THE EFFECTS OF CURCUMIN TREATMENT FOR ARTHRITIS IN DECREASING INFLAMMATION

A Systematic Review

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Brenda Labador Bebal

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Abstract

of

THE EFFECTS OF CURCUMIN TREATMENT FOR ARTHRITIS

IN DECREASING INFLAMMATION: A SYSTEMATIC REVIEW

by

Brenda Labador Bebal

Statement of Problem

Persons who suffer from arthritis have chronic and extensive inflammation, pain and joint damage. Current conventional pharmacological treatment halts the progression of joint damage, decreases inflammation and pain but may have devastating side effects. This is the impetus to consider alternative intervention that has lesser side effects but can yield similar caliber of reducing inflammation and subsequent pain.

Sources of Data

Three databases were searched to evaluate research studies fitting the inclusion criteria of curcumin therapy to reduce inflammation in arthritis. Eight articles were selected for systematic review. Studies reviewed included meta-analyses, previous systematic reviews, randomized controlled trials, cross- sectional survey studies and controlled trials.

Conclusions Reached

Curcumin has multiple molecular targets and good potential as therapeutic agent for various inflammatory conditions. The inflammatory process has a major role in most chronic diseases such as arthritis. Studies support Curcumin as an intervention to decrease inflammation and may offer an alternative for patients with arthritis.

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INTRODUCTION

Chronic diseases such as cancer, diabetes, stroke and arthritis are the leading cause of death and disability in the United States (Centers for Disease Control, 2013). In fact, it was estimated that in 2005 there was at least one chronic illness among 133 million Americans or one out of every two adults (Wu & Green, 2000). In addition, it has been projected that by 2030, there will be 67 million adults with arthritis (Centers for Disease Control and Prevention, 2013). Though it may be more common among 65 years and older, chronic diseases affect all ages including children.

The term arthritis is any disorder that affects the joints and generally categorized as rheumatic diseases (National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2014). Collectively these diseases are characterized by inflammation and loss of function of one or more connecting or supporting structures of the body. Rheumatic diseases may involve the internal organs and are described as connective tissue disease, and when they affect the immune system, they are known as autoimmune diseases (NIAMS, 2012). Arthritis has more than 100 different rheumatic diseases (CDC, 2013), the most common are conditions such as osteoarthritis, rheumatoid arthritis, systemic lupus erythematous, fibromyalgia; and gout (NIAMS, 2012). This paper will use the Centers for Disease Control and Prevention definition of arthritis, "a systemic inflammatory disease that mainly affects the joints and symptoms include pain, stiffness, and swelling around the joints (CDC, 2013)."

Within the past half- century, there has been a major breakthrough about inflammation, and a paradigm shift that chronic inflammation may be the primary cause of most if not all diseases. Some diseases that are initiated by inflammation may not remain local and this makes the patient susceptible to other illnesses because of chronic inflammation. When inflammation sets in the body, it subsequently alters the immune system and autoimmune diseases may ensue. A variety of autoimmune diseases including arthritis (osteoarthritis, rheumatoid arthritis, psoriatic arthritis), atherosclerosis; and coronary artery disease are linked to inflammation as a risk factor and may also be the primary cause of the disease (Frostegard, 2005).

Osteoarthritis (OA) is the most common arthritis and considered the second largest cause of disability and high cost of treatment (Dieppe, 2008). Sometimes OA is called the disease of aging. It is characterized by Ratiner (2001) as the result of a mixed process of degeneration and inflammation, as OA is manifested by the degeneration of cartilage with increased leukocyte count and pro-inflammatory cytokines in synovial fluid of the affected joints. The pharmacologic treatment includes analgesics such as acetaminophen, NSAIDs, opioids and intra- articular therapies such as glucocorticoids and hyaluronans.

Rheumatoid arthritis (RA) is the third most common arthritis and it affects 1% of the adult population. A majority of the women are afflicted with this disease, commonly between the ages of 30 and 50 years. It is characterized by hyperplasia of the synovial fibroblasts caused by apoptosis, joint stiffness and swelling. It is often manifested in a symmetrical pattern on both sides of the body. After clinical diagnosis, 20% to 30% of

people with RA will be unable to work if untreated within a period of three years (Edworthy, Zummer, Garner, 2006). Eventually, the disability can significantly affect a patient's physical, emotional and social functioning. There is no preventative or curative option for RA. The current management goals are focused on improving quality of life and reducing disability (Pollard, Choy, & Scott, 2005).

The aging process and the proteolytic degradation of extracellular matrix (ECM) macromolecules in articular cartilage in the joints are the important catabolic events in OA (Loeser, 2009) and RA (Feldmann, 1996). Further, Interleukin- 1 Beta (IL-1B) and Tumor Necrosis Factor- alpha (TNF-a) are the key pro-inflammatory cytokines mediating cartilage degradation in patients with RA (Feldman, 1996) and OA (Pelletier, 2001). IL-1B and TNF-a participate in these processes by stimulating chondrocytes synoviocytes to produce matric proteases, chemokines, nitric oxide and eicosanoids such as prostaglandins and leukotrienes (Feldman, 1996; Pelletier, 2001). Almost all of the pro-inflammatory factors involved in the pathogenesis of OA and RA are regulated by the transcription factor Nuclear Factor kappa- light chain-enhancer of activated B-cells (NF-kB) (Kumar et al, 2004).

The conventional treatment for OA and RA are temporary and for symptomatic treatment with adverse effects. There are molecular studies that reveal the anti-inflammatory effects of curcumin through inhibition of the activator protein-1 (AP-1) and NF-kB pathways. These are pathways that are primarily activated in response to IL-1B stimulation and subsequently activate cycooxygease-2 (COX-2); which is the key inflammatory mediator involved in downstream activation and release of matrix-

degrading matrix metalloproteinases (MMPs) (Bharti et al, 2003). The pathways for signaling are dysfunctional in the chondrocytes and synovial cells in OA and RA. An effective treatment for arthritis that targets simultaneously the multiple cellular signaling pathways to reduce the inflammation in chondrocytes and synovial cells is needed.

THE PROBLEM

Background

The pharmacologic treatment for osteoarthritis includes acetaminophen, non-steroidal anti- inflammatory drugs (NSAIDs), opioids and intra- articular therapies such as glucocorticoids and hyaluronans. Likewise, for rheumatoid arthritis it includes NSAIDs, low-dose oral or intra-articular glucocorticoid, Disease-Modifying Anti-Rheumatic drugs (DMARDs) and the newer biological treatments (BRMs) (Rinfleisch & Muller, 2005). At present, DMARDs and biological agents that target cytokines such as the Tumor Necrosis Factor-alpha (TNF-a) antibodies, are important treatment for RA through modifying the immune system. The major challenges of these drugs are associated with severe side effects including gastrointestinal bleeding, elevated blood pressure, accelerated osteoporosis, myelosuppresion, hepatotoxicity, ocular toxicity, hypersensitivity and allergic reactions, as well as increased risk of infections (Lipsky, van der Heijde, & St. Clair, 2000; Rahme & Bernatsky, 2010).

There are numerous popular herbals such as ginger, curcumin (found in Turmeric), red chili peppers, fennel, anise, coriander, cloves, and garlic are known for their anti-inflammatory effects. Further, because of the apparent adverse effects of conventional pharmacological treatment, medical physicians and other healthcare providers may consider these alternatives to treat chronic inflammatory conditions with considerably lower cost as long as there is an assurance of their effectiveness. Afterall, many patients with arthritis seek and utilize herbal medicine or alternative therapy to relieve their symptoms. Barnes (2004) estimates about 28% to 90% of RA patients in the

United States uses herbal alternatives and the primary reason for seeking alternative treatment was palliative or to relieve pain (Taibi, 2003).

Recent research investigation, specifically with Curcumin or Tumeric, revealed that it has substantial therapeutic value. In fact, Curcumin is a common concept, and used in households for centuries. It has been used for culinary purposes as a food additive (Chandran, 2012), and as a coloring agent in dyes for hair and fur (Carroll, 2011). It has an extensive reputation in traditional medicine, such as Ayurvedic medicine in India, mainly for its anti-inflammatory effects on arthritis. In China, it has been used as part of their traditional Chinese medicine for topical analgesia, anti- flatulence, colic, ringworm, hepatitis and chest pain (Lee, 2011).

