup>242</sup>               | Y     | N     | Y     | U     | N     | Y     | Y      | Y      | Y      | Y      | Moderate              |
| Nieman.et al. <sup>173</sup>              | Y     | Y     | Y     | U     | U     | Y     | Y      | Y      | Y      | Y      | Moderate              |
| Udani.et al. <sup>243</sup>               | U     | Y     | U     | N/A   | U     | Y     | Y      | Y      | Y      | Y      | Weak                  |
| Esmaeili Vardanjani.et al. <sup>244</sup> | Y     | Y     | Y     | Y     | Y     | Y     | Y      | Y      | Y      | Y      | Strong                |
| Chopra.et al. <sup>179</sup>              | Y     | Y     | Y     | Y     | Y     | N     | Y      | Y      | Y      | Y      | Strong                |
| % of total count                          | 76.92 | 61.54 | 69.23 | 66.67 | 46.15 | 92.31 | 100.00 | 100.00 | 100.00 | 100.00 |                       |

Legend: Y =Yes, N=No, U= Unclear; N/A= Not Applicable

### 3.3 Systematic review findings

Of the thirteen studies included in this review; three studies investigated the effects of curcumin versus placebo<sup>180, 184, 241</sup>, four investigated curcumin versus active control (NSAIDs),<sup>181, 203, 239, 244</sup> and six investigated presentations of curcumin-containing herbomineral mixtures versus placebo or active controls.<sup>173, 179, 197, 240, 242, 243</sup>

All studies were randomized control trials (RCTs). Population sizes ranged from 10 participants<sup>243</sup> to 367 participants,<sup>181</sup> and were conducted in India,<sup>179, 203, 240, 242</sup> Iran,<sup>110, 180, 244</sup>, Thailand<sup>181, 197, 239</sup>, USA<sup>173, 243</sup> and Japan<sup>184</sup>. The combined population was 1101; with subtotals for curcumin versus placebo of n=110, curcumin versus active control of n=639, and curcumin containing complexes versus any control n=352. Additional data was requested and received from Panahi et al.<sup>180</sup> Further detail regarding the characteristics of included studies are provided in Appendix IV.

The findings are discussed in the three broad categories of curcuminoids versus placebo, curcuminoids versus active control(s), and curcuminoid-containing herbomineral mixtures versus placebo or active controls. Each category of discussion presents sub-heading findings for pain, function and adverse effects.

#### 3.3.1 Curcuminoids vs placebo

Three studies<sup>180, 184, 241</sup> that compared the effects of curcuminoids with placebo were included in this review and are summarised in Table 2. Panahi et al<sup>180</sup> and Nakagawa et al<sup>184</sup> examined the effects of curcuminoids on knee osteoarthritis (OA) pain; while Drobic et al<sup>241</sup> examined the effects of curcuminoids on the pain of delayed onset muscle soreness.

Panahi et al<sup>180</sup> evaluated the clinical efficacy of curcuminoids (1500mg/day, prepared with 5mg bioprene to enhance bioavailability) as measured by changes in VAS and WOMAC in a double-



blind placebo-controlled trial where subjects (N=40) were mostly female (73.7%) Iranian knee OA sufferers. Comparable baseline characteristics of both groups existed on entry.

Nakagawa et al<sup>184</sup> evaluated the short-term effects of highly bioavailable curcuminoids (presented as Theracurmin®, a registered product from Theravalues, Tokyo, Japan giving the equivalent of 180mg/day curcumin) for treating knee OA measured by changes in VAS. They designed a randomized double-blind placebo-controlled prospective study of 50 participants (78.9% female; similar baseline characteristics between groups) which was carried out in Japan over 8 weeks. Drobic et al<sup>241</sup> examined the effect of a commercial lecithinised curcumin (Meriva®) at an equivalent dose of curcumin 200mg twice a day taken for four days following induction of delayed onset muscle soreness (DOMS) in a small study of 20 healthy moderately-active (undergoing regular aerobic exercise for at least 4 hours per week) males. Both treatment group and placebo group commenced supplementation 24hrs prior to a downhill running test designed to induce DOMS. Patient-reported pain intensity was recorded as an outcome, in addition to other biochemical parameters and Magnetic Resonance Imaging (MRI) scanning results.

**TABLE 2: CURCUMINOIDS VS PLACEBO-CONTROLLED STUDIES**

| Author                        | Sample Size | Study Design | Participants/ Condition/ Setting  | Treatment   | Comparison  | Adverse Events  | Analysis  | Reported Results  |
|-------------------------------|-------------|--------------|---|---|---|---|---|---|
| DROBNIC et al. <sup>241</sup> | N=20        | RCT          | All Healthy Males<br>Leg Muscles-Delayed Onset Muscle Soreness (DOMS)<br>Moderate Activity at Least 4 Hrs/Week, Non=Smoking | N=10 (9 after dropout)<br>Phylosome (Meriva®) 1 Gram<br>Bd = 200mg<br>Curcumin Bd | N= 10 Matched Placebo                                     | No AEs Recorded   | Pain Intensity with 0-4 Pain Scale.<br>Two-Way Anova and Tukey-Kramer Test for Pair-Wise Comparisons  | Total Pain in lower limbs at 48 hours No statistically significant differences.<br>Curcumin group total score 23.3 +/-7.9 [17.2;29.4] versus placebo 30.6+/- 7.9[24.9;36.2] P=0.06                          |
| PANAHI et al. <sup>180</sup>  | N=40        | RCT          | Aged < 80yrs with Degenerative Knee OA.<br>Tehran, Iran<br>VAS >= 40mm  | N= 21 (5 Males)<br>Curcuminoids 1500mg/Day capsules for 6/52                      | N= 19 (4 Males)<br>Placebo- inert starch matched capsules | No Serious AEs. No Withdrawal due to AEs.<br>Mild Gastrointestinal Symptoms Reported in 7 Curcuminoid group and 4 Placebo group | Change in WOMAC, VAS, Lequesne's Pain Functional Index.<br>Comparison of Baseline Vs End-Trial Values Used Paired Samples T-Test, Magnitude of Changes Used Independent Samples T-Test. | Statistically significant difference in VAS and WOMAC global favouring the use of curcuminoids:<br>Curcuminoids VAS 66.32±14.2 Baseline 36.3±17.7 Endpt<br>Placebo: VAS 59.05±17.3 Baseline 56.2±14.6 Endpt |

|                                |      |     |   |   |  |  |  |   |
|--------------------------------|------|-----|---|---|--|--|--|---|
|                                |      |     |   |   |  |  |  | Curcuminoids WOMAC global<br>42.4±18.3 Baseline<br>25.0±13 Endpt<br>Placebo WOMAC global<br>44.6±17.3 Baseline<br>40.6±12.6 Endpt<br>p=0.001  |
| NAKAGAWA et al. <sup>184</sup> | N=50 | RCT | Aged > 40 Yrs<br>Knee OA<br>Kellgren – Lawrence Grade II or III.<br>No entry level VAS stipulated | N = 25 (18 after dropouts)<br>5/18 males<br>Theracurmin = 180mg<br>Curcumin/Day for eight weeks | N= 25 (23 after dropouts)<br>4/23 males<br>Placebo for eight weeks | Subjective AEs Resulting in Dropout<br>Curcumin 2, Placebo 1 | Japanese Knee Osteoarthritis Measure (JKOM), VAS from the JKOM with unspecified anchors or scale.<br>2-Sample One-Sided T-Test, Chi-Squared Test | Both treatment group and placebo group showed significant reduction in VAS with no significant difference between groups.<br>Theracurmin Mean VAS 0.52→ 0.20, Placebo Mean VAS 0.42→ 0.21 |

N = number of subjects, RCT = Randomised Controlled Trial, OA = Osteoarthritis, ANOVA = analysis of variance, Sig= significant, VAS = Visual Analogue Scale, Bd = twice daily, Yrs = years, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, Endpt = endpoint

### 3.3.2 Curcuminoids versus Placebo: Measurement of Pain Outcomes

Pain was measured in Panahi et al.<sup>180</sup> using a 0 to 10 cm VAS with the left anchor '0' meaning "no pain" and the right anchor '10' meaning "worst possible pain". Nakagawa et al.<sup>184</sup> measured pain with VAS but did not specify anchors or descriptors. Other measures, including use of rescue medication and reports of joint tenderness, were also recorded. Drobic et al.<sup>241</sup> used a 0-4 pain scale (with '0'= no pain and '4' = disabling pain") on ascending or descending stairs, with patients indicating on a diagram the site of that pain. Drobic et al.<sup>241</sup> did not discuss validation of the scale used.

Panahi et al.<sup>180</sup> measured severity of OA pain with a 0-100mm VAS, and found that treatment with curcuminoids was associated with statistically and clinically significantly greater reductions in VAS scores (of over 15mm (Table 2) compared with placebo after 42 days of curcuminoids treatment.

Nakagawa et al.<sup>184</sup> reported improvements in VAS measures of pain for both intervention and placebo groups compared with baseline data over the length of their study period, with the intervention group showing a greater improvement in VAS, however this did not reach statistical significance. The authors reported that the differences in VAS between groups became significant if those individuals with baseline VAS scores less than 0.15, and therefore with a lesser potential to improve, (three in each group- 16.6% in treatment group, 13.1% in placebo group) were omitted. Raw VAS data, including scale, anchors, and specific before and after measures were not reported by the authors in the study and could not be secured despite a request. The longitudinal nature of the reported findings and the indeterminate nature of the VAS measures prevented their inclusion in any meta-analysis.

In their small study, Drobnic et al.<sup>241</sup> examined experimentally-induced delayed onset muscle soreness (DOMS) and found a non-significant reduction in pain scores in the lower legs for the treatment group compared with the placebo group. However, reduction in soreness between groups was statistically significant for the right and left anterior thigh sites when sites were examined individually.

Panahi et al.<sup>180</sup> recorded the use of naproxen (a non-steroidal anti-inflammatory drug- NSAID) as a rescue medication during the trial. A significantly larger proportion of the subjects (11 of 19= 84%) in the curcuminoids group self-reported a reduction (of unknown amount) of their naproxen use by the end of the study compared with the placebo group (4 of 21). Over one quarter of the curcuminoids group (5 of 19) ceased naproxen use compared with no members of the placebo group over the course of the study.

### **3.3.3 Curcumin versus Placebo: Measurement of Function Outcomes**

Panahi et al.<sup>180</sup> investigated function using the WOMAC scale as a primary measure, and Lequesne's pain functional index (LPFI), as an additional functional measure. The data from the reported results showed that treatment with curcuminoids was associated with significantly greater reductions in WOMAC scores when compared with placebo after 42 days of treatment with curcuminoids. (Table 2) The authors presented LPFI results in graphic form only and stated that the LPFI showed significantly greater reductions when compared with placebo after 42 days of treatment with curcuminoids. The data for Nakagawa et al.<sup>184</sup> who used Japanese Knee Osteoarthritis Measure (JKOM) as a primary functional outcome measure could not be incorporated into a meta-analysis due to its longitudinal nature. That data showed improvements in function over the treatment period for both treatment and placebo groups without a significant difference between the groups.

