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The Role of Curcumin in Inflammatory pathogenesis and the Benefits in Treatment of Osteoarthritis

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Running Head: CURCURMIN ROLE IN PATHOGENESIS AND TREATMENT OF OA

The Role of Curcumin in Inflammatory Pathogenesis and the Benefits in Treatment of Osteoarthritis

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Abstract

Curcumin is a perennial herb that originated in India, and its scientific name is Curcuma longa that belongs to the Zingiberaceae family. The active ingredients in turmeric are demethoxycurcumin, bisdemethoxycurcumin, and the particularly important compound is curcumin polyphenols. Curcumin has been recognized as a polyphenolic compound that has antioxidant, anti-inflammatory, anti-tumor, anti-diabetic, immunomodulatory and anti-depressant abilities, and may counteract underlying cellular mechanisms, which often leads to oxidative stress and inflammation that plays an important part in OA pathogenesis. The main factors responsible for cartilage degeneration are interleukin- one (IL-1) and tumor necrosis factor-alpha (TNF-alpha).[13] These factors are responsible for amplifying the synthesis of MMP or prostanoid, and also causing chondrocyte apoptosis. In vitro studies confirmed that curcumin might inhibit the apoptosis of chondrocytes, or restrict the release of metal metalloproteases, proteoglycans, decrease the composition of cyclooxygenases, inflammatory cytokines, and prostaglandin E-2 by preventing the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) system in the chondrocytes. Curcumin also was able to reduce the production of the basal IL-1 beta, prostaglandin E-2, IL-6, IL-8 and MMP-3 in the human chondrocytes in strength determined way. The efficacy of Curcumin in comparison with Ibuprofen for pain relief was equal, yet Curcumin showed less side effects. Overall, scientific literature demonstrates that curcumin possesses anti-inflammatory effects and may be beneficial to mitigate complications and improve pain.

Keywords: curcumin, anti-inflammatory, osteoarthritis, pathogenesis

The Role of Curcumin in Inflammatory Pathogenesis and the Benefits in Treatment of Osteoarthritis

Curcumin is acknowledged for its anti-inflammatory and anti-oxidative properties, which could potentially be beneficial and safe for the treatment of OA in patients with chronic comorbidities. By exploring the new avenues of the use of Curcumin, we might be creating the new path of OA treatment. The importance of this project is to explore the substance Curcumin, and its suitability as an alternative or an adjunct for treatment of OA in patients whose management options are limited by their medical conditions or the current pharmacological management is unsatisfactory for controlling their pain. Curcumin has shown through different studies with minimal or no apparent side effects, which makes it an excellent candidate for consideration as an adjunct for future use in treatments of anti-inflammatory conditions. This project will explore the safety and benefits of Curcumin, the favorable dosing of Curcumin per day, and the forms of Curcumin that seem to be most effective in improving the inflammation and pain of these patients. Curcumin could be used as a primary or an adjunct therapy along with the standard treatment of OA and may also largely contribute in the improvement of unbearable pain, which ultimately should improve patient mobility and quality of life.

Arthritis and its medical burden have been known for centuries. The first documentation of this disease was found in the third millennium B.C.[1] Osteoarthritis (OA) is the most common form of Arthritis, which severely affects millions of individuals. [1,2] According to the World Healthcare Organization (WHO),[2] OA of the hip and knee are one of the leading causes of worldwide disability and morbidity with a subsequent economic burden on society, leading to a massive healthcare disbursement and loss of employment.[1,2] In 2013, the total medical expenditures and earnings losses due to arthritis rose to approximately $304 billion,[3] and it is

estimated that this number will reach 78 million by the year 2040.[4] The recent estimates point out that 91 millions of Americans ages 18-64 are affected by arthritis.[5] Nearly half of all adults with diabetes have some type of arthritis, and over 50 percent of adults with arthritis and diabetes have activity restrictions.[6]

