Journal of Medical Sciences at NEOMED
Volume 1, Issue 1, August 2022

Using Ancient Spices to Treat Chronic Diseases: Turmeric's Potential to Modulate Disease Pathogenesis in Rheumatoid Arthritis and Inflammatory Bowel Disease

Kelly M. Kimball, BS[1]*†, Giovanna Leone, BS[1]†, Bina Mehta, MD[2]

1. *Northeast Ohio Medical University, College of Medicine, Rootstown, OH, 44272*
2. *Akron General – Cleveland Clinic, Akron, Ohio*

* *Corresponding author*
† *Joint first authorship*

ABSTRACT

This review aims to highlight two major health conditions that could benefit from regular supplementation of turmeric, as well as to discuss the importance of more widespread uses of this natural therapeutic in commonly used multivitamins and multi-drug regimens. There is a wide range of potential benefits patients could gain from this supplement, but we will be focusing only on the effects on inflammation in two of the most prevalent chronic inflammatory diseases, rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). We propose that turmeric supplementation could be more commonly used in a healthcare setting as an adjuvant treatment in these inflammatory conditions. Future studies investigating turmeric's role for treatment in RA and IBD must aim to further evaluate the effects of curcumin on the human microbiota and how its bioavailability can be increased to provide therapeutic results.

Keywords: Turmeric, Anti-inflammatory, Irritable Bowel Disease, Rheumatoid Arthritis

INTRODUCTION

Turmeric is a rhizomatous herb that has been utilized in various capacities in both Chinese and Ayurvedic medicine for almost 4000 years (*1*). This spice has been utilized in the management of many anti-inflammatory disease processes throughout the world and has been documented in Ayurvedic medicine as a remedy for respiratory conditions, such as asthma, as well as for rheumatism, muscle aches, and wounds (*2*). The ancient Chinese documented similar usages, along with relief for abdominal pain (*2*). There is much evidence supporting the multiple health benefits of turmeric, suggesting the potential for it to serve as a more widespread option for inclusion in the treatment regimen for certain diseases, especially chronic inflammatory diseases (*3*). Modern medicine has slowly been catching on to the benefits of turmeric described by ancient civilizations. Today, many over-the-counter multivitamin supplements incorporate small doses of turmeric amongst their ingredients of fat-soluble vitamins, B vitamins, and other micronutrients (*1*).

Oxidative stress has been proven to be the pathological process behind many chronic diseases and cancers, making routine utilization of this natural anti-inflammatory herb something to consider in a healthcare setting (*3*). The mechanisms of turmeric's effects utilize antioxidant mechanisms similar to vitamins E and A, as it can neutralize free radicals that are damaging to normal body functions (*1*). The active component of turmeric is curcumin, and it is a compound that possesses many different actions *in vitro* and in experimental animal models (*4*). It has been shown to favorably affect lipid metabolism, antioxidant concentrations, multiple anti-inflammatory reactions, and numerous signaling pathways (*4*). Additionally, recent literature suggests that turmeric not only benefits those in inflammatory-mediated diseased states, but also healthy individuals, as well. A study by DiSilvestro et al. illustrated that low doses of lipidated curcumin promote a diverse range of health-promoting effects, such as lowering serum

triglycerides and proinflammatory cytokines, in healthy individuals without any underlying medical conditions (*4*). This has led investigators to believe that supplementation with low doses of curcumin could be of benefit in healthy individuals, as well. Additionally, curcumin has been shown to exert a multitude of effects on the human microbiome and intestinal system, which will be explored throughout this paper.

Despite these numerous potential benefits, the efficacy of turmeric as an anti-inflammatory agent has been questioned and seldom recommended clinically due to its poor bioavailability (*4*). For this reason, it is often combined with piperidine, a component found in black pepper, which increases its bioavailability by 2000% (*5*). The DiSilvestro study also managed to navigate its low bioavailability by utilizing a lipidated curcumin, which was able to enhance its anti-inflammatory effects (*4*). Therefore, it is clear that when bioavailability is increased, curcumin possesses its most potent and promising effects as an anti-inflammatory agent (*5*). Due to this, researchers have been investigating ways in which oral turmeric supplements can be chemically modified in order to increase the bioavailability of curcumin. Therefore, the low natural bioavailability should not dissuade its use, as there will likely be ways in which this can be adequately addressed in the near future.