Theoretical Framework

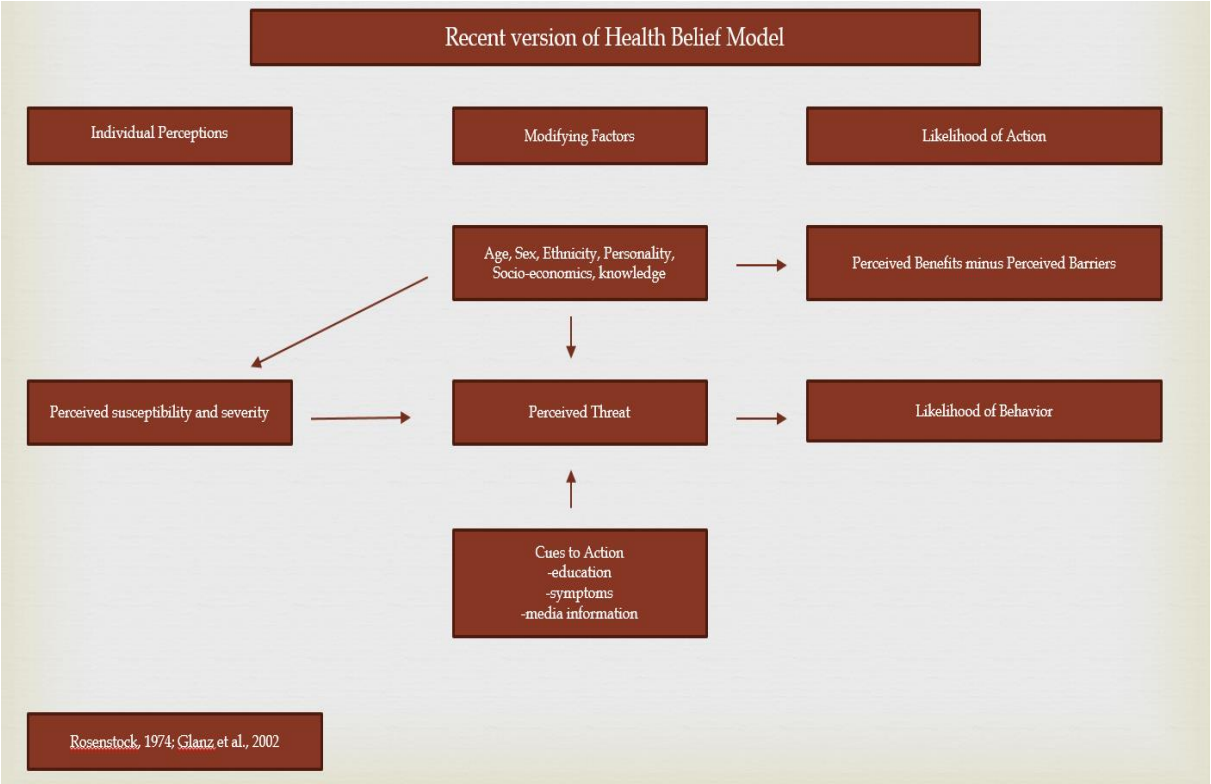
The Health Belief Model (HBM) was developed in the 1950s and 1960s by the U.S. Public Health Services to understand and explain preventive health behaviors in response to a widespread failure of people to accept disease prevention and screening tests for early detection of asymptomatic disease (Janz, & Becker, 1984). This model assisted in explaining the reason why individual patients accepted or refused a specific preventative health intervention or adopted healthy behaviors. The HBM model operates on the premise that a person's health related behavior depends on the person's perception of four critical areas: the severity of a potential illness, the person's susceptibility to that illness, the benefits of taking a preventive action, and the barriers to taking that action (Hochbaum, 1958; Rosenstock, 1960). There are modifying factors that would include the media, health professionals, personal relationships, incentives, and self-efficacy of the

recommended health action. The HBM was utilized by Goodacre (2004) in his study to find, "the factors influencing the beliefs of patients with rheumatoid arthritis regarding disease-modifying medication." He found that understanding the patients' complex and evolving belief systems relating to DMARDs aided in identifying the appropriate information and effective support for decision-making, treatment choice and when to discontinue the treatment.

Originally, the HBM included only four constructs: perceived susceptibility, perceived severity, perceived benefits, and perceived barriers (Rosenstock, 1974) but subsequent constructs were added to the model including cues to action and self- efficacy (Glanz, Rimer, Lewis, 2002). Interventions that used the HBM were able to assess individual perceptions of susceptibility or the chances of getting a condition. This construct guides the healthcare provider to identify the populations at risk, levels of risk, tailor risk information based on individual characteristics or behaviors, and help individuals develop accurate perceptions of their own risk. Perceived severity is the belief of the individual about the seriousness of their condition and its consequences. Individuals should be informed on the specific consequences of a condition and the recommended actions. Perceived benefits is the beliefs of the individual about the effectiveness of taking action or reduce risk or seriousness. Interventions should be explained clearly by answering basic questions such as how, where and when to take action and the potential positive results. Perceived barriers are the beliefs about the material and psychological costs of taking action. The success of the intervention should offer reassurance, incentives, assistance and correct misinformation as needed to the

individual. Moreover, incentive to take action is paramount in chronic illness; individuals have to feel a need to change their behavior and a belief that a specific change such as a health intervention will be beneficial. Cues to action are the factors that activate "readiness to change." The interventions are sustained with the provision of how-to-information, awareness promotions and utilization of reminder systems. Self- efficacy is the individual's confidence in one's ability to carry out or take action to change the behavior (Bandura, 1977). Individuals that have self- efficacy are influenced by their own accomplishments, the experiences of the people that the individual relates to, societal influences that encourage or discourage a behavior, and the individual's physical state (Bandura, 1977).

Figure 1: The Recent Version of the Health Belief Model: Rosenstock, 1974



Research Variables

In this systematic review, the intervention of curcumin as part of a treatment plan for reducing the inflammation will be evaluated for effectiveness in reducing symptoms of arthritis. The primary interest will be the overall effectiveness of curcumin in reducing symptoms such as inflammation and subsequent decrease of pain and improvement of physical function or activity. Inflammation is the dependent variable, manipulated in various studies to affect the independent variable, curcumin treatment as anti-inflammatory in arthritis. For this review, curcumin was defined by Recio (2012) as the active component of the spice tumeric with remarkable anti-inflammatory, antitumor and anti- oxidant properties. The alternative terms of tumeric were Diferuloymethane, curcuminoid; Curcuma domestica; and Curcuma longa. Examples include any type of curcumin extract or bio- optimized curcumin such as Biocurcumax-95 (BCM-95), Meriva complex or Flexofytol. Curcumin is bio- optimized or complexed with phospholipids to increase its bioavailability or systemic absorption.

Problem Statement

The problem in this systematic review is that the conventional treatment goal for OA and RA are short term and symptomatic. Further, the conventional treatment drugs available yields substantial side effects with steep monetary cost. There is strong evidence that curcumin is an effective alternative to reduce inflammation in arthritis. There are molecular studies that reveal the anti- inflammatory effects of curcumin through inhibition of the AP-1 and NF-kB pathways; these are the pathways that are primarily activated in response to IL-1B stimulation and subsequently activate COX-2;

which is the key inflammatory mediator involved in downstream activation and release of matrix- degrading MMPs (Bharti et al, 2003). The pathways for signaling are dysfunctional in the chondrocytes and synovial cells in OA and RA. This systematic review will look at the evidence of Curcumin's effectiveness in decreasing inflammation in arthritis by targeting simultaneously the multiple cellular signaling pathways to reduce the inflammation in chondrocytes and synovial cells with lesser or without side effects.

Research Question

Current published research was reviewed in an attempt to answer the following question. Does curcumin therapy induce reduction of inflammation in arthritis?