OA is a condition with a multi-dimensional etiology and historically has been known for its wear and tear damage.[7] Today medicine has recognized that apart from the destruction and loss of articular cartilage, there have been multiple pathophysiological changes involved in OA.[7] Some of the changes constitute of the transformation of sub-articular bone, formation of osteophytes, changes in ligaments stability, diminishing of peri-articular muscle functions, and synovial inflammation of the joint.[8] Since most osteoarthritic changes are irreversible, preventive strategies have superiority over other therapeutic methods.[6-8] Extensive reports show that several bioactive dietary compounds (known as nutraceuticals), such as polyphenols, can counteract underlying cellular mechanisms which often lead to oxidative stress and inflammation that is involved in OA pathogenesis.[9] Curcumin has been recognized as a polyphenolic compound and has received significant attention in the medical community due to its effective antioxidant, anti-inflammatory, anti-tumor, anti-diabetic, immunomodulatory and anti-depressant abilities.[7,9,10,13] Curcumin can be considered safe since it has been commonly used in the traditional and modern medicine, as well as in culinary consumption. [11,12] Extensive evidence has demonstrated the promising role and safety of curcumin as an adjunct for the treatment of OA, diabetes and its complications via modulating several cellular mechanisms.[9-12]

Overview of OA Pathogenesis

Cartilage is a connective tissue that is made of an interstitial matrix of fibers called collagens type II, chondrocytes, and ground base substance named proteoglycans.[13] In healthy

individuals, the balance between synthesizing and degrading enzymes is maintained in equilibrium. However, in cartilage affected by OA, the balance gets disrupted by overproduction of destructive proteins, which consequently leads to the reduction of the quantity of collagen and proteoglycans in the matrix.[13-14] Eventually, the synthesizing enzymes are grossly outmatched by progressive degradation that leads to degeneration of cartilage and worsening of the disease as demonstrated in appendix A. The matrix metalloproteinases (MMPs) that are secreted by the chondrocytes and synovial cells are responsible for cartilage degradation and are organized into three groups - a) collagenases, b) stromelysins and c) gelatinases. The main factors responsible for cartilage degeneration are interleukin- one (IL-1) and tumor necrosis factor-alpha (TNF-alpha).[13] These factors are responsible for amplifying the synthesis of MMP or prostanoid, and also causing chondrocyte apoptosis. [13,14] The opposition group for MMPs are the protease inhibitors –a) tissue inhibitor metalloproteinase -1(TIMP-1), b) TIMP-2, c) alpha-2-macroglobulin, these markers will counteract the destructive processes, which are IL-1 receptor antagonist (IL-1ra) and TIMP. [7,13-14] In addition to the inhibitors, the growth hormones also play a role in repairing the cartilage by a) increasing proliferation of chondrocytes b) uprising the expression of IL-ra, TIMP, type II collagen, and proteoglycans, c) decreasing the expression of IL-1 and TNF-alpha.[13,15] All of these factors are significant facilitators in the process of cartilage destruction in OA and should be considered as a structural and developmental tool for numerous possibilities of new treatments or in evaluations of herbal supplements in the clinical trials.[13-15]

The potentials for herbal supplements are massive as they are vastly distributed over the world. Herbaceous medicine has played an essential role in the past, present, and should be further considered in the future research as an essential addition to the patient care.[16] The number of consumers that utilize herbal supplements has been substantially rising, and according to

WHO, 80% of the world population have used them for their primary health care needs, which includes 38 % of adults in the USA.[17] The use of herbal additions in the treatment of OA should not be a surprise, especially in patients that have poorly controlled pain and constant inflammation.[16,17] There are many herbal and dietary supplements on the market that advertise the benefits for OA treatment.

Curcumin Overview

Curcumin is a perennial herb that originated in India, and its scientific name is Curcuma longa that belongs to the Zingiberaceae family.[18] The herb itself is acquired from the rhizome of the plant, which is dried before the useful powdered form can be obtained.[17,18] The active ingredients in turmeric are demethoxycurcumin, bisdemethoxycurcumin, and the particularly important compound is curcumin.[17] Curcumin has at least 4000 years of documented use in traditional medicine and socio-religious practices.[17,18] There are approximately 55 different names for turmeric in Sanskrit, where Curcumin was associated with both medicinal and religious uses.[17] In English, Curcumin has also been referred to as yellow root, Turmeric, and Indian saffron. Curcumin has been accepted in all of the major traditional medical systems: Ayurveda, Siddha, Unani, and Tibetan.[18] This substance has received significant attention in the medical community due to its potent antioxidant, anti-inflammatory, anti-tumor, anti-diabetic, immunomodulatory and anti-depressant abilities.[10-17]