This review aims to highlight two major health conditions that could benefit from regular supplementation of turmeric, as well as to discuss the importance of more widespread uses of this natural therapeutic in commonly used multivitamins and multi-drug regimens. There is a wide range of potential benefits from this supplement, but we will be focusing only on the effects on inflammation in two of the most prevalent chronic inflammatory diseases, rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). We propose that turmeric supplementation should be more commonly used in a healthcare setting as an adjuvant treatment in these inflammatory conditions.

TURMERIC'S USE IN CHRONIC INFLAMMATORY DISEASES

Rheumatoid arthritis (RA) is the most common systemic inflammatory diagnosis. The prevalence of this chronic inflammatory disease is as high as 0.6% in North America (*6, 7*). Markers of this disease include anti-citrullinated protein, rheumatoid factor, elevated erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), all of which contribute to the destructive inflammatory component seen in this disease process (*8*). There are several proposed mechanisms of the inflammation seen in RA, and many that have not been explored yet. Most known mechanisms involve the machinery seen in the body's own defense mechanisms against foreign pathogens, including innate and adaptive immune systems (*9*). Turmeric may have the ability to tone down these widespread inflammatory effects, potentially relieving symptoms and slowing the destruction of tissue.

RA has multiple treatment options that come with various side effects. One option being methotrexate, which is often of clinical benefit but comes with many systemic side effects such as myelosuppression, mucositis, hepatotoxicity, and more (*10, 11*). Furthermore, exploring effective treatment options that have fewer side effects, such as turmeric, is very desirable considering the harsh effects drugs like methotrexate have on the body (*11*). Moreover, several studies on curcumin have shown effects in reducing proinflammatory biomarkers (*11*). A recent study revealed that curcumin, the active component of turmeric, has biochemical effects that can inhibit inflammation, synovial hyperplasia, and other aspects of CIA-induced rats via the mTOR pathway. (CIA-induced rats are collagen-induced arthritis specimens, a widely used animal model for rheumatoid arthritis) (*12*). Furthermore, curcumin inhibited the increased levels of proinflammatory cytokines and proteinases such as interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), matrix metalloproteinase-1 (MMP-1), and MMP-3 in CIA rats (*12*). A meta-analysis published in 2014 consisting of 342 subjects reveals a significant difference in CRP levels between curcumin and control groups. CRP directly correlates to bodily inflammation, further suggesting curcumin use can combat inflammation. This effect seemed to depend on the bioavailability and duration of supplementation (*13*). Additionally, a meta-analysis conducted in 2016 determined there is compelling evidence supporting the use of curcumin adjuvant to conventional RA therapy (*12*).

In addition to RA, inflammatory bowel disease has been increasing in prevalence over the last twenty years (*14*). According to the CDC, IBD, which includes Crohn's disease and ulcerative colitis, now affects approximately 3 million people or 1.3% of adults in the United States (*14*). While the pathogenesis of IBD remains largely unknown, it is thought to arise due to a dysfunctional or overly sensitive host immune response to bacterial and dietary antigens (*15*). The result is the breakdown of the microbiome and intestinal barrier, which is usually due to excess production of pro-inflammatory cytokines, such as TNF-α, IL-1 β, IL-6, and interferon-gamma (IFN-γ), all of which are triggered by the activation of nuclear factor kappa beta (NF-ϰB) (*15*). This ultimately results in unchecked intestinal inflammation and can lead to changes in the intestinal microbiome (*15*). If left

untreated, this inflammation can become chronic, result in systemic inflammation and even serve as a nidus for cancer (*15*).