Significance to Nursing

For nursing, our role encompasses understanding the effect of inflammation and molding our treatment plans for patients with arthritis. In addition to our nursing role, addressing chronic disease such as arthritis requires new strategies to delay health deterioration, improve activities of daily living and consideration of the challenges that the patients face in their daily lives such as the affordability of treatment option, and the availability of a natural product such as curcumin which is devoid of substantial side effects.

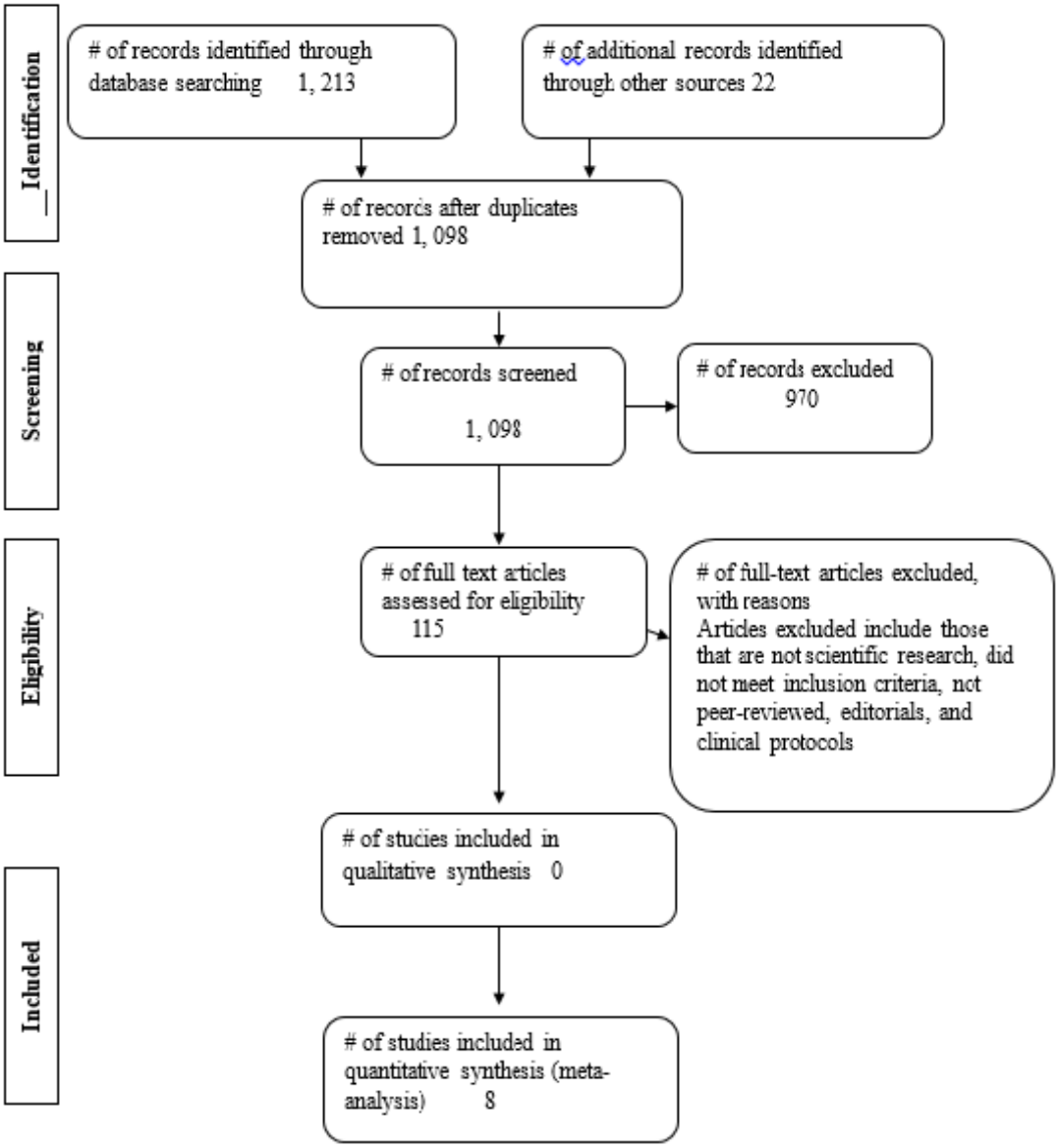
Further, due to paradigm shift on the concept of inflammation, advanced practice nurses, especially in primary care, correspondingly need to shift traditional chronic disease management that focuses on single conditions with co-morbidities. Our system remains fragmented, and the patients with multiple co-morbidities would seek care from different medical providers and may receive multiple medication regimens. This

contributes to unsustainability and will be complicated by rising health care costs. Nurses have an intrinsic role to promote optimum care and manage patients with chronic illnesses such as arthritis in primary care. Opportunities to educate patients regarding feasible alternatives such as curcumin therapy to reduce inflammation may help patients to cope. It may help patients control the effects of chronic inflammation and give patients an important role in managing their disease effectively. Consequently, this decreases health care costs, improves family well- being and promotes quality of life. Additionally, prolonged management and excellent control of arthritic symptoms in patients will subsequently prevent disease flares and delay surgical interventions for many years, which will be considered the last resort to manage uncontrolled symptoms and disease progression in the future.

SEARCH STRATEGY

The reason for this systematic review was to find previous research on the effects of curcumin therapy to reduce inflammation in arthritis. A literature search was conducted using PubMed Central, CINAHL Plus with full text, and Google Scholar. The year was limited to when the publication was conducted in order to gather as many studies. The searched terms were, “arthritis,” “osteoarthritis,” “rheumatic arthritis,” “Curcumin,” “Curcuma longa,” “Tumeric,” and “anti-inflammatory. These searches yielded a total of 1, 213 articles. Then the search became more explicit in trying to find more articles that matched the intent of the review. The terms used to narrow the search, were: “anti- inflammatory effect of Curcumin,” “Curcumin for reducing inflammation in arthritis,” “Curcumin for reducing inflammation in rheumatoid arthritis,” “Curcumin for reducing inflammation in osteoarthritis.”

Figure 2. **Flow Chart of Systematic review**



THE SAMPLE

Selection Criteria

In order to find articles that met the requirement for this systematic review, multiple articles were collected from the database and reference lists. The articles that were included utilized specific outcome measures to the anti-inflammatory effect of Curcumin in arthritis, RA and OA. The terms that were used to select the criteria in the articles were, “anti-inflammatory,” “arthritis,” “rheumatoid arthritis,” “osteoarthritis.” After entering the words individually in the database, each key note produced thousands of articles. To continue narrowing the search, the words were combined to produce a more specific search. Searches included the combinations, ”Curcumin therapy,” “chronic inflammation in rheumatoid arthritis,” “Curcumin reduces chronic inflammation in rheumatoid arthritis,” “Curcumin reduces cartilage destruction in osteoarthritis.” This was conducted in three separate searches, one for each search term and by combining search terms. Any duplicated articles were removed. Finally, all articles that did not meet either the inclusion or the exclusion criteria were removed.

Inclusion Criteria

The published articles used for this systematic review met the inclusion criteria. In order to acquire as many articles as possible, an abstract review was conducted. The abstract was reviewed for settings where the study took place, whether inpatient or outpatient treatment facility, and if the study was conducted in a different country. The articles that were selected included studies that tested the intervention Curcumin for

arthritis, RA or OA as monotherapy, bio-optimized Curcumin or in combination with other therapy. The studies which investigated the dependent variable were included if Curcumin as anti-inflammatory was used independently from other variables. Moreover, inclusion criteria included that Curcumin treatment was conducted by a medical health professional that included nurses, nurse practitioners, and physicians. Any race or ethnicity group, or gender was included in the study. There was no age limitation. The years of the study was not limited. Studies included were randomized controlled trials, systematic reviews, meta- analyses and controlled trials. The published articles were from a peer reviewed journals and were published in English. The subjects must have a diagnosis of arthritis, rheumatoid arthritis, or osteoarthritis. The studies that were included had a validated, reputable measurement scale such as: safety endpoints included rates of adverse events (AEs) and serious adverse events (SAEs); efficacy endpoints included American College of Rheumatology (ACR) 20, ACR50, and ACR70; 28- joint disease activity score (DAS28), DAS28 <2.6; and select ACR core components (swollen joint count- SJC), tender joint count (TJC), and patient assessment of pain visual analogue scale (VAS).