Anti-inflammatory Properties of Curcumin

Anti-inflammatory properties of Curcumin were demonstrated in several studies. One of the studies that was performed in vitro confirmed that curcumin should be able to inhibit the apoptosis of chondrocytes, restrict the release of metal metalloproteases, proteoglycans, decrease the composition of cyclooxygenases, prostaglandin E-2, and inflammatory cytokines by

counteracting the initiation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) system in the chondrocytes and by limiting an activation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha, phosphorylation, and translocation of the p65 subunit of NF-κB complexes into the nucleus.[19] Mathy-Hartert et al.[14] explored the involvement of Curcumin on the extracellular matrix, its protein metabolism and the inhibitory effect on the inflammatory mediators of the articular chondrocytes in the alginate beads and human cartilage explants. The results of this study showed that Curcumin reduced the production of the basal IL-1 beta, prostaglandin E-2, IL-6, IL-8 and MMP-3 in the human chondrocytes in absorption dependent manner.[14] The TIMP-1 and aggrecans manufacture have not been influenced by Curcumin substance in this experiment.[14] As of these findings, it was concluded that Curcumin could be potentially useful in the treatment of OA by exhibiting the inhibition of the inflammatory and catabolic mediators in the articular chondrocytes.[14] Another study was done by Pulikkotil and Nath that evaluated anti-inflammatory properties of topical Curcumin compared to chlorhexidine (CHX) and chlorhexidine-metronidazole (CHX-MTZ) in an investigational gingivitis human model by evaluating levels of IL-1 beta and chemokine (C-C motif) ligand 28 (CCL28).[20] Even though this study used topical Curcumin, it seemed to be appropriate as patients may use turmeric orally and also apply Curcumin as topical compresses or wraps to the affected knee.[20] The study measured the inhibition of IL-1 beta, which is part of the degrading process of cartilage.[20] Curcumin demonstrated the equivalent anti-inflammatory power of CHX-MTZ and was extra efficient when compared to CHX.[20] In the review by Henroitin et al., it was recapped that Curcumin exhibited protective properties against catabolic actions of IL- 1beta, MMPs- 3 up-regulation, down-regulation of collagen type II and beta 1-integrin expressions in human chondrocytes.[21] Curcumin also demonstrated the effect of

impeding IL- 1 beta-induced proteoglycan degradation, AP-1/NF-kappa B signaling, and chondrocyte apoptosis.[21] This review suggested that more basic research is needed before extensive clinical trials can be introduced in this area.[21]

Curcumin versus NSAIDS Treatment

That leads us to the question of how Curcumin's anti-inflammatory properties compared to the treatment of OA with NSAIDs and its efficacy. In the study that was completed by Kuptniratsaiku et al., the primary focus was directed on the comparison between Curcumin and Ibuprofen by pain reduction and functional improvement.[22] The population was randomly selected and contained 367 participants who were diagnosed with primary OA of the knee. Each participant received either Ibuprofen 1200 mg/day or turmeric extract 1500mg/day for a total of 30 days.[22] The WOMAC scale was used for evaluation of pain and improvement of knee function. In conclusion, this study supports that turmeric has the same efficacy in controlling pain as Ibuprofen.[22] Additional study included the evaluation of the efficacy of Flexofytol, which is more bioavailable Curcumin in knee OA form.[23] The study inclusion criteria consisted of a population of 45-80 year-olds, with symptomatic knee pain, knee pain for the last 24 hours of at least 40 mm on VAS, Kellgren & Laurence grade II to II, patients who were able to avoid NSAIDS, could follow instructions, and participate in follow-ups.[23] The quality of the study was not disclosed but brought up the need for further evaluation of Curcumin in OA treatment.[23]