### **3.3.4 Curcuminoids versus Placebo: Adverse events**

Panahi et al.<sup>180</sup> stated that no serious AEs were recorded and noted 11 cases of mild gastrointestinal disturbance; 7 in the curcuminoid group and 4 in the placebo group (no significant difference.) Nakagawa et al.<sup>184</sup> reported 2 dropouts in the curcumin group (one with a feeling of tachycardia and hypertension on day 50, and another with redness of the tongue on day 6) and one dropout in the placebo group (from feeling unwell) on day 7. Drobic et al.<sup>241</sup> recorded no AEs in their 20 subjects, with one dropout before the exercise phase due to “personal reasons”.

### **3.3.5 Curcuminoids versus a Positive/Active control**

Four studies comparing the use of curcuminoids versus a positive/active control have been included. Chandran and Goel<sup>203</sup> assessed the use of curcumin, 500mg twice daily, against and in combination with diclofenac sodium (an nsNSAID) 50mg in a study of 45 subjects with RA (7 males and 38 females) over 8 weeks (Table 3). Subjects were randomized into three treatment groups of 15 subjects each; curcuminoids alone, curcuminoids plus diclofenac sodium and diclofenac sodium alone. Baseline characteristics were comparable. Kuptniratsaikul et al.<sup>239</sup> assessed the efficacy of 500mg 4 times daily curcuma domestica extracts against ibuprofen 400mg 2 times daily (an nsNSAID) in a study of 107 subjects with OA over 6 weeks. Kuptniratsaikul et al.<sup>181</sup> enrolled 367 OA subjects in a large multicentre study to examine the efficacy of 1500mg/day curcuma domestica extracts versus 1200mg/day ibuprofen assessed by pain reduction and functional improvement over 4 weeks. Esmaeili Vardanjani et al.<sup>244</sup> compared the effects of an applied curcumin solution and applied povidone-iodine solution in the wound healing and pain associated with episiotomy in 120 primiparous subjects.

**TABLE 3: CURCUMIN VS ACTIVE CONTROL STUDIES**

| Author                                | Sample Size | Study Design | Participants/ Condition/ Setting   | Treatment  | Comparison   | Adverse Events (AEs)   | Analysis   | Reported Results   |
|---------------------------------------|-------------|--------------|--|--|--|--|--|--|
| CHANDRAN and GOEL <sup>203</sup>      | N = 45      | RCT          | Adult, 18-65 years Active RA Men (7) and Women (38)                            | N= 15 Curcumin (500mg as BCM – 95mg) bd for 8/52               | Two comparison groups N= 15 Curcuminoids 500mg with Diclofenac (50mg) bd group and N= 15 Diclofenac (50 mg) bd group | 3 AEs in diclofenac group, 2 in curcuminoids group and 1 in diclofenac/curcuminoids group. No significant differences. | Independent T test, ANOVA, Student's T-test  | VAS - mean baseline scores similar with % change from baseline highest in curcuminoids + diclofenac (13.3%). Curcuminoids group showed highest reduction in pain from baseline (59.9%). % changes in all 3 groups statistically significant. |
| KUPTNIRATSAIKUL et al. <sup>239</sup> | N=107       | RCT          | Adult, primary Knee OA, Tertiary Care Medical Centre Bangkok, Thailand VAS ≥ 5 | N=52 (45 after dropouts) Curcuma extracts 500mg/4xday for 6/52 | N=55 (46 after dropouts) Ibuprofen 400mg/2 x Day for 6/52  | 16 AEs in treatment group, 23 AEs in comparison group. NO significant difference.                                      | Repeated ANOVA used to analyse main outcomes. Differences in mean values of pain analysed by independent | Change in pain scores baseline 6/52 assessed between two groups. No sig differences except pain on stairs with Curcumin group  |

|   |         |     |   |   |   |  |  |   |
|---|---------|-----|---|---|---|--|--|---|
|   |         |     |   |   |   |  | T-test. Chi-Square test to analyse adverse events  | sig less pain (p=0.016)   |
| KUPTNIRATSAIKUL et al. <sup>181</sup>     | N = 367 | RCT | Adult, OA Knee (Thai) aged 50 yrs + and Knee Pain VAS ≥ 5/10                                      | N=185 (171 after dropouts) 1500mg curcuma extracts/day for 4/52 | N=182 (160 after dropouts) 1200 mg ibuprofen/day for 4/52 | 55 AEs in treatment group, 65 AEs in comparison group <i>No significant difference</i> | Repeated-measures analysis of variance Mean differences (95% CI) Chi Square test, T Test | No sig difference (not-inferior) between groups in WOMAC scores (p = 0.326, P= 0.531, P= 0.522 and P = 0.278 for WOMAC total, pain, stiffness and functional subscales respectively |
| ESMAEILI VARDANJANI et al. <sup>244</sup> | N=120   | RCT | Primiparous women with no acute chronic disease/allergy. Normal pregnancy & delivery after 37 wks | N=60 (59 after dropout) Curcumin solution 3x day                | N= 60 (58 after dropouts) Povidone Iodine solution 3x day | No AEs specifically recorded, REEDA measures recorded as outcomes                      | Independent 2 sample T test. Mann – Whitney U test.                                      | VAS – no significant Difference. (p= 0.027) @c 24 hrs. At 10 days vs 1 <sup>st</sup> day p = 0.963 .  |

Legend: N = number of subjects, RCT = Randomised Controlled Trial, OA = Osteoarthritis, ANOVA = analysis of variance, Sig= significant, VAS = Visual Analogue Scale, Bd = twice daily, Yrs = years, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, REEDA = Redness, Edema, Ecchymosis, Discharge, Approximation



### 3.3.6 Curcumin versus a Positive/Active Control: Measurement of Pain Outcomes

Pain in the four curcuminoid versus active/positive control studies was measured using four different scales. Chandran and Goel<sup>203</sup> measured with 0-100mm VAS (left anchor 0 =no pain; right anchor 100 = severe pain), Esmaili Vardanjani et al.<sup>244</sup> measured with 0-10cm VAS with 10mm intervals (left anchor 0 = no pain; right anchor 10 = unbearable pain), Kuptniratsaikul et al.<sup>181</sup> with validated Thai modified WOMAC pain measures<sup>188</sup> (0-10cm VAS with the higher measures representing more pain), and Kuptniratsaikul et al.<sup>239</sup> with an 11 point numerical pain scale from 0-10 that related to functional measures (pain on level walking and pain on stairs with unspecified left and right anchor descriptors.)

Esmaili Vardanjani et al.<sup>244</sup> found no significant differences in VAS measures at 24, 48 or 240 hrs after episiotomy. Chandran and Goel<sup>203</sup> reported that mean VAS scores for three study groups (curcuminoids alone, curcuminoids plus diclofenac sodium and diclofenac sodium alone) were comparable at baseline. All groups in the Chandran and Goel<sup>203</sup> study showed a reduction in pain as measured by a 10 cm VAS over the course of the study with the percentages of change in VAS compared with baseline being significant at the end of study. The curcuminoids group showed the greatest reduction in VAS from baseline (59.9%), but this reduction was not significantly different from the reductions found for the other groups. Kuptniratsaikul et al.<sup>239</sup> reported statistically significant improvements in all outcome measures in both groups over the course of the study, and reported that there were no significant between-group differences, with the exception of “pain on stairs”, which was reported as being statistically significantly less in the curcuma domestica extract (curcuminoids) group than in the ibuprofen group. Raw numerical pain scale data was not available for this measure; as such the clinical significance could not be assessed. Kuptniratsaikul et al. reported that both groups showed significant improvements in

WOMAC pain scores over the 4-week study duration, and the non-inferiority test indicated that curcuma domestica extracts (curcuminoids) were non-inferior to ibuprofen when the WOMAC pain subscale was examined. Both groups improved to a similar extent and the improvement represented a clinically significant change (defined as a change in chronic pain levels of 10-20% by the Initiative on Measurement, Methods and Pain Assessment in Clinical Trials (IMMPACT)<sup>245</sup>)

Meta-analysis of pain results from the studies examining curcuminoids versus a positive/active control could not be performed due to dosage differences and differences in study design.

### **3.3.7 Curcuminoids versus a Positive/Active Control: Measurement of Function Outcomes**

To assess function Chandran and Goel<sup>203</sup> used DAS28 (Disease Activity Scale) – a composite index based on the assessment of 28 joints – and a Health Assessment Questionnaire (HAQ) which included 4 categories; dressing and grooming, arising, eating, and walking. The DAS28 and HAQ both showed significant improvement over the course of study for all groups without showing a significant difference between groups. Kuptniratsaikul et al.<sup>239</sup> assessed function with a timed 100m walk and timed stairs ascent and descent. No significant difference was found between groups at the completion of the study. Kuptniratsaikul et al.<sup>181</sup> used WOMAC functional measures with both groups showing significant improvement in WOMAC scores over the study duration. The results of non-inferiority testing indicated that curcuma domestica extracts (curcuminoids) were non-inferior to ibuprofen for the WOMAC function subscale. The heterogeneity of study designs, durations and individual outcome measurement tools precluded meta-analysis of function results from the included curcuminoids versus positive/active control studies.

### **3.3.8 Curcuminoids versus a Positive/Active Control: Adverse Events**

Chandran and Goel<sup>203</sup> reported that adverse events (AEs) were more common in the diclofenac sodium group than in the other groups; three AEs were recorded in the diclofenac group (itching around the eyes, an increase in serum glutamic pyruvic transaminase (SGPT) and SGOT, worsening of condition, and a stated unrelated case of fever), while two AEs were reported for the curcuminoid group (mild fever and throat infection). One case of worsening of condition was reported for the diclofenac sodium plus curcumin group. Kuptniratsaikul et al.<sup>239</sup> reported 16 AEs in the curcuminoid group and 23 AEs in the ibuprofen group continuing the trend of more AEs in the NSAIDS group. The majority of these AEs were dyspepsia, dizziness and stool consistency differences. The rate of AEs was lower in the curcuminoid group (33.3%) than in the ibuprofen group (44.2%), but this did not reach statistical significance. Kuptniratsaikul et al.<sup>181</sup> similarly found that the rate of AEs was lower in the curcuminoid group (29.7%) than in the ibuprofen group (35.7%) with the result not reaching statistical significance. AEs were mainly abdominal pain/distension 33/20, dyspepsia 29/21 and nausea 15/9 for ibuprofen and curcuminoid groups, respectively. Two cases of melena were noted in the ibuprofen group, but none in the curcuminoid group. Esmaili Vardanjani et al.<sup>244</sup> did not specifically report AEs in their study, but did measure and report on REEDA parameters (redness, discharge, ecchymosis and oedema). Those results showed a statistically significant decrease in the curcumin group (a positive finding) compared with the active control (povidone-iodine) group.