Exclusion Criteria

Studies were excluded if the arthritic disease, rheumatoid arthritis or osteoarthritis was in the late stages, meaning the candidate was a candidate for surgical intervention. Studies that were conducted outside the United States were considered if it met the inclusion and exclusion criteria and was peer reviewed. Studies were also excluded if written in language other than English without available English translation.

Strengths

The studies that were included in this systematic review were conducted in different settings and countries. There was variety of different genders, ages, and races included in the studies. The use of Curcumin was supported in almost every study. The articles have measurement tools to measure effectiveness of Curcumin and there was a variety of different tools and outcomes.

Limitations

The purpose of this review was to examine the evidence of the effects of Curcumin in reducing inflammation in arthritis. The main limitation for this review was the number of studies that used human subjects and implemented monotherapy with Curcumin as an anti-inflammatory agent to control the inflammation in arthritis. The original intent of this review was focused on the anti- inflammatory effectiveness of Curcumin in RA patients however it was determined that there was a limited research specific to the use of Curcumin on RA patients hence OA was also included as an independent research variable.

Some studies included different countries in the world which can sensibly alter the outcome. For example, some of the studies were done in a country with a developing economy that may have lesser resources such as the accessibility and availability of outpatient clinics, medical physicians and specialists such as a rheumatologist. The amount of social or family support for the subjects being studied can be speculated to directly result in inconsistent outcomes with similar studies done in a country with advanced economy such as the United States of America. Skewed results based on the

location of the study can be anticipated however the inclusion of all study locations increases the strength of the study by universal application of the results.

There may be some bias in certain studies due to the organization that funded the study. There were two studies that were funded by the manufacturer of the complexed formulation of Curcumin. Introducing bias in studies that were funded by an organization that has a vested interest in the outcome of the study always yield expected risks. Some of the studies did not clearly identify the source of their funding and this could have introduced bias into the result of the studies.

QUALITY APPRAISAL

The Level of Evidence Table (Melnyk & Fineout-Overholt, 2011) was used to assess each article for quality. This table rates research articles on a scale of I- VII with a level I rating reflecting a study with the highest quality of evidence and level VII being the lowest quality of evidence. The aim of this systematic review was to use high quality studies so that the results would include a high level of reliability, allowing this review to provide strong evidence. The level of evidence for each article was recorded in a table created by Melnyk & Fineout- Overholt (2011). The results for each article can be viewed in Level of Evidence Table found in Appendix A. All studies achieved a rating of II- IV. No studies had a quality rating of V or higher. The key for the Melynk & Fineout-Overholt (2011) table is shown below.

Figure 3

Level Scale: I- VII (for each study) (Melynk & Fineout-Overholt, 2011)

Level 1- Systematic review & meta- analysis of randomized controlled trials; clinical guidelines based on systematic reviews or meta- analyses

Level 2- One or more randomized controlled trials

Level 3- Controlled trial (no randomization)

Level 4- Case- control or cohort study

Level 5- Systematic review of descriptive & qualitative studies

Level 6- Single descriptive or qualitative study

Level 7- Expert opinion

Source: Melnyk, B.M. & Fineout-Overholt, E. (2011). *Evidence-based practice in nursing and healthcare: A guide to best practice.* Philadelphia: Lippincott, Williams & Wilkins.

Results for Level of Evidence

A variety of types of studies were included in this systematic review. Strong efforts were made to assure that only studies using scientific research designs with clear documentation of proper methodology for securing participation, obtaining data, and analyzing data were included. Adhering to a strict set of inclusion and exclusion criteria was difficult. Some flexibility was required but all studies met high quality standards. Prospective randomized controlled trials that contained significant information were also included in this review. The majority of the studies in this review met all criteria for this systematic review.

Level of evidence for each article

A total of 8 articles met the criteria for this systematic review. The level of evidence assigned to each article was based on type of research design and the use of proper research methods in the study using the Level of Evidence Table by Melnyk & Fineout-Overholt, 2011. The table identifies the level of evidence of each article. The key for table can be found above. The Level of Evidence Table can be found in Appendix A. Each study was ranked on I-VII scale with "I" being the highest quality of evidence and "VII" being lowest quality of evidence. All articles had valid research designs but some designs supplied higher reliability of data because of their design. Non- randomized controlled trials were included in this review because they provided sufficient significant

data to warrant inclusion but they did not supply as high quality of reliability as the randomized controlled trials.

Dependent variable

Level of inflammation

Six studies chose to measure the level of inflammation as the dependent variable. Studies used a wide variety of validated tools to measure inflammation. Two of the 6 studies achieved a level 2 rating. One study achieved a level of 3 rating, and three studies achieved a level IV rating. No studies were rated level V or greater. Overall, the level of evidence was high in the six articles that measured inflammation as the dependent variable.

Instruments for Measurement of Dependent Variables

There were variety of instruments used to measure inflammation. All instruments chosen in these studies had been previously validated and their reliability was discussed in each article.

Serum Inflammatory Markers

C- reactive protein (CRP) is mainly an inflammatory marker. For this review, there were 3 studies that measured CRP levels of the patients or subjects (Chandran et al., 2012; Belcaro et al., 2010, & Henrotin et al., 2014). Measuring CRP level is also useful to detect effectiveness of a treatment but may be elevated with liver failure, pregnancy, mild inflammation, and viral or bacterial infections. As a result, seven studies excluded patients with peptic ulcer, duodenal ulcer or those with significant hepatic or renal disease.

The studies done by Deodhar et al. (1980) and Belcaro et al. (2010) used the serum levels of Erythrocyte sedimentation rate (ESR) to measure inflammation. In addition, Nyoman et al. (2011), used the level of the reactive oxygen intermediates (ROI) secreted by the monocytes in the synovial fluid of the affected joints to determine the severity of the inflammation. Further, Henrotin et al. (2014) measured inflammation by the extent of cartilage degradation in OA by the serum level of Collagen 2-1 (Coll2-1). His study also revealed that COLL2-1 was a sensitive biochemical marker to detect the efficacy of Curcumin to halt cartilage degradation in OA.

Western Ontario and McMaster Universities OA Index (WOMAC)

The Western Ontario and McMaster Universities developed a questionnaire that assisted in describing and rating the symptoms of OA such as pain, stiffness, and physical function (Baron, G., Tubach, F., Ravaud, P., Logeart, I. & Dougados, M., 2007). The WOMAC scoring and interpretation is associated with a conventional score expressed in points for each response of the patient. The patient received 1 point if the response was none, 2 points if response was slight, 3 points if the response was moderate, 4 points if the response was severe and 5 points if the response was extreme. There were three studies which used the WOMAC tool.

American College of Rheumatology Criteria (ACR 20, 50 & 70)

The American College of Rheumatology Criteria (ACR 20, 50 & 70) is a common validated tool used as a standard measurement to indicate the improvement of a person's rheumatoid arthritis symptoms by noting the number of tender and swollen joints. It also includes assessment of at least three of the following five areas: the person's overall

(global) assessment of his or her own RA, the physician's global assessment of the person's RA and the person's own assessment of her/his own pain. An ACR20 score means RA symptoms improved 20%, ACR50 means symptoms improved by 50%; and ACR 70 means symptoms improved by 70%.

Disease Activity Score (DAS)

The Disease Activity Score (DAS) is a tool used to measure RA activity to monitor the effectiveness of current RA treatment. First, the DAS score is calculated based on the number of tender or swollen joints, measurement of the serum inflammatory marker (ESR) and C-reactive protein (CRP) and the result of the Visual Analogue Scale (VAS). The VAS measures the personal assessment of how the subject felt about her RA symptoms; marked as not active at all or extremely active. Overall, the DAS score is from less than 2.6 to more than 5.1; a score of 5.1 indicates having severe disease activity that needs a change in therapy, and less than 2.6 means the patient is in disease remission.

Karnofsky Performance Scale Index

Karnofsky Performance Scale Index was used in one study (Belcaro et al., 2010) to classify the functional impairment of the patients. It was used to compare the effectiveness of different therapies and to assess the prognosis of each subject. The score range from 0-100 with 100 indicating that the patient was able to carry on normal activity with no special care needed. The zero (0) score indicated that the patient was unable to care for self and required the equivalent of institutional or hospital care, and the disease may be progressing rapidly.