Kuptniratsaikul et al. have evaluated the safety of Curcumin in a study where Ibuprofen and Curcumin were compared.[22] The study reports that the number of patients who developed side effects did not differ among the tested groups, however, the occurrences in an abdominal discomfort and distress were considerably higher in the group that was treated with Ibuprofen.[22] Another study by Kizhakkedath that compared the mixture of Curcumin with Boswellia Serrate

extract (TBS) to selective COX-2 inhibitor – Celecoxib in the treatment of OA.[24] In this study, 30 candidates were enrolled, and 28 of them completed the study. As reported the treatment was tolerated well without any side effect that may cause alterations in the Vital signs, hemogram, hepatic or kidney functions tests. The results demonstrated that TBS given 500mg twice a day scored better on medical assessment and indicators logging compare to Celecoxib 100 mg twice a day.[24] An additional study was found that evaluated the safety of Curcumin in patients with kidney disease. The results demonstrated that Curcumin and Boswellia serrata are harmless and acceptable to improve the levels of an inflammatory cytokine in patients with kidney disease see Appendix B.[25]

Bioavailability of Curcumin

Curcumin, as by countless literature reviews has very poor absorption, metabolism, bio-distribution, and its biological availability, which contradicts the systemic effects observed with Curcumin treatments, such as anti-inflammatory effects in the treatment OA and it is mainly due to its low absorption, rapid metabolism, and quick elimination.[9] Therefore, more attention has been given to the systems for enhancing the bioavailability, improving its permeability, extending the circulation time of Curcumin in the circulation system.[19] Curcumin has hydrophobic characteristics (poorly dissolves in aqueous solution) and can be easily degraded by UV light.[9,19] There have been several approaches to invent the best bioavailable Curcumin formulations in combinations, which contain nanoparticles, liposomes, micelles, and phospholipid complexes.[19] One of the elements, besides the natural compounds, is Piperine. Piperine is a constituent of black pepper, and it has been exhibited that intensifies the bioavailability of Curcumin.[26] The study by Sharma et al.[27] demonstrated that Curcumin (2g/kg orally), which was administered with Piperine (20 mg/kg orally) simultaneously, increased the

bioavailability by 20 folds more than when given alone in the epileptic rat. There have been several different forms of Curcumin introduced to the market as of today. Meriva, which is lecithin derivative of Curcumin has shown in the four months long observational study, that when used together with glucosamine it has a significantly better outcome compared to the combination of chondroitin and glucosamine. Based on the WOMAC score and Karnofsky index, results in the faster onset of improvement in the patient outcome.[28]

Dosing of Curcumin and Adverse Effects

Dosing of Curcumin has displayed differences based on the individuality of the clinical trial. In Randomized, Double-Blind, Placebo-Controlled, Two-Dose, Three-Arm, and Parallel-Group study by Amalraj et al.,[29] included 36 patients who were given different doses of Curcumin 250mg or 500 mg twice a day in the length of three months. This study determined that as the minimal dose of Curcumin 250 mg twice a day are sufficient and safe for patients with Rheumatoid Arthritis.[29] These interpretations were based on substantial modifications in ESR, CRP, and RF values in patients receiving Turmeric compared to the other groups.[29] While there is no established agreement on effective Curcumin doses, the following dose has been recommended for osteoarthritis 500 mg of turmeric extract up to twice daily. High doses of Curcumin long- term are not recommended as of this time since further research validating their safety is needed.[31,32] However, the FDA recommendations are 400 mg – 1800 mg a day, and it is determined based on the formulation of Curcumin.[11] Curcumin tested in clinical trials in which doses reached up to eight grams per day has shown minimal or none toxic effects, however, side effects have been reported.[33] The frequent adverse effects involve allergic reactions, nausea, vomiting, stomach pain, diarrhea, or constipation.[26,28]

Although Curcumin is considered to be harmless for most individuals, particular people may have to avoid it. Several conditions warrant extreme caution with Curcumin intake, pregnancy and breastfeeding as there is not sufficient research to conclude if Curcumin supplements are safe, gallbladder disease as Curcumin increases the gallbladder contraction thus worsening symptoms.[34] Individuals prone for kidney stones as Curcumin is high in oxalate and binds with calcium that causes kidney stones formation.[34] Patients with bleeding disorders or on blood thinners (Warfarin) as Curcumin increase bleeding time.[34,35]