### **3.3.9 Herbomineral combinations including curcuminoids versus placebo, mixed or singular active controls**

Six studies examining the effects of various combinations of herbs and minerals (including curcuminoids) on inflammation/ pain were included in this review. The heterogeneous nature of these studies precluded their being combined in a meta-analysis, or being treated as a collective

for comment, as all differed in the treatment makeup, dosage, duration of application and/or comparator. Specifically, treatment-related effects could not be confirmed as being due to curcuminoids, as curcuminoids were presented in combination with other compounds.

Nieman et al.,<sup>173</sup> Chopra et al.<sup>179</sup> and Udani et al.<sup>243</sup> compared differing herbomineral compounds containing curcumin with placebo. Kizhakkedath<sup>242</sup> compared a curcumin/boswellia combination spray with an active control (diclofenac) spray. Kizhakkedath<sup>240</sup> compared a curcumin/boswellia compound in capsule form with celecoxib (an NSAID) in capsule form while Pinsornsak and Niepoog<sup>246</sup> compared the effects of diclofenac (NSAID) plus curcumin with diclofenac plus placebo. (Table 4)

**TABLE 4 CURCUMINOID/COMPLEX MIXTURE VS PLACEBO OR ACTIVE CONTROL**

| Author                                 | Sample Size | Study Design | Participants/ Condition/ Setting   | Treatment   | Comparison   | Adverse Events (AEs)   | Analysis   | Reported Results  |
|--|-------------|--------------|--|---|--|--|--|---|
| Nieman et al. <sup>173</sup>           | N = 108     | RCT          | Charlotte NC USA, subjects 50 – 75 yrs, > 3 mths OA joint pain knees, hips, ankles, shoulders, hands WOMAC 2 (+) | N=54 (50 after 4 dropouts) Instaflex for 8 weeks – 3 capsules per day (1 TID 3 x day)<br>Note: instaflex = 8 substances combined including white willow bark, Boswellia serrata extract, turmeric extract, cayenne, hyaluronic acid, glucosamine sulphate, Methylsulfonylmethane (MSM), ginger root concentrate | N= 54 (51 after 3 dropouts) Placebo (magnesium sterate) for 8 weeks - 3 capsules per day (1 TID 3 x day) | Dropouts N= 4 Instaflex, n=3 placebo (health reasons and non-compliance)                             | Means+/- SD<br>Student T test<br>Generalised estimating equation, response variables<br>Repeated ANOVA | Total WOMAC score: A = 29.4 +/- 2.0 to 19.0 +/- 1.9, placebo 30.0 +/- 2.0 to 24.6 +/- 1.0<br>Joint Pain severity reduced in Instaflex compared with placebo (8 week WOMAC, ↓37% vs 16%, P = 0.025.<br>WOMAC joint stiffness ↓26%vs 18%, P = 0.035.<br>Joint Function index scores ↓36% vs 19%, P = 0.117 (NS) |
| Kizhakkedath <sup>242</sup> (Jan 2013) | N= 26       | RCT          | Medical Centre Kochi Kerala India Subjects 19- 67 yrs both   | N= 13 Curcuma Longa (CL) extract in combination with Boswellia presented in a Spray Bottle  | N= 13 Diclofenac Spray Bottle (metal)  | No adverse events related to Medication. No adverse effects in treatment group; Comparison group one | VAS expressed in mm; averaged and Verbal Rating  | VAS- mean baseline scores → diff in scores baseline to end of study (7 days)  |

|  |       |     |  |  |   |  |  |  |
|--|-------|-----|--|--|---|--|--|--|
|  |       |     | sexes, recent soft-tissue injury last 24hrs, VAS $\geq$ 5,                                       |  |   | G/I event-mild aching and one burning sensation at application site  | Score expressed. One-way ANOVA followed by Dunnet's Test   | % pain reduction after 7 days 72.13% diclofenac 92.06% CL/Boswellia, No stat diff B/W groups; significant changes within each group baseline $\rightarrow$ end |
| Kizhakkedath <sup>240</sup> (Aug 2013) | N= 30 | RCT | Medical Centre in Kochi, Kerala India Adult 18 – 65 yrs with mod OA.                             | N=15 (14 after dropout) CB Formulation (CL 350mg + Boswellia 150mg =500mg) bd over 12 weeks        | N=15 (14 after dropout) Celecoxib (100mg bd)                  | No adverse events. Four dropouts for "own reasons"   | Improvement in 4-point pain scale over 12 weeks. Change expressed as a %                               | 4-point pain scale (no, mild, moderate, severe) Significant change within both groups from baseline to end. NO significant change between groups               |
| Chopra et al. <sup>179</sup>           | N= 90 | RCT | India (PUNE) – arthritis Camps @ centre for Rheumatic Diseases. VAS > 4. Age limit not specified | N=45 (31 after 14 withdrawals) 10males: RA -11 (extracts of curcumin and other herbs) for 32 weeks | N=45 (31 after 14 withdrawals) 13 males; Placebo for 32 weeks | Comprehensive reporting of AEs –no sig diff treatment group vs placebo group. 28 patient withdrawals 14treatment/14placebo | VAS, WOMAC scores, Mean, SD/ change in efficacy over time<br>ITT, with last observations was performed | VAS & WOMAC improved significantly better over time in curcumin and other herbs group than Placebo group<br>Note: no rescue medication                         |

|                             |       |                        |  |  |                         |                            |  |  |
|-----------------------------|-------|------------------------|--|--|-------------------------|----------------------------|--|--|
|                             |       |                        |  |  |                         |                            |  | permitted in this study (32 weeks)   |
| Udani et al. <sup>243</sup> | N= 10 | RCT x-Over Pilot study | Healthy community dwelling untrained Adult subjects b/w 18 and 45 yrs<br>5 men and 5 women | Bounce-Back™ mixture of bromelain, proteases, turmeric extract, phytosterols blend plus Vit C and Japanese knotweed. | Matched Placebo capsule | No adverse events reported | Primary outcome measures pain and tenderness. Pain assessed with VAS, Tenderness with pressure algometer/VAS | Mean differences within and between groups were assessed inferentially at each data collection point using t-tests. Subjects taking the test product experienced significant reductions in <i>current</i> pain at 6 hours (p=0.038) and 48 hours (p=0.001) with no sig diffs at other measurement points. When VAS scores of the four questions asked were summed, the Pre-exercise and 48 hrs post exercise totals were significantly |

|  |      |     |                                |   |   |  |   |   |
|--|------|-----|--------------------------------|---|---|--|---|---|
|  |      |     |                                |   |   |  |   | lower in the test group.  |
| Pinsornsak and Niempoog <sup>197</sup> | N=88 | RCT | Adult 38 – 80 years<br>Knee OA | N = 44 (37 after dropouts) Diclofenac + Curcuminoids for 3 months | N= 44 (36 after dropouts) Diclofenac + placebo for three months | Renal function deterioration 2/37 and facial swelling 1/37 in diclofenac plus placebo group, Hair loss in 1/37 in diclofenac plus curcumin group; [. | Linear model repeated measures<br>Descriptive T test<br>ANOVA | No differences in VAS (P= 0.923), KOOS – no signif diff (p = 0.056) |

N = number of subjects, RCT = Randomised Controlled Trial, OA = Osteoarthritis, ANOVA = analysis of variance, Sig= significant, VAS = Visual Analogue Scale, Bd = twice daily, Yrs = years, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index



### 3.3.9 Herbomineral combinations including curcuminoids versus placebo, mixed or singular active controls: Measurement of Pain Outcome

Different pain scales were implemented across studies. Pain was measured with a 0-10cm VAS by Pinsornsak and Niepoog,<sup>246</sup> and a 0-100mm VAS by Chopra et al.,<sup>179</sup> Kizhakkedath,<sup>242</sup> and Udani et al.<sup>243</sup> Pain was measured with a 4 point verbal scale (“no”, mild”, moderate”, “severe”) by Kizhakkedath,<sup>240</sup> a 0-10 point VRS (no anchors defined) by Kizhakkedath,<sup>242</sup> and with a 12-point Likert scale (12-VS with 1= none at all and 12 = very high levels) by Nieman et al.<sup>173</sup>

Chopra et al.<sup>247</sup> examined the effects of RA -11, a standardised multiplant Ayurvedic supplement (Withania Somnifera, Boswellia Serrata, Zingiber Officinale and curcuma longa) versus placebo on 90 subjects with OA. The supplement was taken twice daily for 32 weeks. No rescue medication was allowed. The authors reported pain assessment results from a 0-100 mm horizontal line VAS graded at 10 mm intervals anchored at 0 and 100 mm (with 0 indicating nil pain). A statistically significant difference in improvement in the treatment group was evident compared with the placebo group.

Kizhakkedath<sup>242</sup> examined the effects of a curcumin/boswellia serrata combination of essential oils topically applied as a spray thrice daily for 7 days compared with spray application of diclofenac in the treatment of the pain of acute soft tissue injury in an open-label study. Outcome measures were VAS and Verbal Rating Scale (VRS). In both groups, results showed a significant difference in pain scores from baseline to day seven (curcumin/boswellia spray 92.06% reduction versus diclofenac 72.13% reduction), with no significant difference seen between groups.

Pinsornsak and Niempoog<sup>197</sup> evaluated the efficacy of curcumin as an adjuvant therapy for diclofenac in primary knee OA. Overall, 44 subjects took diclofenac 75mg/day with curcumin 1000mg/day, and 44 subjects took diclofenac 75mg and a placebo for the study period of 3 months. A 0-10 cm VAS and the Knee Injury and Osteoarthritis Outcome Score (KOOS, which

measures 42 items on 5 separate score subscales), were evaluated monthly as outcome measures. No significant differences were seen between groups in VAS or KOOS at the end of the study, or at any of the time points.

Udani et al.<sup>243</sup> examined the efficacy of a proprietary dietary supplement BounceBack™ (containing proteolytic enzymes including bromelain, curcumin, phytosterols, Vitamin C and resveratrol) to alleviate the severity of DOMS in a small sample of 10 healthy, community-dwelling subjects. Outcomes for pain were measured with 0-10 cm VAS and tenderness measured with a pressure algometer (a device used to measure mechanical tissue sensitivity<sup>248, 249</sup>). This study found that at some (not all) time points in the study interval, BounceBack™ significantly lessened the complaint of pain and tenderness from DOMS compared with the placebo.