Methods for Intervention Delivery

Curcumin was the intervention common to all studies collected for this review but it was administered in varied forms such as an extract, supplement, complexed with phospholipid and bio-optimized. Specifically, two studies (Kuptniratsaikul, 2009 & 2014) used C. domestica extracts as an intervention and it that was prepared from the dried rhizomes of C. domestica and was grounded into powder. Then the turmeric powder was extracted with ethanol and then evaporated at low pressure to obtain ethanol extract in the form of a semisolid containing oleoresin and curcuminoids. The extract was calculated to have 250 mg of curcuminoids which was filled into a capsule.

Chandran et al. (2012) used BCM-95 Curcumin which has a patent and was a registered formulation of Curcumin with enhanced bioavailability. Another study done by Deodhar et al. (1980) used the supplement Curcumin (diferuloyl methane) drug as an intervention. It was filled in opaque colored capsules to mask the yellow color of Curcumin but there was no further description regarding its preparation.

In Indonesia, Kertia et al. (2011) used curcuma domestica Val extract. It was prepared by sorting first the curcuma domestica Val rhizome. It was washed, cut into pieces with a thickness of 1-2 mm then dried on a drying cupboard for 24 hours at 40 degrees Celsius to obtain maximum water content off. Then it was powderized, mixed with ethanol, macerated (soaked) for 24 hours and then filtered with a Buchner funnel (with vacuum pressure). The collected filtrate was evaporated at 45 degrees Celsius in a vacuum. The extract obtained was scanned by a Thin Layer Chromatography scanner. The extract was filled in the capsules with a dose of 30 mg curcuminoid. In Italy, Belcaro

et al. (2010) used complexed curcumin called Meriva. It was developed by combining curcumin and phosphatidylcholine in a 1:2 ratio. The complexation with phospholipids improved the aqueous stability and oral absorption of Curcumin. For Henrotin et al. (2014) in Belgium, a bio-optimized Curcumin called Flexofytol was used with an equivalence of 42 mg Curcumin mixed with polysorbate.

Instruments for Measurement of the Independent Variable

Liquid chromatography/tandem mass; spectrometry (LC-MS/MS)

The plasma level of Curcumin and its metabolites (tetrahydrocurcumin-THC, curcumin 0- glucuronide –COG; and curcumin 0- sulfate-COS) can be measured through the United States Food and Drug Administration- Good Laboratory Practice (US FDA-GLP) validated tool called Liquid Chromatography/Tandem Mass spectrometry (LC-MS/MS) (Guidance for Industry Bioanalytical Method Validation, p.5). The highest dose of Curcumin given from all the eight studies was 2 grams per day. Curcumin has very low absorption even after oral administration of 12 grams/day. For this reason, there were two studies that used complexed Curcumin and 1 study that used bio-optimized Curcumin to increase its bioavailability. From the eight studies, no single study measured the plasma level of Curcumin or its metabolites.

Results of Studies Included in This Systematic Review

All of the studies reported some type of positive effect of Curcumin on inflammation. Each study added its own body of information to the current collective information regarding the use of Curcumin as an intervention for treatment of inflammation in arthritis. This study clearly supports the HBM to understand and explain

the reason why individual patients accept or refuse a specific preventive health intervention or adopt healthy behaviors. These studies show that patients with arthritis might be able to benefit from the anti-inflammatory effect of Curcumin. Understanding the reason why Curcumin is acceptable or not acceptable through information such as side effects, efficacy and cost. This is significant information to gather and it will be investigated or addressed accordingly so it can be used to determine if Curcumin intervention is a good intervention for arthritis.

Please see the table below created by this author for the results of each study included in this review. Additional tables regarding grading of recommendations and levels of evidence are included later in this paper.

Table 1: Results of Systematic Review

Study	Sample/ Characteristics	Type of Study	Results
Kuptniratsaikul, Thanakhumtorn, Chinswangwatanakul, Wattanamongkonsil,& Thamlikitkul, 2009	N= 107 with knee OA Treatment group (N= 52) received Curcuma domestica extracts 2g daily for 6 weeks Comparison group (N=55) received ibuprofen 800 mg daily for 6 weeks. Study was conducted at the Siriraj Tertiary hospital in Bangkok, Thailand.	Randomized cross-sectional study	Decreased pain on level walking, time spent on 100 m walk, and time spent on going up and down stairs in both groups
Kuptniratdaikul, Dajoratham, Taechaarpornkul, Buntragulpoontawee,	N=367 with knee OA N=185 (Treatment group) received	Double- blind Randomized Controlled Trial	Curcuma domestica extracts have similar

Lukkanapichonchut, Chootip, Saegsuwan, Tantayakom, & Laongpech, 2014	curcuma domestica 1,500 mg/day N= 182 (Comparison group) received ibuprofen 1,200 mg/day Study was conducted at eight tertiary hospitals in Thailand.		effectivity as ibuprofen for the treatment of knee osteoarthritis. The profile for side effects were the same but with fewer gastrointestinal adverse complaints from the curcuma domestica extracts group.
Chandran, & Goel, 2012	N=45 patients with RA Group1= Curcumin 500 mg Group 2= Curcumin 500 mg + Diclofenac sodium 50 mg Group 3= Diclofenac sodium 50 mg Study was conducted at the Nirmala Medical Center in Muvattupuzha, Kerala, India	Randomized Controlled Trial	There was reduction in Disease Activity Score (DAS) 28. There was reduction in the American College of Rheumatology (ACR) criteria for tenderness and swelling of joint scores. Patients in all 3 groups showed statistically significant changes in their DAS scores. Curcumin group showed the highest percentage of improvement in overall DAS and ACR scores (ACR 20, 50 & 70) and these scores were significantly

			better than the patients in the diclofenac group. Curcumin group did not have adverse events.
Deodhar, Sethi, & Srimal, 1980	N= 18 pts with RA Curcumin (1,200 mg/day) administered in 3 divided doses. Phenylbutazone (300 mg/day) administered in 3 divided doses. Age mean: 36.3 yo (22- 48 yo) with Articular s/s range from 9- 96 months Study was conducted at the Central Drug Research Institute, Lucknow, Pradesh, India	Double-blind randomized controlled trial	Curcumin given at 1200 mg daily was effective in improving joint swelling, morning stiffness, and walking time. No side effects reported by either group. No significant change in blood pressure, pulse, hemoglobin, hepatic or renal function during the study. Both curcumin and phenylbutazone showed antirheumatic activity (improved morning stiffness, walking time, and joint swelling). Neither group has an improved grip strength,

			articular index or ESR. Fatigue time improved with phenylbutazone. Both patient and observer assessed improvement at the end of phenylbutazone. Improvement was noted by observer alone at the end of curcumin period.
Kertia, Asdie, Rochmah, & Marsetyawan 2011	N= 80 pts with OA Group1(curcuminoid group) 39 patients (15 men and 24 women; mean age was 64.05 +- 8.83 years) = received 3 x 30mg of curcuminoid from Curcuma domestica Val. Extract for 4 weeks Group 2(diclofenac group/comparison group) 41 patients (12 men and 29 women; mean age was 64.56 +- 8.86 years)= received 3 x 25 mg of diclofenac sodium for 4 weeks Study was conducted at the Rheumatology	Prospective Randomized open end blinded evaluations= PROBE study	The secretion of reactive oxygen intermediates (ROI) by synovial fluid monocytes was significantly decreased in both groups ($p < 0.001$). There was no significant difference in decreasing of ROI secretion of synovial fluid monocytes between both treatment groups ($P = 0.92$).