Conclusion

Even though Curcumin has great potentials as an effective anti-inflammatory drug for osteoarthritis, a major drawback that is linked to its low bioavailability that is due to poor absorption, and rapid systemic elimination. There have been several approaches to invent the best bioavailable turmeric formulations in combinations, which contain nanoparticles, liposomes, micelles, and phospholipid complexes. Different approaches have become important in enhancing the bioavailability, improving its permeability, extending the circulation time of Curcumin in the circulation system. The current recommendation dose for treatment of OA with Curcumin is 500 mg twice a day. The side effects of Curcumin are almost none, which make it so attractive for the new possibility of therapy. Although data from various clinical trials are promising, moreover clinical trials will be required that will be implemented on a larger scale and prolong duration of time.

Conflict of Interest
The Author confirm that this article content has no conflict of interest.

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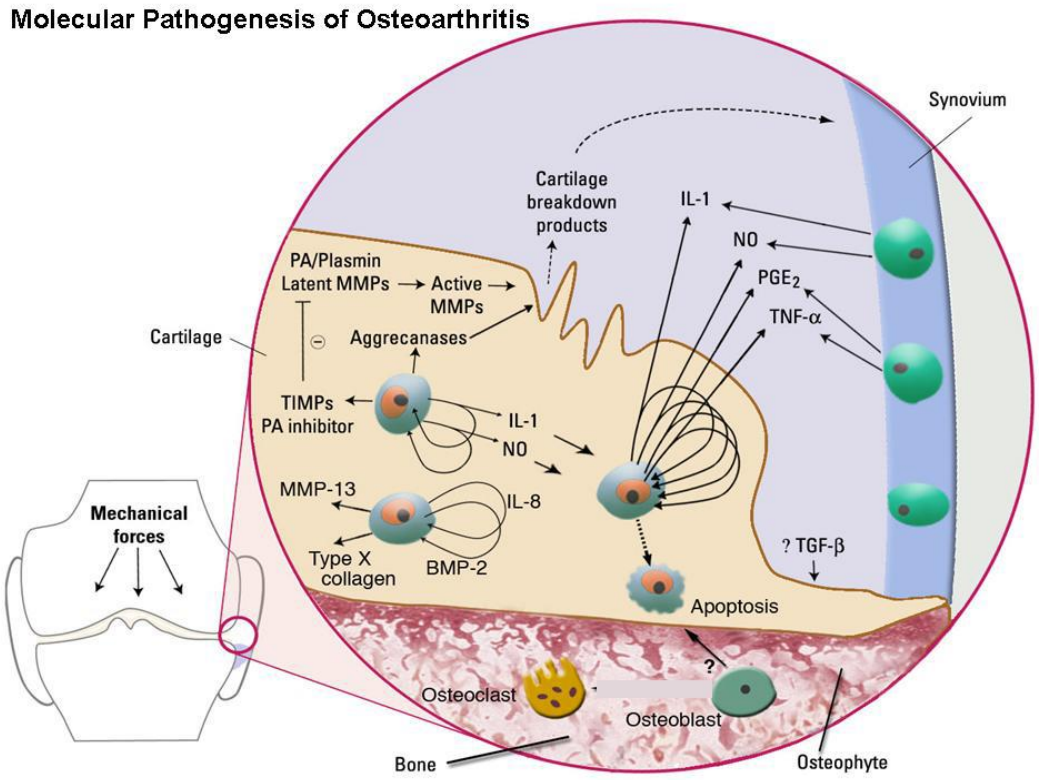
Appendix A

Schematic Representation of Key Pathological Events and Some of the Potential Targets Considered for Disease Modification in Osteoarthritis.