Kizhakkedath<sup>240</sup> evaluated the effects of a combination of 350mg curcuma longa extract and 150mg boswellia serrata extract (CB formulation) = 500mg bd against celecoxib (an NSAID) 100mg twice daily over 12 weeks in a small study of 28 OA subjects. Symptom scoring and evaluations were carried out by an orthopaedist using questioning (4-point pain scale “no”, “mild”, “moderate”, “severe”) and clinical evaluation of joint-line tenderness. The results showed significant improvements in symptom scores within both groups over the study for pain and joint-line tenderness. There were significant differences between groups in measures of pain and joint-line tenderness, with the CB formulation being associated with the greater improvement in these measures.

Nieman et al.<sup>173</sup> examined the effects of ingestion of Instaflex™ joint supplement (a cocktail of seven different components that included curcumin, boswellia serrata, white willow bark extract and four others) versus placebo, over 8 weeks in a 50-75 years population. Primary outcome

measures obtained pre-and post-study were joint-pain severity, stiffness and function (WOMAC). Joint pain symptom severity was measured with a 12-point Likert visual scale (12-VS). Results obtained showed a statistically significant reduction in joint pain severity in the Instaflex™ group compared with the placebo group commencing after 4 weeks of the study.

### **3.3.10 Herbomineral combinations including curcuminoids versus placebo, mixed or singular active controls: Measurement of Function Outcome**

Nieman et al.<sup>173</sup> measured function with WOMAC measures, which include measures of stiffness and joint function that showed no significant differences over their study. Udani et al.<sup>243</sup> measured function with flexion/extension ROM measures. These measures showed no significant difference over their study, with the exception of a single time-point measure (6 hrs post exercise) on the right leg only, which significantly favoured the test product. Chopra et al.<sup>179</sup> used WOMAC to assess functional efficacy. Results showed a significant difference in improvement of WOMAC in the treatment group vs placebo group. Kizhakkedath (Aug 2013)<sup>240</sup> measured function with walking distance and ROM. Walking distance and ROM increased significantly for both groups with no significant difference between groups. The author drew the conclusion that the CB formulation was as efficacious as celoxicoxib (NSAID) in improving ROM and distance walked. Pinsornsak and Niepoog<sup>246</sup> measured function using the KOOS, which was used by the authors as a validated extension of the WOMAC. They found no statistically significant difference between groups in KOOS score.

### **3.3.11 Herbomineral combinations including curcuminoids versus placebo, mixed or singular active controls: Adverse events**

Udani et al.<sup>243</sup> and Kizhakkedath (Aug 2013)<sup>240</sup> reported that there were no AEs in their studies. Kizhakkedath (Jan 2013)<sup>242</sup> reported no AEs in the curcuminoid/boswellia group and 2 events in the diclofenac group (one mild GI disturbance, and one redness at the application site). Chopra

et al.<sup>179</sup> reported a total of 28 withdrawals in their study; 14 from the treatment group and 14 from the placebo group; however, they stated that no withdrawals in their study were due to drug toxicity. Chopra et al.<sup>179</sup> reported two deaths in the treatment group (myocardial infarct and cerebral haemorrhage) which were ascribed to pre-existing known medical conditions. Nieman et al.<sup>173</sup> reported a total of seven dropouts in their study (four in the curcuminoid-containing-cocktail group and three in the placebo group), not related to study medication. No other AEs were recorded in the study. Pinsornsak and Niepoog<sup>246</sup> reported two cases of renal function deterioration and one case of facial swelling in the control group (diclofenac plus placebo), against one case of hair loss in the diclofenac plus curcuminoid group.

## **Chapter 4: Discussion and Conclusions**

### **4.1 Introduction**

The use of curcuminoids for the relief of pain and inflammation has a long history in traditional medicine across SE Asia and the subcontinent. The support for this traditional use is found primarily in anecdote, ritual and folklore.<sup>24</sup> This thesis examined available evidence in studies aiming to test the effectiveness of curcuminoids in experimental and clinical musculoskeletal pain states. The systematic review was successful in identifying 13 studies of sufficient quality to assist in answering this question of effect.

#### **4.1.2 Structure of the discussion**

This discussion firstly examines the influences from the systematic review on the systematic review findings. Heterogeneity of the included studies is noted in this part with a brief elaboration on the risks of biases in the included studies.

The findings are then discussed with respect to effects of curcuminoids in acute pain states. The discussion then comments on effects of curcuminoids in chronic pain states, acknowledging that all included studies had short durations.

Size of dose and effect of curcuminoids on pain is next discussed with special comment on adjuvants. Following dose and effect, is an examination of the issue of statistical significance versus clinical significance in the measurement of pain and function.

The body of the discussion concludes with comment on the safety of curcuminoids from a wider literature focus narrowing to the specific findings of the systematic review.

## **4.2 Heterogeneity of Included Studies**

### **4.2.1 Characteristic Variation**

Studies included in the systematic review fulfilled predetermined criteria and aimed to examine (as a primary or secondary outcome) the effects of curcuminoids on musculoskeletal pain. As it was not predetermined that the studies included should be homogenous in all characteristics, this resulted in considerable heterogeneity being seen in the five major characteristics of the included studies; namely site and structure affected by musculoskeletal pain, duration of intervention, dose and dose frequency, comparator, and rigour of recording. These characteristics are discussed below in greater detail.

### **4.2.2 Site of musculoskeletal condition and heterogeneity**

The site of the musculoskeletal pain condition considered in the studies included in this review varied from osteoarthritic joints,<sup>137, 173, 179-181, 184, 197, 239, 240</sup> and rheumatoid joints,<sup>203</sup> to perineum episiotomy wounds<sup>244</sup> and acute clinical soft-tissue injury.<sup>242</sup> This was a complication because scales and tools of measurement used to assess pain at the different sites are often validated for a particular joint (as illustrated by the KOOS<sup>6, 189</sup>) or validated for a particular population and joint (as illustrated by the JKOM<sup>183</sup>). This resulted in considerable variation in methods used for assessing outcome measures, creating the potential for varying operator and assessor biases, which reduced the confidence with which results could be compared across studies.

### **4.2.3 Duration of intervention and heterogeneity**

The characteristic of duration of intervention examined in the included studies varied from 4 days to 32 weeks, with this heterogeneity limiting the ability to pool data on duration of treatment/duration of effect seen from treatment. This issue is covered in greater detail with a wider literature focus in section 4.8 (Dose/effect and duration of effect).

#### 4.2.4 Dose/frequency or level of intervention

The characteristic of dose of intervention was heterogeneous across the studies included in this review. The total dose of treatment curcuminoids (or curcuminoid equivalent in mixtures) given to subjects varied considerably, with a range from 180mg/day equivalent to 2000mg daily. (Further discussion on dose and effect can be seen in section 4.8 below). Compounding the issue of dose-variation as a source of heterogeneity, six studies<sup>173, 179, 197, 240, 242, 243</sup> combined other bioactive materials with differing amounts of curcuminoids in their active treatments. In these studies, there was variation in both the dose or fractional amount of curcuminoids and also the types of compounds (and their dosages) that were presented with the curcuminoids. In all of these cases, no cross-study comparisons could be made due to heterogeneity.

The assessment of the use of curcuminoids for musculoskeletal pain can be considered to still be in its infancy, and few quality studies using human subjects have been undertaken using the administration of curcuminoids alone as the active treatment. A total of two studies included in this review used the same daily dose of curcuminoids. However, their results could not be directly compared or statistically pooled as the comparators they used differed (placebo and NSAIDS) along with other characteristics.

#### 4.2.5 Variation of comparator or treatment

Interpretation of findings was further complicated as the comparison treatment in the studies varied between placebo,<sup>137, 173, 179, 180, 184, 241</sup> NSAIDS (4 studies- 2 studies with the NSAID comparator ibuprofen,<sup>181, 239</sup> one study diclofenac<sup>242</sup> and one study celecoxib<sup>240</sup>), antibacterial agent,<sup>244</sup> or other nutraceuticals.<sup>197</sup> This variation of comparator across the review precluded the statistical pooling of results of the included studies as a whole or in subgroupings.

With respect to treatment, included in the review were four studies<sup>173, 179, 240, 242, 243</sup> which used curcuminoids combined with other herbs and minerals as treatments compared with some form of active control or placebo. Four of these studies reported significant findings reporting that the curcuminoid-containing treatment substance significantly reduced pain. No definitive conclusion can be drawn from these studies however, as no two or more studies used the same mixture of ingredients with comparable study structure thereby precluding meta-analysis due to heterogeneity. Additionally, as there were mixtures of ingredients (with each individual ingredient in the mixture having the potential to modulate pain or function), curcuminoids cannot be singled out as the reason for the improvement in these studies in pain or function. Specifically, treatment related effects could not be confirmed as being due to curcuminoids, as curcuminoids were presented in combination with other compounds.

#### **4.2.6 Differences in recording outcomes**

Differences in recording and reporting the primary and secondary outcomes existed between most of the included studies. Visual analogue scales used had varying anchor descriptors or none stipulated, and varied as to the unit of measurement (present or absent) in the scale. Changes in VAS over study durations were not recorded uniformly across studies with some studies omitting full disclosure of raw figures and using line graphs alone to demonstrate changes. This increased the potential inaccuracy of comparisons of changes in VAS values for pain across studies. Secondary outcomes of function were generally poorly examined across studies with variable recording of four different scales of function (WOMAC, JKOM, KOOS and LPFI). Differing scales of measurement of function precluded pooling of function data across studies.



In summary, high heterogeneity of individual characteristics of studies in the review precluded the ability to pool data across studies. As a result, conclusions able to be drawn from the review are limited.

### **4.3 Risk of bias in included studies**

The critical appraisal process undertaken as part of this systematic review aimed to exclude studies of insufficient quality. As such, studies with an unacceptably high level of potential of bias (see section 1.12.1) were excluded. However, the included studies still had methodological weaknesses.

Overall, the risk of selection and performance bias in the included studies was low due to randomised allocation to treatment groups and the blinding of subjects. Furthermore, the baseline characteristics of the different treatment groups did not significantly differ within any of the included studies. With respect to assessor or detection bias, three studies out of the thirteen did not blind the assessors while a further four studies were unclear in their reporting. As such, half of the included studies were open to potential assessor bias. The consequences of assessor bias include the possibility that by knowing the group which a participant belongs to (treatment or comparator), conscious or unconscious changes to responses or measurements can be recorded or influenced by the assessor.<sup>222</sup> Responses highlighting or supporting a particular hypothesis may be afforded more attention by the assessor than those responses opposing that hypothesis. This creates an increased risk that any reported changes are due to knowledge of which intervention was received, rather than the effect of the intervention itself.<sup>222</sup> Contextually, the overall effect of assessor bias is likely to be an increase in the possibility of an overestimation of treatment effect. The attrition rates between groups were not significantly different in any studies, and reasons for withdrawal or loss to follow-up were well described. Similarly, as outcomes were

measured using validated measures, scales and tools and methods of reporting were transparent, the overall risk of reporting bias for the review was assessed to be low.