	Clinic, Universitas Gadjah Mada/ Dr. Sardjito Hospital-Yogyakarta, Indonesia		
Belcaro, Cesarone, Dugall, Pellegrini, Ledda, Grossi, Togni, & Appendino, 2010	N=50 pts with OA Duration of study= 3 months Group A/ Control group (N= 25) Received standard txt or the "best available txt "as defined by patients' GP & by specialists. Group B or Treatment group (N= 25) Received standard txt or the " best available txt" as defined by patients' GP & by specialist plus 1G of Meriva complex per day (curcumin 200 mg per day) Study was conducted at the San Valentino Vascular Screening Project in Italy	Cohort study with control group	After 3 months, the result showed significant improvements for the Meriva complex supplemented group in walking performance (The walking distance was increased from 76m to 332 m), painkiller use, and gastrointestinal complaints. WOMAC scores (median 83.4 at inclusion vs. 80.6 in controls) decreased at 3 months to 34.8 (vs. 78.8 in controls) ($P<0.05$). The improvements were better than what was achieved from the group that received standard treatment alone.

Belcaro, Cesarone, Dugall, Pellegrini, Ledda, Grossi, Togni, & Appendino, 2010	N= 100 pts with OA Duration of study= 8 months Control group (50); (received best avail txt as defined by Patient's GP and specialist.) Meriva group (50) = received 1G of Meriva x 8 mos. +received best avail txt as defined by patient's GP and Specialist. Meriva group received Meriva 500 mg po; one after breakfast and one after Dinner (1000 mg/day correspond to 200 mg curcuminoids/per day). Study was conducted at the San Valentino Vascular Screening Project in Italy Meriva tablets composition: Natural curcuminoid mixture (20%), phosphatidylcholine (40%), & microcrystalline cellulose (40%). composition of the curcuminoids mixture was 75% curcumin, 15% demethoxycurcumin and 10% bisdemethoxyxurcumin	Cohort study with control groups .	After the 8 month study, the group taking Meriva complex experienced significantly greater improvements in the treadmill walking test, pain level and mood and mobility as compared to the group that received the standard treatment alone. Serum inflammatory markers such as IL-1B, IL-6, soluble CD40 ligand, soluble vascular cell adhesion molecule- 1, and erythrocyte sedimentation rate were significantly decreased in the treatment group. WOMAC score decreased more than 50%, treadmill walking performance was increased almost threefold compared to control

			Decrease in GI complications, distal edema, & use of NSAIDs or painkillers by patients were noted after Meriva Treatment Hospital admissions, consultation and patient tests were also decreased after Meriva txt.
Henrotin, Gharbi, Dierckxsens, Priem, Marty, Seidel, Albert, Heuse, Bonnet, & Castermans, 2014	N= 22 pts with knee OA Age: 49- 77 years old Patients were asked to take Flexofytol 3 caps in the am (on empty stomach, before breakfast); and 3 caps in the evening every day for 3 months. Subjects were monitored after 7, 14, 28 and 84 days of treatment. Study was conducted at the rheumatology center of the Citadelle Hospital of Liege, Belgium Bio- optimized Curcumin was called Flexofytol.	Cohort study without a control group	Treatment with Curcumin was well tolerated. Curcumin in the form of bio-optimized FleIofytol significantly reduced the serum level of Coll 2-1 ($p < 0.002$) and decreased CRP. Curcumin significantly reduced the global assessment of disease activity by the patient.

	One caps of Flexofytol contains 42 mg Curcumin mixed with polysorbate.		

Grading of Recommendations

Grading of recommendations was completed using the Joanna Briggs Institute (2008) tool. The tool was used to determine four aspects of Curcumin as an intervention: feasibility, appropriateness, meaningfulness, and effectiveness. Each of these four areas were ranked using an ABC scale with A representing strong support for use, B representing moderate support for use, and C representing no support for use. The tool was used once to determine recommendations for Curcumin as an intervention for OA and once to determine recommendations for Curcumin as an intervention for RA. The determination for recommendations of Curcumin for OA was based on six studies with levels of evidence ranging from II- IV. The determination for recommendations of Curcumin for RA was based on two studies with a level of evidence score of II (Melnyk & Fineout-Overholt, 2011). Please see the tables below on the grading recommendations using the Joanna Briggs Institute (2008) instrument.

Table 2a. Grading of Recommendations Table: Curcumin as intervention for OA

Grade of Rec	**Feasibility**	**A B C**	**Appropriateness**	**A B C**	**Meaningfulness**	**A B C**	**Effectiveness**	**A B C**
A	Strong support that merits application		Strong support that merits application		Strong support that merits application		Strong support that merits application	

B	Moderate support that merits consideration for application	**X**	Moderate support that merits consideration for application	**X**	Moderate support that merits consideration for application	**X**	Moderate support that merits consideration for application	**X**
C	Not supported		Not supported		Not supported		Not supported	

From the Joanna Briggs Institute (Joanna Briggs Institute {JBI}, 200

Table 2b. Grading of Recommendations Table: Curcumin as intervention for RA

Grade of Rec	**Feasibility**	**A B C**	**Appropriateness**	**A B C**	**Meaningfulness**	**A B C**	**Effectiveness**	**A B C**
Study was conducted at the rheumatology center of the Citadelle Hospital of Liege, Belgium	Strong support that merits application		Strong support that merits application		Strong support that merits application		Strong support that merits application	
B	Moderate support that merits consideration for application	**X**	Moderate support that merits consideration for application	**X**	Moderate support that merits consideration for application	**X**	Moderate support that merits consideration for application	**X**
C	Not supported		Not supported		Not supported		Not supported	

From the Joanna Briggs Institute (Joanna Briggs Institute {JBI}, 2008)

Feasibility

The Joanna Briggs Institute defines feasibility as "practicality and utility of an intervention … factors that affect the decision making among policy makers, clinicians, and patients" (Joanna Briggs Institute {JBI}, 2008, p.2). Curcumin treatment as an intervention for arthritis received a "B" recommendation representing that there was evidence supporting its use, although this may not be of high quality. There were two reasons for this ranking. The first was that the evidence from the study supports effectiveness of Curcumin as anti-inflammatory for arthritis as evidenced by decreased hospitalization and costs of patient testing, but it was only for one study. However, there was sufficient competency available since there were six studies that measured serum inflammatory markers but only five studies revealed decreased serum levels. In addition, all eight studies showed improvement with activities which supported the anti-inflammatory effect of Curcumin because an increase in function is considered alleviation from pain due to decreased inflammation. The second reason was that the resource of Curcumin treatment may be cost effective, however the cost of the bio-enhanced and complexated Curcumin was not divulged.

Appropriateness

The Joanna Briggs Institute defines appropriateness as," evidence about the extent to which an activity or intervention is ethical or culturally apt or acceptable." (Joanna Briggs Institute {JBI}, 2008, p.4). As an anti-inflammatory intervention for arthritis, Curcumin received an appropriateness rating of "B." The studies in this review covered a variety of cultures, ages ranged from young adult to older adults; and both genders were

included. However, two studies were conducted in India, two in Thailand, and one in Indonesia where Curcumin may be part of the participants' daily diet. In addition, two studies were done in Italy and one was done in Belgium. For all these studies, there was no indication that Curcumin as an intervention was not culturally acceptable. The Curcumin intervention in all the studies was acceptable by any age range and the majority of the population.

Meaningfulness

The Joanna Briggs Institute defines meaningfulness as," evidence about the personal opinions, experiences, values, thoughts, beliefs or interpretations of clients and their families or significant others" (JBI, 2008, p. 5). All eight studies were quantitative, not qualitative. In these studies, there was no evidence related to the subject or family's positive or negative experiences with the Curcumin intervention. This may be influenced by the fact that most of these studies were done in countries where Curcumin is part of their daily diet. The opinions and thoughts of the researchers and the subjects were considered in one observational study with small sample size but there was no information regarding the number of subjects who completed the study.

Effectiveness

The Joanna Briggs Institute defines effectiveness as," the evidence about the effects of specific interventions on specific outcomes" (JBI, 2008, p. 5). There were six studies which measured serum markers for inflammation but only four reported decreased serum markers for inflammation with Curcumin. Further, all eight studies measured improved disease activity and pain which were the primary goal of treatment

for arthritis. The majority of the researchers from these studies recommended further large samples research with Curcumin as an intervention for arthritis. Curcumin as an intervention for reducing inflammation in arthritis was given a “B” rating for effectiveness. The reason for this rating was due to the limited human trials available. Only one observational, descriptive study with a large sample size specifically showed that Curcumin has a positive anti-inflammatory effect on arthritis as evidenced by the decreased serum markers. However, Belcaro et al. (2010) was the sponsor of the study of bio-optimized Curcumin while being associated as the manager and distributor of the manufacturing company of the complexed curcumin, Meriva.