Reprinted from The Abramson Lab. (n.d.). Retrieved from https://med.nyu.edu/medicine/labs/abramsonlab/osteoarth-research.html

Appendix B

Comparison of Safety, Tolerability and Effectiveness for Different Treatment of OA

Medications or supplements	Safety	Tolerability	Effectiveness
Acetaminophen	Hepatotoxicity Renal toxicity	Excellent	**
Aspirin	Bronchospasm GI irritation Platelet inhibition	Good	*
Cyclooxygenase-2 selective NSAIDs (e.g., celecoxib [Celebrex])	Hepatic dysfunction Renal dysfunction	Good	***
Nonselective NSAIDs (e.g., ibuprofen)	GI irritation GI ulceration and bleeding Platelet inhibition Renal dysfunction Renal failure	Good	***
Opioid	Nausea/vomiting Respiratory depression Sedation	Good	***
Turmeric forms	None In high doses may cause nausea, vomiting, and diarrhea	Excellent	**

Appendix C

The Journal Author Guidelines

The Journal of Family Practice (JFP)

JFP is a peer-reviewed medical journal specifically intended to meet the needs of the specialty of family medicine.

Guidelines for submitting

An Applied Evidence article is a clinically oriented, evidence-based review article that summarizes the best available evidence for a broader topic, such as the diagnosis or management of a common condition. An Applied Evidence article is a 6- to 8-page review of the best and most current clinical evidence on a timely topic, supported by clear level-of-evidence and strength-of-recommendation ratings defined by the Strength of Recommendation Taxonomy (SORT). Authors should supplement such evidence with expert commentary on how to apply the recommendations to practice. While an Applied Evidence article is not intended to be a systematic review or a meta-analysis, it should reflect a thorough search of the highest quality sources of evidence-based information.

Preparing your Article

Limit your manuscript to 2000 to 2200 words, and the number of art elements (charts, graphs, tables) to 3 or 4. Refer to the following outline as a guide to the article's general format.

1) Title page: Include article title, author(s) affiliations, address of corresponding author, phone, fax, and e-mail address.
2) Article title: Write a title that reflects new information, changes in patient care, or a clear clinical benefit. Readers should infer that the article would teach them something they

don't already know.

3) Practice Recommendations: A bulleted list of 3 or 4 "take home" points—i.e., the clinical pearls you want every reader to remember. The strength of recommendation should be noted as per the SORT system.

4) Lead paragraph(s): Please state the point of your article immediately and explain why the information is important to clinical practice now. Avoid starting with well-known demographic information.

5) Headings: JFP uses three levels of headings within the text. Consult an article on this Web site for style.

6) Figures and tables: Figures display a brief title at top that tells the main teaching point of the figure. At bottom, a caption explains the illustration, graph, or flowchart completely and succinctly. A reader in a hurry should be able to look at each art element and thoroughly understand it's meaning without having to search the text for an explanation. Likewise, tables carry a descriptive title and use footnotes, as needed, to qualify data and other entries.

7) References: Please limit references to approximately 30. If your article is accepted, you will be asked to provide, via email or Drop box, PDFs of all references with the cited information highlighted.

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be directed to jfp.eic@gmail.com

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Manuscripts should conform to the International Committee of Medical Journal Editors (ICMJE) Recommendations, which are available at www.icmje.org. For questions about style, consult the American Medical Association Manual of Style: A Guide for Authors and Editors. 9th ed. Baltimore, Md.: Williams and Wilkins, 1998. Keep abbreviations and acronyms to a minimum and spell out on first reference, e.g., American Academy of Family Physicians (AAFP). Regarding medications, generic drug names should generally be used. When proprietary brands are used in research, include the brand name in parentheses in the Methods section. The title page should include from top to bottom: article title; name, degree, and institutional affiliation of each author; previous presentation of the work, if any; name and address/fax/E-mail of the corresponding author; and manuscript word count, excluding tables, figures, and abstract. Pages should be numbered consecutively in the upper right corner beginning with the title page. Please see the links, above, for detailed information on specific article types and departments. Unsolicited manuscripts are not considered for Clinical Inquiries.

Acknowledgements

This section is optional and may be used to acknowledge substantial contributions to the research of preparation of the manuscript made by individuals other than the authors. Conflict of interest: Each article should have a statement acknowledging any potential conflict of interest. If there is none, please state "No conflict of interest."

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Appendix D

Peer-review Form

Manuscript title: The Role of Curcumin in Inflammatory pathogenesis and the Benefits in Treatment of Osteoarthritis

Colleague Author: Beth Hart

Peer reviewer's name: Ada Cheng

Peer Reviewer Expertise:

Which of the following best describes your level of knowledge of the manuscript's topic?

o Expert

o Competent

o Familiar

o **No knowledge**

Comments related to your level of knowledge:

I have no background regarding the patho-physiology of curcumin or turmeric.