#### **4.4 Curcumin or turmeric and use in acute pain states.**

Four studies were included in this review which dealt with acute pain. Two of these studies investigated experimentally induced DOMS, one investigated acute joint pain from joint sprains and strains, and one investigated acute pain from recent episiotomy wounds. In all these studies, pain was of recent onset, with duration measured in days and well-less than three months. Note that pain enduring for three months or longer can be considered chronic pain.

With specific reference to the study dealing with the pain of episiotomy wound, where the use of a Povidone-iodine solution was compared with the use of a curcuminoid solution, no significant difference was found in pain levels between the curcuminoid group and the povidone-iodine group in pain over the course of the study. However, the authors' focus in this study was to assess wound healing, with pain being a secondary measure. Pain in this study was measured at only two time-points. The first point at 24-48 hours post-delivery, with the second ten days post-delivery. There were no interim pain measures taken. Both groups were similarly painful at day one with a relatively fresh wound, and similarly close-to pain-free at Day 10. It could be concluded that both groups reporting minimal pain at day ten of the study was reflective of the progression of the wound-healing process. The reduction of pain may have been assisted or impaired, accelerated (or decelerated) by the use of curcuminoids but the study design in lacking interim pain assessment points was unable to detect this data.

The other three studies dealing with acute pain states similarly did not generate statistically significant findings. Subject numbers were small to very small; potentially under-powering the studies.

In the systematic review, the lack of evidence for curcumin moderating acute pain states is due to the paucity of studies of any quality, the small numbers of subjects in those studies and study-design heterogeneity. As a result, the anecdotal references to curcuminoids and turmeric being useful in pain control in acute pain states have neither been supported or disproven in this systematic review. More substantial studies with similar study methods are required before any conclusion can be made as to the effectiveness or efficacy of the use of curcuminoids or turmeric in acute clinical or experimental pain states.

#### **4.5 Curcuminoid or turmeric use in chronic pain states**

Most studies included in the systematic review involved pain associated with the clinical condition of osteoarthritis. OA is a chronic health condition and the commonest form of arthritis. OA affects joint surfaces as well as the joint capsule and surrounding ligaments.<sup>250</sup> It commonly results in a low-grade ache felt in and around a joint punctuated with periodic flare-ups of inflammation and pain. As such, the pain experienced can be of extended duration, and if that duration exceeds three months, falls into the category of chronic pain.<sup>1, 251</sup>

The majority of the studies examining the pain of osteoarthritic joints in the systematic review did stipulate some osteoarthritic changes be visible on radiological imaging (most commonly Kellgren-Lawrence Gd II changes) for the individual to be included in the study. Thus, in those individuals in those studies it can be accepted that the chronic condition of OA was present.

However, radiological changes and the severity of such changes do not necessarily correlate with levels of pain or pain complaints.<sup>252</sup>

The systematic review found insufficient evidence to support the use of curcuminoids in chronic musculoskeletal pain states where the duration of pain experienced was of three months or greater. Problematically, none of the studies examined used durations of treatment greater than 12 weeks. Additionally, none of the studies included long-term follow-up beyond the end of the study period or beyond three months. Not only was no long-term follow up carried out, but no studies followed up any treatment period with assessment of symptoms at time intervals when the subjects were not ingesting either treatment or comparator. To be able to make cogent comment on effects of a treatment on chronic conditions which include pain states, follow-up assessments should be made at time intervals which reasonably could encompass common periods of remission and exacerbation. In literature, such follow-up points have been set at varying intervals, from six months<sup>253</sup>, one year,<sup>254</sup> to 5 years<sup>67</sup> or longer.

There is a cultural and historical use of turmeric and curcuminoids in the short term (< 12 weeks) for the reduction of pain associated with osteoarthritic joints.<sup>33, 255</sup> There is insufficient evidence from the few studies as identified by the systematic review to support or dispute this practice of short-term pain relief. Animal studies do support the use of curcuminoids for the reduction of inflammation as measured by inflammatory markers. Human in-vitro studies show reduction of inflammatory markers with use of curcuminoids. The inflammation associated with OA can be linked with the appreciation of pain associated with the condition, although pain and inflammation do not always closely align.<sup>80, 148</sup> It would seem reasonable that further human studies may clarify this link.

## 4.6 VAS/NRS and pain assessment- general

As pain is a subjective experience, it is difficult to measure objectively. In examining levels of pain and fluctuations in levels, meaningful, reliable, repeatable and robust measures are required.

Standardised pain questionnaires, visual analogue scales (VAS) and numerical Rating Scales (NRS) for pain, are in widespread use and are accepted as reliable and valid.<sup>256</sup> All studies in the systematic review used pain questionnaires and/or VAS or NRS to measure pain and changes in pain over the time of the studies. Several of the studies found a statistical difference in pain measures between groups in their study and reported on these significant findings. Seven out of thirteen studies in this review<sup>179, 184, 197, 203, 242, 244, 257</sup> used VAS, which is a patient-reported measure, however the specific scales used were not uniform across the studies. Some studies used a 10cm visual analogue scale with divisions at 1cm intervals whereas some used a 100mm scale with no divisions; with differing anchor descriptions or no anchor descriptions. Studies were also not uniform in stating whether their VAS or NRS was administered relating to pain experienced over the previous 24hrs or pain experienced at the time.

## 4.7 VAS- statistical significance versus clinical significance

When assessing levels of pain, patient-reported measures such as VASs and NRSs are by definition applied from the point of view of each individual subject. Even though the scale of measurement used by each subject in a particular study is the same (e.g. 10 cm VAS), the subjective meaning of each increment or division to each individual can vary. Not all changes in pain levels will be considered by the patient important and considerations of importance may be related to magnitudes of change from their baseline. For example, if a subject has no pain at all and their baseline is zero, any additional pain that is felt will be measured on the scale. To that subject, going from nothing to something, however small an increment, may assume great

importance and imply tissue damage or seriousness. To another subject who is already experiencing high levels of pain, a change from say 7 to 8 on the scale may assume a lesser importance.

Clinical significance refers to a change in outcome measures that represents a clinically important difference for the subject, which should be sufficient to influence a clinician to consider a change in clinical management.<sup>258</sup>

Seven out of thirteen studies in this review<sup>179, 184, 197, 203, 242, 244, 257</sup> used VAS to assess levels of pain. For VAS, the Initiative on Measurement, Methods and Pain Assessment in Clinical Trials (IMMPACT)<sup>245</sup> identifies difficulties in determining minimal clinically important differences (MCID). This body has tabulated provisional benchmarks which suggest that reductions in chronic pain intensity of at least 10-20% appear to reflect a minimal clinically important difference (MCID), while reductions of 30% or greater reflect a moderate clinically important difference. Salaffi et al<sup>259</sup> directly address this issue and conclude that in chronic OA states a two-point difference on a 0-10cm VAS represents a clinically-important outcome. Six studies in this review examined OA states, thus it follows that a two-point difference in VAS in those studies could be considered to represent a clinically-important outcome.

Only one of the two OA placebo-controlled studies (Panahi et al<sup>180</sup>) in the systematic review demonstrated just over two-points of difference on the VAS, favouring the use of curcuminoids. As such, their statistically significant finding also represented a clinically important difference. The study design used by Panahi et al<sup>180</sup> had an important point of difference which distinguished it from the other placebo-controlled, OA study. Panahi et al<sup>180</sup> stipulated baseline entry-point VAS measures of  $\geq 4$  which meant that a reduction or an increase in pain levels of 2 points was available on the scale and able to be recorded if it did occur. This reduced the potential for a

potentially-confounding floor effect. On the other hand, the other placebo-controlled study in the systematic review (Nakagawa et al<sup>184</sup>) did not stipulate a baseline entry-point of any VAS value, which resulted in some subjects entering the study with minimal levels of pain as measured on the VAS. It can be extrapolated that by not setting a minimum-baseline VAS for entry into the study and accepting subjects with minimal entry-levels of pain, the authors of the study may have encountered floor effects in their VAS measurements. Nakagawa et al<sup>184</sup> found non-significant findings with respect to change in pain levels over their study, but did find significant changes if they analysed their data by removing the data of those subjects which entered the study with very small VAS levels. While not confirming the presence of significant floor effects, this finding supports the idea that floor effects may have contributed to the authors' non-significant findings.

#### **4.8 Dose/effect and duration of effect**

There were insufficient studies utilising similar designs included in the systematic review to construct a meaningful dose/effect graph for curcuminoid use. However, the majority of studies utilised a curcuminoid dosage of 1000+mg/day and related this dose to previous dose-tolerance studies of curcumin.<sup>130, 239, 260, 261</sup> It should be noted that although the included studies referred to previous dose-tolerance research on curcuminoids, none referred to any previous dose/effect studies to justify the dose used in their respective trials.

All four studies that reported statistically significant reductions in pain associated with OA<sup>137, 180, 181, 239</sup> used oral doses of curcuminoids of 1000mg or more per day. The only study which utilised less than 1000mg/day in examining the pain of osteoarthritis (the authors used 180mg of Theracumin®), showed a reduction in pain that did not reach statistical significance.<sup>184</sup> Not reaching significance in this instance may well have been related to magnitude of dosage of curcumin, but also could have been related to the study design. The Nakagawa et al.<sup>184</sup> study

appropriately incorporated subjects who had radiographical measures of OA (Kellgren-Lawrence II or III), but did not specify a baseline cut off for pain intensity at entry into the study (as previously discussed above in 4.7-( VAS- statistical significance versus clinical significance). All other studies using VAS as a measure of pain in this review,<sup>137, 180, 181, 239</sup> stipulated that subjects experienced a VAS pain level of 4cm or greater (a pain level close to the midpoint of the 0-10cm VAS) on entry to the study This ensured that if there was a potential MCID to be detected (a change of over around 18% in VAS) it could be seen, and not precluded by a floor effect.

Measures to improve bioavailability of curcuminoids such as co-administering with piperine are carried out to make the oral use more effective.<sup>126, 257</sup> Only one study<sup>180</sup> included in the systematic review co-administered curcuminoids with piperine. That study (Panahi et al.<sup>180</sup>) found a statistically significant and clinically significant improvement over the study period of pain levels in the curcuminoid group versus the placebo group as measured by VAS. Further studies using piperine are needed to clarify this finding.