CONCLUSIONS

Evidence Related to Research Question

Based on the literature reviewed, there was evidence to support the utilization of Curcumin to reduce inflammation in arthritis. It is important for medical providers who are prescribing anti- inflammatories for arthritis to assess, evaluate and educate patient on the side effects of their medications and offer available and affordable adjunctive and or alternative treatment such as Curcumin. This allows patients to have additional information on their choices. By decreasing inflammation and pain and increasing affordability by using Curcumin, the quality of life of the clients may improve. There will be an overall decrease in healthcare costs and fewer adverse effects with use of Curcumin. However, there is still a considerable need for additional large samples studies that similarly confirm the effectiveness of Curcumin as an intervention to reduce inflammation in arthritis either as monotherapy or as a complementary treatment.

Limitations of Systematic Review

From the studies, it was evident that Curcumin has multiple molecular targets which was advantageous to reduce most sources of inflammation in arthritis but also for other chronic diseases associated with inflammation. However, the question that was not addressed in this systematic review was finding the short and long term side effects, therapeutic dose and toxicity level or dose of Curcumin.

The majority of the clients that are afflicted with arthritis belongs to the young adult and older adult age ranges. These age ranges are considerably the productive years and it is concerning that Curcumin has also been considered to be developed as a non-

steroidal contraceptive having both spermicidal and microbial properties against vaginal infections. This may bring about temporary benefit but it is unknown if Curcumin will eventually affect fertility or reproduction in the long term.

Although Curcumin is part of the daily diet of some countries or cultures, this is not an assurance that this substance is safe unless long term studies on toxicity of Curcumin in clients taking forms of the substance as a supplement are completed. In addition to the necessity of long term studies regarding Curcumin, there is also a need to develop standard therapeutic dosing of Curcumin that corresponds to achieving its desirable effects. The Curcumin dose of 8grams per day was appropriate for short duration (Anand, Sundaram, Jhurani, Kunnumakkara, & Aggarwal, 2008), however the human trials with Cucumin doses that range from 0.9 to 3.6 grams per day for 1-4 months has some adverse effects that include diarrhea and nausea, and increased the lab values for serum tumor markers alkaline phosphatase and lactate dehydrogenase (Sharma, Euden, Platton, Cooke, Shafayat, Hewitt, Marczylo, Morgan, Hemingway, Plummer, Pirmohamed, Gescher, Steward, 2004).

Last, due to Curcumin's multiple molecular targets to control inflammation in arthritis and other chronic diseases associated with inflammation, it is important to consider that Curcumin inhibits the activity of the drug-metabolizing enzymes cytochrome P450, glutathione-S-transferase, and UDP- glucutonosyltransferase (Appiah-Opong, Commandeur, Vugt-Lussenburg, Vermeulen, 2007). If Curcumin intake inhibits these enzymes, it is important to consider that this may lead to increased plasma concentrations of medications and can cause toxicity (Mancuso & Barone, 2009). This

directly defies the primary reasons why there is much interest in pursuing Curcumin studies to find alternatives in reducing inflammation in arthritis with fewer adverse effects, less toxicity and its affordability.

Implications for Nursing and Future Research

Utilization of disease modifying anti-rheumatic drugs (DMARDs) or biological response modifiers (BRMs) and NSAIDs yield multiple side effects to chronic arthritis patients, which are generally evaluated during clinical visits and follow up appointments. Evaluation is always required especially of individuals receiving DMARDs and biologics (BRMs). When patients present with multiple symptoms, the following question should be elicited: are the symptoms secondary to other causes or due to adverse side effects of NSAIDS, DMARDs or BRMs? What are the available alternative options for intervention to reduce inflammation in arthritis?

RA and OA are not identical in terms of etiology and pathology. However, Curcumin exhibits immune modulation as evidenced by reductions of Rheumatoid Factor (RF) titers in studies, and it also exhibits anabolic effects of potential chondroprotective benefit to degenerating cartilage in OA. Some patients have reservations towards the current conventional pharmacological treatments for arthritis due to known side effects. In these circumstances, providers such as physicians and nurse practitioners may need to offer an alternative treatment such as Curcumin. This review shows that Curcumin may be an effective treatment to some extent to reduce inflammation in arthritis.

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Appendix A

Table 3. Levels of Evidence of each Article

No	Year	Author; Title; Journal; issue, vol, pg	Method/ Variables/ Instrument	Sample/ Characteristics	Results	Critique: Strengths Limitations	Level
1	2009	Kuptniratsaikul, V., Thanakhumtorn, S., Chinswangwatanakul, P., Wattanamongkonsil, L., Thamlikitkul, V.; Efficacy and safety of Curcuma domestica Extracts in Patients with Knee Osteoarthritis. The Journal of Alternative and Complementary Medicine. p. 891-97.	Randomized cross-sectional study Knee pain & functions of knee assessed by time spent during 100 m- walk and going up and down a flight of stairs C. domestica extracts & Ibuprofen Pain Score Time spent with activity (up & down of stairs) Adverse events	N= 107 all with knee OA Adult patients with primary knee OA according to the criteria proposed by the American Rheumatism Association. Subject must have knee pain score of > or = 5 and radiographic osteophytes. Subjects with peptic ulcer, hepatobiliary	Dec pain on level walking, time spent on 100 m walk, and time spent on going up and down stairs in both groups	Strengths: RCT; comparison group strengthen the study Weakness: Small sample Subtherapeutic dosage of ibuprofen (800 mg per day) Single- blinded assessor Unequal frequency of drug intake between the two groups	II

				tract disease or allergy to curcumin & ibuprofen were excluded.			
2	2014	Kuptniratdaikul, V., Dajoratham, P., Taechaarpornkul, W., Buntragulpoontawee, M., Lukkanapichonchut, P., Chootip. C., Saegsuwan, J., Tantayakom, K., & Laongpech, S.; Efficacy and safety of Curcuma domestica extracts compared with Ibuprofen in patients with knee osteoarthritis: a multicenter study.	Double- blind randomized controlled trials (RCT) C. domestica extracts, ibuprofen, Knee Pain, 6 min walking distance, Knee function, Stiffness Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) modified Thai version, and a 6 minute walk distance; Adverse events	N= 367 with knee OA Patients were those who have primary knee OA according to the American Rheumatism Association criteria who had numerical rating scale of knee pain of > or = 5 out of 10 and age 50 years old or older. Patients with abnormal liver function or renal function, history of peptic ulcer, allergy to curcumin or	Curcuma domestica extracts have similar effectivity as ibuprofen for the treatment of knee osteoarthritis. The profile for side effects were the same but with fewer gastrointestinal adverse complaints from the curcuma domestica extracts group.	Strengths: Double- blind RCT; Adequate sample Lower dosage of curcumin with a shortened duration to 4 weeks to determine the efficacy and safety of 1, 500 mg/day of curcuma domestica extracts in pain reduction and functional improvement compared with 1, 200 mg/day of ibuprofen.	II

				ibuprofen or were unable to walk were excluded.		Weaknesses: Multicenter study; unknown if the standards are equal.	
3	2012	Chandran, B., & Goel, A.; A Randominzed, Pilot Study to Assess the Efficacy and Safety of Curcumin in Patients with Active Rheumatoid Arthritis. Phytotherapy Res., Wiley Online Library DOI: 10.1002/ptr.4639.	Randomized Single-blinded Pilot study Curcumin in the form of BCM- 95 (patented and registered formulation of curcumin with enhanced bioavailability), Diclofenac sodium, tenderness and swelling of joints and disease activity Variety of validated instruments used.	N=45 patients with RA (38 female, 7 male; mean age 47.88 yr.) With active RA were prospectively enrolled. Patients were of 18-65 yr. of age and were diagnosed to have RA according to the revised 1987 American College of Rheumatology criteria.	There was reduction in Disease Activity Score (DAS) 28; & American College of Rheumatology (ACR) criteria for tenderness and swelling of joint scores. Patients in all 3 groups showed statistically significant changes in their DAS scores. Curcumin group showed the highest percentage of improvement in overall DAS and	Strengths: CRP, a serum markers for inflammation concurrently reveals improvement in inflammation (p value <0.05) Limitations: Study was designed as 2 month trial, not long enough to detect radiographic changes.	II