Manuscript Rating Worksheet

Practicality: The topic is appropriate for publication in the target journal identified by the author.

Rating: NA

Comments: Well-written paper, but the author did not indicate which journal or publication is intended for her scholarly project.

Quality of sources:

Rating: Needs one change/improvement

Comments: Citation 9 should also be included in the following statement: “Curcumin has been recognized as a polyphenolic compound and received significant attention in the medical community due to its effective antioxidant, anti-inflammatory, anti-tumor, anti- diabetic, immunomodulatory and anti-depressant abilities”

Citation 7, 10, 11, and 13 are appropriate.

Accuracy: The paper presents information that is up-to-date, accurate, and evidence-based.

The most recent literature is cited, and the manuscript critically appraises the cited works in a way that supports the reader’s application of the material to patient care.

Rating: Satisfactory

Comments: Cited resources are recent, and cited literature were published from the years 2008 to 2018.

Usefulness: The paper addresses as appropriate the PA competencies of medical knowledge, interpersonal and communication skills, patient care, professionalism, practice-based learning and improvement, and systems-based practice.

Rating: Satisfactory

Comments: Alternative treatment to osteoarthritis is most appropriate for primary care settings.

Readability: The paper is well-written and easy to read.

Specifically, consider the following elements: Information is presented in an organized way. Headings and subheadings are used effectively. Paragraphs are coherent. The style is readable and easy to follow. Meanings are clear.

Rating: Excellent

Comments: The structure of the paper is logically; there is an introduction, explanation of action of Curcumin, reported risks, reported benefits, and conclusion.

Quality of accessories: Art and other accessories (i.e. tables, figures, graphics, photos, illustrations, etc.) provide value to the reader and agree with the text.

Rating: Needs improvement.

Comments: No tables, figures, graphics, photos, or illustrations were provided with this

scholarly project. The author may consider illustrating the pathophysiology of arthritis or proposed mechanism of action for Curcumin.

Originality: The manuscript is novel and interesting to publish for a PA audience. The reviewer has no concerns about the originality of the work (plagiarism). Ideas and materials of others are appropriately attributed.

Rating: Satisfactory

Comments: The author presents a review of alternative treatment to osteoarthritis.

Suggest accessories

Please indicate any x-rays, anatomic drawings, illustrations, tables, algorithms, or other accessories that might improve the article. If you know of online resources that might benefit the reader, please indicate these as well so that the links can be included in the online version of the article.

As mentioned in the tables, figures, graphs, and/or illustration section, it may be helpful to the readers for a visual illustration of proposed curcumin mechanism of action in treating osteoarthritis and/or illustration of pathophysiology of osteoarthritis.

Your final recommendation (select one)

_____ Accept manuscript for publication (the author does not need to make any revisions)

X Ask author to revise manuscript and re-submit (if revisions are adequate, the manuscript should be published)

_____ Reject manuscript (the article is not suitable for publication, either because the topic is not suitable or the quality of the manuscript is too poor)

Please add any final comments.

Great job! It is a well-written review paper for alternative treatment of osteoarthritis. I proposed a few suggestions before submission to a journal. Your manuscript is almost complete, and I can’t wait to read the final manuscript after a few changes.

A note of caution

Once completed you are asked to directly forward this peer-review un-blinded to the author whether the manuscript is accepted or rejected. Please make sure that the tone and content of your review are appropriate. Your comments should be honest, specific, fair, constructive, and professional.

Peer-Reviewer Name: Ada Cheng Date: 11/14/18

Appendix E

Response to Peer-reviewer

Quality of Sources: I agree with the suggestion of the reviewer that reference number nine should be used also for the particular part of the text, and the reference was added.

Quality of Accessories: Appendix A and B was added for an easier demonstration of information given in the article, which includes the illustration of pathogenesis and the factors that play an important role in it.

The journal author guidelines were added as an appendix.

Response to Instructor Feedback

No response needed based on instructor feedback.