Duration of administration of curcuminoids varied considerably in the studies included in the systematic review. The shortest duration of administration was 4 weeks, with the longest being twelve weeks. The studies' outcome measures were measured only over the duration of the administration period and not beyond. There were no long-term follow-ups or collections of data reported beyond the end-points of the studies. A lack of long-term follow-up means that no comment can be made about the durability of effect seen (if any) or the lack of any durability of effect of the administration of curcuminoids. It also means that no comment can be made from the results around effects on chronic pain, as the length of administration and follow up never exceeded 12 weeks in any of the studies (as discussed above in section 4.5). As such, the findings on effect may well only be pertinent to the time in which the curcuminoids were present



in the participants' systems. No reliable human studies discuss clearance times of curcuminoids,<sup>262</sup> while animal studies have been unable to clearly establish parameters such as time to peak levels in the serum or half-life of curcuminoids in vivo.<sup>262</sup>

Duration of effect is also important in discussing potential or actual adverse effects and their occurrence and relation to dose. As curcuminoids are rapidly eliminated from the system it could be assumed that the duration of effect is transient. However, this assumption cannot be established as fact unless long-term follow-up studies are conducted in which curcuminoids are first administered and then withdrawn with outcomes continuing to be monitored for an extended period of time. The studies included in this systematic review do not extend the discussion on duration of the effects of curcuminoids as no follow-up data was collected or presented.

#### **4.9 WOMAC and function assessment**

WOMAC measures of function were examined as secondary outcomes in four included studies in this systematic review.<sup>173, 179-181</sup> Only one of these studies (Panahi et al.<sup>180</sup>) directly compared curcuminoid use with placebo and showed a statistical significant change (improvement) in function as assessed with WOMAC.

As with VAS measures, an understanding of what constitutes a clinically significant difference in WOMAC measures needs to be examined, as small, statistically significant results can be recorded which would have little clinical relevance to a patient.

Stratford et al<sup>263</sup> suggest that for the pain subscale of the WOMAC, a 4-point difference (4/20) or 20% from baseline to the end of study would constitute a true change, and by extension, an MCID. Hmamouchi et al<sup>264</sup> suggest a 16% reduction in the total WOMAC represents the MCID in a Moroccan OA knee population. Using these guidelines, the statistically significant WOMAC

measures of function changes seen in the placebo-controlled study of Panahi et al<sup>180</sup> achieve minimal to moderate clinical significance. As an isolated result, unable to be statistically pooled with other findings, caution should be used in considering its relevance to clinical practice.

#### **4.10 Safety of Curcuminoids**

Use of curcuminoids in large doses (up to 8g/day), and as a daily dose for up to three months, is considered safe in humans.<sup>261, 265, 266</sup> Across all studies assessed in this systematic review, the reported AEs were not significantly different in number of events or seriousness of events comparing the placebo groups or active control groups. This finding supports these claims of safety. Animal studies in general support these claims of safety of curcuminoids, although a study identifies adverse effects of curcuminoids on isolated blastocysts of pregnant mice.<sup>267</sup>

Caution concerning extended use of NSAIDS<sup>9, 268</sup> and paracetamol is recommended in literature<sup>269, 270</sup>, with a recent review of randomised controlled trials (RCTs) of spinal and osteoarthritic pain<sup>8</sup> commenting that patients taking paracetamol are nearly four times more likely to have abnormal results on liver-function tests compared with those subjects taking placebo. The four studies in the systematic review which directly compared curcuminoid use with that of nsNSAIDS showed a trend of fewer AEs in the curcumin groups, but did not report specifically on liver-function or kidney function tests. As a result, there can be no comment or discussion forthcoming about the relative merits of curcuminoids versus nsNSAIDS with respect to kidney or liver function from the findings of the systematic review.

Likewise, as no studies in the systematic review or literature search examined curcuminoid use against paracetamol use for pain modulation, no comment can be made on the comparative effects of paracetamol and curcuminoids on pain modulation.

## 4.11 Significance of the findings

The findings of this systematic review extend the understanding around the use of curcuminoids in the short term (< 12 weeks) for the amelioration of pain but are insufficient to make recommendations for or against its use in musculoskeletal pain states. This systematic review matters because it clarifies those areas around the use of curcuminoids where our knowledge is strong. It also importantly outlines numerous areas where our knowledge is insufficient to make evidence-based recommendations for practice pertaining to the use of curcuminoids. At present, paracetamol<sup>6, 269</sup> and NSAIDS<sup>250, 269, 271, 272</sup> are commonly recommended for use as simple analgesics for pain control in specific or non-specific acute or persistent musculoskeletal pain states<sup>251</sup> including pain arising from OA. Current best-practice recommendations are silent on the use of curcuminoids in these pain states. This is probably an appropriate reflection on the current literature where there is a lack of high level evidence to support the use of curcuminoids in musculoskeletal pain states.

## 4.12 Limitations of the review

The systematic review upon which this thesis is based was limited by several internal features its design. The scope of the review was limited by the examination of only studies available in the English language. This potentially resulted in the exclusion of otherwise relevant studies. This limitation may be particularly important as the characteristics of the studies which were found suggest that the majority of research being carried out in this field was conducted in non-English speaking countries. It can be reasonably assumed that publishing findings in English represents a challenge to many researchers from non-English speaking background. As such, limiting by language could have created the potential for systematic reporting bias, as researchers with negative or non-significant results might have been less likely to invest time and effort into

translation compared to researchers with significant positive findings. The review was further limited by the acceptance of studies which compared the effects of combinations of potentially bioactive ingredients including curcuminoids with placebo or other compounds. For these studies it was impossible to determine which, if any, effects on musculoskeletal pain states could be attributed to curcuminoids as they were not presented as isolated treatments.

With respect to pain measurement (the primary outcome) in the review, the systematic review did stipulate types of pain measurement tools acceptable for the included studies (VAS and pain questionnaires) but did not clearly stipulate all parameters of the presentation or use of those tools. There are different measurement tools/scales for VAS and also different possible baselines, entry points and cut-offs for VAS. By not stipulating these details, studies were included in the systematic review with heterogeneous VAS anchors, descriptors and entry points (as discussed above in section 4.6). Those differences introduced heterogeneity into the assessment of pain levels across the review. Further heterogeneity of data was introduced by the systematic review protocol not stipulating whether VAS should be used as a retrospective assessment tool for pain (pain experienced over a past period) or pain being experienced at the time of the VAS administration. As a result, VAS data gathered from studies included results where the measurements were for pain experienced over the previous 24 hours, or pain measured where the time point or time frame was not stipulated. These issues of heterogeneity contributed to the preclusion of the meta-analysis of VAS pain data across studies.

With respect to the secondary outcome measured in the review (function), the systematic review protocol discussed the use of measures of functionality including activities of daily living and ROM. It did not stipulate any specific measurement tools to be used, and as a result the systematic review accepted studies which used a wide range of measures of function (including

WOMAC, JKOM, and LPFI as discussed in section 1.9) with differing presentations and usage protocols. The disparity between function measurement tools and the accuracy of their use made the comparisons of changes in function impossible across studies and once again precluded the conduct of meta-analysis.

A number of external factors associated with the characteristics of the included studies further limited the systematic review. The primary external limitation was the small number of studies which satisfied the inclusion criteria and were of sufficient quality for inclusion. Of the thirteen studies included, only three directly compared the use of curcuminoids with placebo in musculoskeletal pain conditions. As discussed above, differences in study design between those three studies (and heterogeneity of all others in the review) precluded statistical pooling of any degree across the review as a whole or when the studies were rendered into subgroupings. Additionally, the small number of studies meant that any assessment of publication bias would have been inappropriate.<sup>273</sup> The next limitation related to the sample sizes of the included studies. Seven of the 13 included studies had small (50 or less) sample sizes. The small sample sizes of these studies reduced their statistical power and created the potential for spurious findings through chance. The studies in the systematic review with the largest sample sizes used nsNSAIDs with known and accepted modulating effects on musculoskeletal pain as comparators. This meant that any findings from those studies could only be related to the relative effect of curcuminoids compared with nsNSAIDs on musculoskeletal pain. These findings therefore did not assist in directly answering the question of the effects of curcuminoids on musculoskeletal pain.

Further limitations in the review arose from a disproportionate representation of gender in the sample subjects. Overall, the studies recruited more women which reduces the validity of

generalising any findings from those studies to the wider population. Additionally, the fact that most study populations were recruited from Thailand, Iran, or Southern India further limited generalisability. Furthermore, caution on the generalisation of findings to the whole musculoskeletal pain population is warranted as most studies primarily dealt with osteoarthritic knee-joint pain. Those studies that evaluated OA knees did use a standardised outcome measure (0-100mm VAS), but there was inconsistency between studies in reporting the pain as measured by VAS being from activity or pain over the previous 24 hours, or pain being experienced currently as discussed above in 4.6 and 4.12. Further heterogeneity was introduced in the assessment of stage of OA experienced by the subjects. Operator assessment of the subjects' stage of OA was inconsistent between studies. The assessment varied from a diagnosis made from radiographs with a standardised assessment scale (Kellgren-Lawrence grade II-III), to clinical orthopaedic comment (mild-moderate OA). No studies commented on intra-operator reliability with respect to the assessment of stage of OA in subjects, or with respect to any of the assessment methods. The inconsistency of reporting of stage of OA, and the lack of comment on intra-operator reliability raises the question of an increased potential for selection and assessor bias in those OA studies. In those studies, there is the potential for one operator to give greater weight or significance to a particular feature than another operator may under the same clinical situation.

## **4.13 Recommendations**

### **4.13.1 Recommendations for practice**

Further research is needed before any strong recommendations for practice relating to the use or non-use of curcuminoids in musculoskeletal pain states can be made. The small number of studies included in the systematic review and the heterogeneity of findings from the review inform

this comment. It should be noted that many of the difficulties seen in the systematic review in pooling data were due to the variation in the assessment tools used and the method of their use and the recording of data. It is recommended that when measuring pain and function researchers and clinicians should use standardised assessment tools, exert rigour in the standard method of use of the tools, record the method used and contemporaneously record data. It is also recommended that researchers include appropriate follow-up intervals in their studies, particularly if dealing with people experiencing chronic musculoskeletal pain.

#### **4.13.2 Recommendations for primary research**

##### ***Curcuminoids versus Placebo using standardised dosages***

At present, despite the numbers of published studies investigating curcuminoids increasing at a rapid rate, there are still very few high-quality studies directly comparing the use of curcuminoids with placebo in musculoskeletal pain conditions. Those studies that exist involve small sample sizes, less-than robust research study design and variable dosages of curcuminoids. Initially, therefore, high quality, larger-scale studies using standardised dosages of curcuminoids are needed to extend the findings from the few existing studies to clarify whether the use of curcuminoids has an effect on musculoskeletal pain states.