					ACR scores (ACR 20, 50 & 70). Curcumin group did not have adverse events.		
4	1980	Deodhar, S.D., Sethi, R., & Srimal, R.C. (1980). Preliminary study on antirheumatic activity of curcumin (diferuloylmethane). Indian J. Medicine Res, 71; pp 632-634.	Double-blind RCT Curcumin, Phenylbutazone, Rheumatic activity Variety of Validated instruments used.	N= 18 pts with RA Eligible patients were with definite rheumatoid arthritis and with the duration of articular symptoms ranged from 9 to 96 months (means: 38.6 months). All subjects had significant reducible disease-activity, as judged by the physician.	Curcumin given at 1200 mg daily was effective in improving joint swelling, morning stiffness, and walking time. No side effects reported by either group. No significant change in blood pressure, pulse, haemoglobin, hepatic or renal function during the study.	Strengths: All 18 patients completed the study Research design is double blind, RCT Inclusion and exclusion criteria were specified. Four days wash out before the study was initiated. Limitations: Small sample= 18 patients	II

				Patients age <20 years old, on second line drugs or with hepatic/renal function impairment or peptic ulcer disease were excluded.	Both curcumin and phenylbutazone showed antirheumatic activity (improved morning stiffness, walking time, and joint swelling). Neither group has an improved grip strength, articular index or ESR. Fatigue time improved with phenylbutazone. Both patient and observer assessed improvement at the end of phenylbutazone. Improvement was noted by observer alone at the end of curcumin period	Lacking control group, it is difficult to draw conclusions. Study was short-term (2 weeks) Unknown if the cause of lacking improvement on grip strength, articular index; and ESR was due to the short period of the study or because of less optimal dosage of curcumin. .	

5	2011	Kertia, N., Asdie, A.H., Rochmah, W., & Marsetyawan (2011). Ability of Curcuminoid from Curcuma domestica Val. In Reducing the Secretion of Reactive Oxygen Intermediates by Synovial Fluid Monocytes in Patients with Osteoarthritis. Indonesian Journal of Biotechnology, (16):1, pp. 111-117.	Prospective Randomized open end blinded evaluations= PROBE Curcuma domestica Val. Extract, diclofenac sodium, inflammation, tissue damage The secretion of ROI by synovial fluid monocytes was calculated by scoring the amount of formazan formation after neutral red staining in nitrobleu tetrazolium reduction assay.	N= 80 patients with OA Patients with OA only, had no other type of arthritis, had no abnormalities of liver, kidney or bone marrow function, had no gastritis, peptic or duodenal ulcer and no hypersensitivity to diclofenac sodium & curcuminoid and no use of anticoagulant or other anti-inflammatory drugs.	The secretion of reactive oxygen intermediates (ROI) by synovial fluid monocytes was significantly decreased in both groups ($p < 0.001$). There was no significant difference in decreasing of ROI secretion of synovial fluid monocytes between both treatment groups (P= 0.92).	Strengths: Random selection of subjects. The subjects were homogenous; that is they have no other type of arthritis except Osteoarthritis. There was a 1 week washed-out before the sample was divided into 2 groups. Limitations: The researchers were not able to investigate the mechanism of action of Curcuma domestica Val. Rhizome extract and diclofenac sodium in suppressing the	III

						secretion of ROI by synovial fluid monocytes	
6	2010	Belcaro, G., Cesarone, M.R., Dugall, M., Pellegrini, L., Ledda, A., Grossi, M.G., Togni, S., & Appendino, G.; Product- evaluation registry of Meriva, a curcumin-phosphatidylcholine complex, for the complementary management of' osteoarthritis. Panminerva Med; 52 (Suppl. 1 to No. 1): 55-62.	Cohort study with control group Meriva (complex of curcumin with soy phosphatidylcholine), mobility, inflammation WOMAC scores Evaluation of physical performance Variety of validated instruments used.	N=50 pts with OA Patients OA with symptoms localized in either or both knees on either.	After three months, the result showed significant improvements for the Meriva complex supplemented group in walking performance (The walking distance was increased from 76m to 332 m), decrease painkiller use, and decrease gastrointestinal complaints. WOMAC scores decreased to 58% after 3 months of treatment. The improvements were better than what was achieved from the group that	Strengths: Curcumin was complexed to improved bioavailability. Limitations: The type of study was observational-descriptive study which is prone to bias. Comparison group was broadly described and the paper also divulged that the principal investigator or author of the study was the manager, producer and distributor of the	IV

					received standard treatment alone.	compounded curcumin-Meriva. Study did not specify the number of subjects who were not able to complete the study.	
7	2010	Belcaro, G., Cesarone, R.M., Dugall, M., Pellegrini, L., Ledda, A., Grossi, M.G., Togni, S., & Appendino, G.; Efficacy and Safety of Meriva, A Curcumin-phosphatidylcholine Complex, during Extended Administration in Osteoarthritis Patients. Alternative Med Rev; 15(4), pp.337-344.	Cohort study with control groups Meriva (complex of curcumin with soy phosphatidylcholine), mobility, inflammation Variety of validated instruments used.	N= 100 pts with OA Patients with primary knee OA (grade 1 or 2) according to the American Rheumatism Association and confirmed by x-ray analysis.	After the 8 month study, the group taking Meriva complex experienced significantly greater improvements in the treadmill walking test, pain level and mood and mobility as compared to the group that received the standard treatment alone.	Strengths: Significant decrease of all inflammatory markers suggests clinical improvement. Limitations: The study was non- RCT, Subjects were recruited. The subjects were not	IV

					Serum inflammatory markers such as IL-1B, IL-6, soluble CD40 ligand, soluble vascular cell adhesion molecule-1, and erythrocyte sedimentation rate were Significantly decreased in the treatment group. WOMAC score decreased more than 50%, treadmill walking performance was increased almost threefold compared to control Decrease in GI complications, distal edema, & use of NSAIDs/painkillers by patients were noted after Meriva	Blinded to the treatment allocation. Short length of treatment period= 8 months Small sample size. 5 patients in the treatment group left the study for non-medical reasons. No comparison study of Meriva vs NSAIDs, observed only the decrease use of NSAIDs Study conducted by the manufacturer and distributor of Meriva or	

					Treatment Hospital admissions, consultation and patient tests were also decreased after Meriva txt.	compounded curcumin.	
8	2014	Henrotin, Y., Gharbi, M., Dierckxsens, Y., Priem, F., Marty, M., Seidel, L., Albert, A., Heuse, E., Bonnet, V., & Castermans, C.; Decrease of a specific biomarker of collagen degradation in osteoarthritis, Coll2-1, by treatment with highly bioavailable curcumin during an exploratory clinical trial. BioMed Central Complementary and Alternative Medicine, 14:159-161.	Cohort study without a control group Flexofytol (bio-optimized curcumin), Coll2-1 (biomarker of collagen degradation in OA) Variety of validated instruments used.	N= 22 pts with knee OA Patients with knee OA (7 males and 15 females) according to the ACR criteria and with radiographic confirmation.	Treatment with curcumin was well tolerated. Curcumin in the form of bio-optimized FleIofytol significantly reduced the serum level of Coll 2-1 ($p < 0.002$) and decreased CRP. Curcumin significantly reduced the global assessment of disease activity of the patient.	Strengths: The study clearly described the inclusion and exclusion criteria. The treatment was delivered by a rheumatologist. Exhibited the potential of curcumin on treating OA. It was reflected by the variation of a cartilage specific biomarker,	IV

						Coll2-1 that was rapidly affected by the treatment. This study qualified Coll2-1 as a biomarker for the evaluation of curcumin in OA treatment. Limitations: There was no control group. There was no washout period mentioned in the study. 2 did not complete the study. One subject discontinued after 14 days into the study due to diarrhea and vomiting; the 2nd subject	

						discontinued after 28 days due to nausea and vomiting	