##### ***Longer trial durations***

The literature on the effect of curcuminoids on musculoskeletal pain is primarily made up of isolated findings from a few short-term studies. As such, further high quality research using robust research design (RCTs with larger clinical samples) is required to examine the use of curcuminoids for longer periods. At present there are no quality primary studies which examine curcuminoid use beyond 12 weeks in modulating musculoskeletal pain. Future research where the study design focusses on the use of curcuminoids mid-to-long term (beyond 12 weeks), will

facilitate insight into the effects of the use of curcuminoids on chronic musculoskeletal pain states.

### ***Curcuminoids versus active alternate pharmacological agents***

Future primary research is recommended to be performed comparing the use of curcuminoids with the use of active alternate pharmacologic agents (such as nsNSAIDS) in musculoskeletal pain conditions. Two studies were included in the systematic review which did compare the use of curcuminoids with ibuprofen. However, further studies utilising a similar study design, but with standardised dosages of curcuminoids are recommended to replicate and clarify their findings and give insight into the relative value of the use of curcuminoids versus the use of ibuprofen. It is also recommended that similar primary research studies be conducted to assess comparison effects of curcuminoids versus other active alternate pharmaceutical agents such as selective NSAIDS (sNSAIDS) and paracetamol (acetaminophen) in various musculoskeletal pain states.

### ***Differing population age-groups***

Studies focussing on different age-group populations are needed as most existing human studies involve older-aged subjects. A lack of studies on younger age groups bring into question whether findings can be generalised to the wider population. Designing studies with a younger age-group (such as 30-50 years) would assist researchers to generalise any findings to the community.

### ***Other categories of musculoskeletal pain***

Many of the present studies in the field of musculoskeletal pain and curcuminoids target OA. It is accepted that one of the major risk factors in osteoarthritis is increasing age<sup>274, 275</sup> and that OA is the most common cause of musculoskeletal disability in the elderly.<sup>276</sup> These are likely to be the underlying reasons behind older subjects constituting the largest proportion of the subjects in OA studies. It is recommended that studies to assess the effects of the use of curcuminoids on other



categories of clinical musculoskeletal pain which have a wider prevalence distribution in the population such as low back pain, or neck pain be designed. Using those categories may allow a more comprehensive assessment of curcuminoid effects on musculoskeletal pain in younger populations as well as adding to the field of general knowledge on the effects of the use of curcuminoids.

***Populations external to South-East Asia, Middle East and the Indian subcontinent***

Most of the current human research in musculoskeletal pain and curcuminoid use is carried out in South-East Asia, the subcontinent or the Middle East. Generalisation of findings from present studies to the wider population would have more validity if there were more studies involving larger representative samples from the wider world community. As such, broadening the current scope of research with more of this research being performed outside South-East Asia and the sub-continent is important.

***Study Design investigating absorption and elimination of curcuminoids in humans***

Several very important questions pertaining to the absorption of curcuminoids in vivo in humans are yet unresolved and are barely studied. These are: the time taken to peak in the serum; whether magnitude of individual dose bolus matters to absorption; and the time taken for curcuminoids to be eliminated from the system. It is conceivable that a single study primary study design could be constructed to assess all three of these questions. Until these questions are answered, any discussions of dose and effect of curcuminoid use lack evidence.

Other remaining questions existing around absorption of curcuminoids relate to whether there is a latency of effect or duration of effect beyond the administration period. These questions would be best asked after further research clarifies if an effect occurs and how magnitude of effect (if any) relates to dose required to produce a MCID in pain.

### ***Study Design utilising non-curcuminoid extracts of turmeric versus placebo in musculoskeletal pain states***

A small number of studies exist which discuss the effects of the non-curcuminoid portion of turmeric on inflammation and pain.<sup>39, 137, 277</sup> More robust primary research using larger sample-sizes is required to clarify their limited findings. Such research could specifically compare the effects on musculoskeletal pain of the non-curcuminoid fractions of turmeric extract with placebo. Elaboration of this primary research to directly compare the effects (if any) of the non-curcuminoid fraction of turmeric extract with the effects of the curcuminoid portion of turmeric extract on musculoskeletal pain would be enlightening.

### **4.13.3 Future secondary research**

#### ***Qualitative Systematic Reviews***

Current primary research shows a dearth of strong evidence for the use of curcuminoids, even while the use of curcuminoids grows in popularity.<sup>262</sup> This growth in popularity could be linked to a groundswell of word-of-mouth opinion concerning the use of curcuminoids or to other unknown factors. No qualitative reviews were found related to the use of curcuminoids in musculoskeletal pain states in the search. Future secondary research could explore this occurrence of increasing use of curcuminoids and give insight to the reasons behind it, utilising a qualitative systematic review approach.

Such a qualitative review could examine “Factors affecting the choice of curcuminoids to modulate musculoskeletal pain”. Another qualitative systematic review could explore the narrative “The lived experience of curcuminoid or turmeric use for musculoskeletal pain” in those already using curcuminoids for this purpose.

### **Quantitative Systematic Reviews**

As there is a growing field of research into neuropathic pain treatments and complementary medicines,<sup>278</sup> a future suggested quantitative systematic review could ask the question “what are the effects of curcuminoids on neuropathic pain?”. Systematic reviews considering the effects of curcuminoids on other categories of pain, such as trigeminal neuralgia or low back pain, would also add to the body of knowledge.

Likewise, the examination of curcuminoids on post-operative wound pain has been explored in primary research<sup>105, 244, 279, 280</sup> but has not yet been examined in a quantitative systematic review. As a field, wound -care with curcuminoids and turmeric has historical roots which have informed some of the primary researchers.

Additionally, it is of note that there are authors suggesting some bioactive effects can be related to the non-curcuminoid portion of turmeric.<sup>137, 277</sup> Secondary research in the form of a quantitative systematic review examining the effects of turmeric or turmeric extract not containing curcuminoids on musculoskeletal pain is recommended. Such a quantitative systematic review would add to the body of knowledge and assist in clarifying which component of turmeric (or group of compounds) if any was most bioactive.

## **4.14 Conclusion**

The systematic review synthesized preliminary data in human studies examining the use of curcuminoids to ameliorate musculoskeletal pain. The major finding from the review was that there is insufficient evidence to support the effectiveness of the use of curcuminoids in musculoskeletal pain states. Interpretation of this finding needs to be considered in the context of significant limitations imposed by the variable quality of relevant studies, small sample sizes and the small number of relevant studies available for examination. The systematic review

underscored the concern that the body of evidence in the use of curcuminoids for musculoskeletal pain is still very small despite a rapidly growing interest in the wider community.

The systematic review found that in the studies examined, the frequency or severity of adverse events relating to the use of curcuminoids was not significantly different from placebo or other study comparators. The findings from the systematic review support the claims of safety in literature of the short-term use of curcuminoids. The absence of long-term follow-up across all studies means that comment on the long-term effect of and safety of the use of curcuminoids in musculoskeletal pain requires further high-quality research.

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# Appendix I: Critical Appraisal Instrument

From the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MASARI)<sup>216</sup>

## JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer ..... Date .....

Author ..... Year ..... Record Number .....

|   | Yes                      | No                       | Unclear                  | Not Applicable           |
|---|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. Was the assignment to treatment groups truly random?                             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Were participants blinded to treatment allocation?                               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Was allocation to treatment groups concealed from the allocator?                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Were the outcomes of people who withdrew described and included in the analysis? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Were those assessing outcomes blind to the treatment allocation?                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Were the control and treatment groups comparable at entry?                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Were groups treated identically other than for the named interventions           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. Were outcomes measured in the same way for all groups?                           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. Were outcomes measured in a reliable way?  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 10. Was appropriate statistical analysis used?                                      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
|   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Overall appraisal:    Include                     Exclude                     Seek further info.

Comments (Including reason for exclusion)

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# Appendix II: Data Extraction Instrument

From the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MASARI)<sup>216</sup>

## JBI Data Extraction Form for Experimental / Observational Studies

Reviewer ..... Date .....

Author ..... Year .....

Journal ..... Record Number .....

### Study Method

RCT                       Quasi-RCT                       Longitudinal

Retrospective                       Observational                       Other

### Participants

Setting \_\_\_\_\_

Population \_\_\_\_\_

### Sample size

Group A \_\_\_\_\_ Group B \_\_\_\_\_

### Interventions

Intervention A \_\_\_\_\_

Intervention B \_\_\_\_\_

Authors Conclusions:  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Reviewers Conclusions:  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Study results**

**Dichotomous data**

| <b>Outcome</b> | <b>Intervention ( )<br/>number / total number</b> | <b>Intervention ( )<br/>number / total number</b> |
|----------------|---|---|
|                |   |   |
|                |   |   |
|                |   |   |
|                |   |   |

**Continuous data**

| <b>Outcome</b> | <b>Intervention ( )<br/>number / total number</b> | <b>Intervention ( )<br/>number / total number</b> |
|----------------|---|---|
|                |   |   |
|                |   |   |
|                |   |   |
|                |   |   |

## Appendix III: Excluded studies

### Studies excluded at Full-Text Stage (N= 8)

Afshariani, R., Farhadi, P., Ghaffarpasand, F., Roozbeh, J., Effectiveness of topical curcumin for treatment of mastitis in breastfeeding women: a randomized, double-blind, placebo-controlled clinical trial. **Reason for exclusion:** Non-musculoskeletal pain

Badria FA, El-Farahaty T, Shabana AA, El-Batoty MF, Hawas SA. Boswellia -- curcumin preparation for treating knee osteoarthritis: a clinical evaluation.<sup>233</sup> **Reason for exclusion:** Non-matched controls

Di Pierro F, Rapacioli G, Di Maio EA, Appendino G, Franceschi F, Togni S. Comparative evaluation of the pain-relieving properties of a lecithinized formulation of curcumin (Meriva®), nimesulide, and acetaminophen.<sup>130</sup> **Reason for exclusion:** Non-musculoskeletal Pain

Henrotin Y, Gharbi M, Dierckxsens Y, *et al.* Decrease of a specific biomarker of collagen degradation in osteoarthritis, Coll2-1, by treatment with highly bioavailable curcumin during an exploratory clinical trial.<sup>132</sup> **Reason for exclusion:** No controls

Kulkarni, M. P., Shakeel, A., Shinde, B. S., Rosenbloom, R. A., Efficacy and safety of E-OA-07 in moderate to severe symptoms of osteoarthritis: a double-blind randomized placebo-controlled study<sup>234</sup> **Reason for exclusion:** No curcumin in the herbomineral mixture

Madhu K, Chanda K Saji MJ, Safety and efficacy of curcuma longa extract in the treatment of painful knee osteoarthritis; a randomised placebo-controlled trial<sup>137</sup> **Reason for exclusion:** Negligible curcuminoids in the extract

Ryan JL, Heckler CE, Ling MN, Williams JP, Pentland AP, Morrow GR. Curcumin for radiation dermatitis: A randomized, double-blind, placebo-controlled clinical trial of 30 breast cancer patients.<sup>112</sup> **Reason for exclusion:** Non-musculoskeletal Pain

Satoskar RR, Shah SJ, Shenoy SG. Evaluation of anti-inflammatory property of curcumin (diferuloyl methane) in patients with postoperative inflammation.<sup>111</sup> **Reason for exclusion:** Non-musculoskeletal Pain

### Studies Excluded at Critical-Appraisal Stage (N= 3)

Belcaro, G., Cesarone, M. R., Dugall, M., Pellegrini, L., Ledda, A., Grossi, M. G., Togni, S., Appendino, G., Efficacy and safety of Meriva(R), a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients<sup>134</sup>**Reason for exclusion:** Did not meet critical appraisal threshold. non-random allocation to groups, free use of rescue medication over the course of the study, 2 authors employees of Indena S.p.A (manufacturers of Meriva® -the material under examination in the study)

Nicol LM, Rowlands DS, Fazakerly R, Kellett J. Curcumin supplementation likely attenuates delayed onset muscle soreness (DOMS)<sup>238</sup>**Reason for exclusion:** Did not meet critical appraisal threshold; due to unclear measurement of outcomes with respect to reliability and uniformity of measurement between groups

Kulkarni, R. R., Patki, P. S., Jog, V. P., Gandage, S. G., Patwardhan, B., Treatment of osteoarthritis with a herbomineral formulation: a double-blind, placebo-controlled, cross-over study<sup>237</sup>**Reason for exclusion:** Did not meet critical appraisal threshold; due to unclear blinding of evaluators, unclear whether data was collected in the same way for both groups through the study- (data missing or incomplete), unclear measurement of outcomes with respect to reliability and uniformity

## Appendix IV: Characteristics of included studies

| Study   | Methods                     | Participants   | Intervention A  | Intervention B                          | Notes   |
|---|-----------------------------|--|---|---|---|
| Chandran, B. and Goel, A., 2012 <sup>203</sup>  | Randomised Controlled Trial | 18-65 YRS Rheumatoid Arthritis functional class I or II and DAS >5.1 | Curcuminoids 500mg twice daily for 8 weeks  | Diclofenac 50mg twice daily for 8 weeks | Curcuminoid treatment is superior in reducing DAS scores in RA pts cf diclofenac and appears similar in effect to diclofenac in reducing the pain of RA over an 8-week administration period.   |
| Chopra, A., Lavin, P., Patwardhan, B., Chitre, D., 2004 <sup>179</sup>  | Randomised Controlled Trial | >35 yrs primary OA one or both knees with VAS pain $\geq$ 4          | RA-11 Ayurvedic medication (combination of curcumin and other herbs for 32 weeks  | Placebo for 32 weeks                    | The study demonstrates the potential safety and efficacy of RA-11 in the symptomatic treatment of OA knees over a 32-week period. VAS & WOMAC improved significantly better over time in curcumin and other herbs group than Placebo group<br><br>Note: no rescue medication permitted in this study (32 weeks) |
| Drobnic, F., Riera, J., Appendino, G., Togni, S., Franceschi, F., Valle, X., Pons, A., Tur, J., 2014 <sup>241</sup> | Randomised Controlled Trial | Male, non-smoking participants with VO2 Max $\geq$ 35ml/kg           | Phylosome 1 g twice daily (curcuminoids 200mg bd)commencing 48hrs prior to downhill running test and continued for 24hrs after completion of test (4 days | Matching placebo Twice a Day            | Study authors measured soreness from multiple sites in the legs and summed the results. The anterior thighs were the expected sites of soreness from a bout of downhill running. Summing  |

|   |                             |   |  |                                       |   |
|---|-----------------------------|---|--|---------------------------------------|---|
|   |                             |   | total)   |                                       | the anterior thigh results with results from other sites (posterior etc) diluted results. Study had very small sample size.   |
| Esmaeili Vardanjani, S. A., Sehati Shafai, F., Mohebi, P., Deyhimi, M., Delazar, A., Ghojazadeh, M., Malekpour, P., 2012 <sup>244</sup> | Randomised Controlled Trial | Primiparous women, without acute or chronic disease or allergy, who had a healthy pregnancy and delivery after 37 weeks | Curcuminoid solution   | Povidone-Iodine solution              | Pain was measured at 24 hrs (no difference in groups) and at 10 days (no difference in groups) but note both groups were minimal pain at 10 days-(VAS 0 and 1)  |
| Kizhakkedath, R., 2013 <sup>242</sup>   | Randomised Controlled Trial | 19-70 years Subjects with a painful soft-tissue injury last 24 hrs VAS $\geq$ 5   | Essential oil containing extracts of Boswellia Serrata and Curcuma Longa applied 3xday | Diclofenac Sodium spray applied 3xday | The results support the efficacy, safety and tolerability profile of Essential oil combination formulation comparable to the commercially available Diclofenac Sodium Spray.  |
| Kizhakkedath, R., 2013 <sup>240</sup>   | Randomised Controlled Trial | Moderate OA Knee pts age 18-65yrs mean age 48.5 years   | Curcumin/Boswellia Serrata (CB) extracts 500mg 2x Day                                  | Celecoxib 100mg 2x Day                | The Curcumin/Boswellia formulation at 500 mg administered twice a day, was more successful than administering celecoxib 100 mg twice a day for symptom scoring and clinical examination. The formulation was found to be safe and no dose-related toxicity was found. Note intervention was a combination of ingredients. |

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| <p>Kuptniratsaikul, V., Dajpratham, P., Taechaarpornkul, W., Buntragulpoontawe, M., Lukkanapichonchut, P., Chootip, C., Saengsuwan, J., Tantayakom, K., Laongpech, S., 2014<sup>181</sup></p> | <p>Randomised Controlled Trial</p> | <p>OA Knee subjects Knee pain <math>\geq 5/10</math> age <math>\geq 50</math> yrs</p>   | <p>Curcuminoids 1500mg/day</p>  | <p>Ibuprofen 1200mg/day</p>             | <p>Curcuma Domestica extracts are as effective as ibuprofen for the treatment of OA Knee. There was a significantly higher number of events of abdominal pain/discomfort in the ibuprofen grp.</p>               |
| <p>Kuptniratsaikul, V., Thanakhumtorn, S., Chinswangwatanakul, P., Wattanamongkonsil, L., Thamlikitkul, V., 2009<sup>239</sup></p>  | <p>Randomised Controlled Trial</p> | <p>107 adult patients with primary knee OA with pain score <math>\geq 5</math> and at least one of age <math>&gt; 50</math>, morning stiffness <math>&gt; 30</math> mins or crepitus.</p> | <p>Curcuma Domestica extracts (500mg 4xday) for 6/52</p>  | <p>Ibuprofen (400mg 2xday) for 6/52</p> | <p>The study suffered from the small sample size. The author's comments are fair.</p>  |
| <p>Nakagawa, Y., Mukai, S., Yamada, S., Matsuoka, M., Tarumi, E., Hashimoto, T., Tamura, C., Imaizumi, A., Nishihira, J., Nakamura, T., 2014<sup>184</sup></p>                                | <p>Randomised Controlled Trial</p> | <p>Primary medial Knee osteoarthritis patients over 40 years of age with Kellgren-Lawrence grades II or III on radiographic classification.</p>   | <p>Theracurmin - 180mg curcumin (six x 30mg tablets) daily for 8 weeks.</p>   | <p>Placebo daily for 8 weeks</p>        | <p>Knee pain VAS scores were significantly lower in the treatment group vs the placebo group after 8 weeks only if the scores of subjects with initial (baseline) pain scores of 0.15 or less were excluded.</p> |
| <p>Nieman, D. C., Shanelly, R. A., Luo, B., Dew, D., Meaney, M. P., Sha, W., 2013<sup>173</sup></p>   | <p>Randomised Controlled Trial</p> | <p>Self-reported knees, hip, ankles shoulder or hands pain sufferers 50-75 years of age with pain duration <math>\geq 3</math> months of WOMAC <math>\geq 2</math> pain index score</p>   | <p>Commercialised joint pain dietary supplement (Instaflex) containing white willow bark extract, glucosamine sulphate, methylsulfonylmethane (MSM) Boswellia, turmeric root extract, cayenne, ginger root concentrate and hyaluronic acid for 8 weeks.</p> | <p>Placebo daily for 8 weeks</p>        | <p>Joint pain severity was significantly reduced in the treatment group vs the placebo group after 8 weeks. Note the intervention was a mixture of 8 components.</p>   |

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| <p>Panahi, Y., Rahimnia, A. R., Sharafi, M., Alishiri, G., Saburi, A., Sahebkar, A., 2014<sup>180</sup></p> | <p>Randomised Controlled Trial</p> | <p>OA pts mild--&gt; moderate &lt; 80 years pain on VAS <math>\geq</math> 4/10</p>             | <p>Curcuminoids C3 complex 1500mg/day (+Bioprene)</p>   | <p>Matched Placebo</p>                                   | <p>Curcuminoids represent an effective and safe alternative treatment for OA. Treatment with curcuminoids was associated with greater reductions in WOMAC, VAS and LPFI scores compared with Placebo</p>   |
| <p>Pinsornsak, P. and Niempoog, S., 2012<sup>197</sup></p>  | <p>Randomised Controlled Trial</p> | <p>Knee OA sufferers <math>\geq</math> 38yrs of age with &lt; 30 mins of morning stiffness</p> | <p>Diclofenac 75mg/day with curcumin 1000mg/day for three months</p>  | <p>Diclofenac 75mg/day with Placebo for three months</p> | <p>No significant difference was seen in VAS between groups at the end of the study</p>  |
| <p>Udani, J. K., Singh, B. B., Singh, V. J., Sandoval, E., 2009<sup>243</sup></p>                           | <p>Randomised Controlled Trial</p> | <p>18-24years community dwelling males</p>   | <p>Bounceback™ capsules (The two capsule daily serving contained 258 mg of a proteolytic enzyme blend that included bromelain as well as proteases from Aspergillus melleus and A. oryzae also 421 mg of turmeric extract (root/rhizome; standardized to 95% curcuminoids), 90 mg of a phytosterol blend (beta-sitosterol, campesterol and stigmasterol), 20 mg vitamin C and 6 mg Japanese knotweed extract (root; standardized to 20% resveratrol). for 30 days prior to eccentric exercise protocol test</p> | <p>Matching placebo for 30 days</p>                      | <p>BounceBack™ capsules were able to significantly reduce standardized measures of pain and tenderness at several post-eccentric exercise time points (but not all) in comparison to placebo. Study limited by very small sample size (10 subjects). Note BounceBack™ capsules were a diverse mixture of proteolytic enzymes and other ingredients including curcuminoids.</p> |