The anti-inflammatory effects of curcumin have been viewed as a potential adjuvant treatment for those suffering from IBD since it has been shown to reduce the proposed inflammatory response implicated in IBD, help restore the integrity of the intestinal barrier and resist the degradation of intestinal epithelial tight junctions (*15*). Normally, the nitric oxide (NO) that is present at the physiological baseline serves to protect the gastrointestinal mucosa. However, the substantial amounts of NO that is released via inducible nitric oxide synthase (iNOS) during gastrointestinal inflammatory disease can result in tissue injury and subsequent necrosis (*15*). During inflammation, iNOS produces NO in pathogenic quantities. Therefore, it is likely that the chronic inflammation found in gastrointestinal inflammatory disease states may lead to the dissolution of the intestinal wall integrity due to the generation of reactive nitrogen species (RNS). Normally, curcumin reduces levels of reactive oxygen species (ROS), such as NO, in the intestinal mucosa (*6*). In a mouse model of ulcerative colitis, curcumin was able to inhibit the generation of iNOS by reducing the T-helper-1 (Th1) cytokine response, which ultimately led to reduced tissue damage (*6*).

Curcumin has been shown to exert a multitude of effects on the human microbiome and intestinal system. One study demonstrated that curcumin possessed bactericidal effects by eradicating *H. pylori* colonization *in vivo* through a proposed mechanism of inhibited bacterial cell division (*15*). In addition to these bactericidal effects, curcumin has been shown to promote and maintain a healthy gastrointestinal microbiome. One possible mechanism is curcumin's ability to promote the growth of short-chain fatty acid (SCFA)-producing bacteria. In a murine study conducted by Feng et al., curcumin supplementation promoted the diversity of SCFA-producing bacteria which have well-described protective effects on gastrointestinal mucosa by inhibiting inflammation *(15, 16, 17)*.

DISCUSSION

Before definite conclusions can be made, future studies must further evaluate the effects of curcumin on the human gastrointestinal microbiota, as most existing studies focus on its effects in animal models. One explanation for the lack of studies exploring this concept is the poor bioavailability of pure curcumin. For patients to be able to reap the anti-inflammatory rewards of turmeric, high doses (500 mg) of the active ingredient, curcumin, must be administered or it must be administered with compounds that help prevent its metabolism and increase its concentration in the body (*5*). As previously mentioned, curcumin is often combined with various organic compounds to drastically increase its bioavailability (*5*). Recent studies have shown that lapidated curcumin mixtures increase its availability, as do mixtures with piperidine, the active component of black pepper (*5*).

Endogenously, curcumin is rapidly metabolized by the *Blautia spp*, a bacterium native to the human microbiome (*5*). One could also glean that those future research directions focusing on downregulating the colonization of *Blautia spp* could also serve to inhibit the metabolism of curcumin, thus increasing its concentration in the body. However, further altering the microbiota possesses its own challenges and could allow for further dysregulation of the immune response in those suffering from inflammatory diseases like RA and IBD. Another route that could potentially increase curcumin's bioavailability is altering its structure or combining it with lipidated or piperidine compounds, as previous groups have done (*4,5*). Investigating ways in which oral turmeric supplements can be chemically modified to increase the bioavailability of curcumin is an active area of research. Therefore, the low natural bioavailability should not dissuade its use, as there will likely be ways in which this can be improved in the near future.

In general, natural and alternative medicine continues to be less explored than modern medicine, despite some evidence working in its favor (*4,5*). Turmeric, a natural supplement that has been used for thousands of years, works to decrease systemic inflammation and better disease trajectory. As discussed in this review, both RA and IBD could benefit from adjuvant turmeric supplementation. While the supplements may not often stand on their own as a sole treatment, the simple addition of one to a complex drug regimen can potentially improve disease trajectory. Furthermore, after validation through more clinical trials, this affordable addition could improve the disease trajectory of patients struggling with these inflammatory diseases (*18*). Due to a lack of human research trials on these supplements, they are often overlooked by healthcare providers, but there may certainly be a role for them in certain clinical situations. Since each person's immune system is unique, responses to turmeric supplementation may vary widely on a patient-to-patient basis. As such, physicians treating individuals with chronic inflammatory conditions such as RA or IBD might consider adding turmeric to their treatment plan.

REFERENCES

1. Slika L, Patra D. Traditional Uses, Therapeutic Effects and Recent Advances of Curcumin: A Mini-Review. Mini Rev Med Chem. 2020;20(12):1072-1082. doi: 10.2174/1389557520666200414161316.

2. Prasad S, Aggarwal BB. Turmeric, the Golden Spice: From Traditional Medicine to Modern Medicine. In: Benzie IFF, Wachtel-Galor S, editors. *Herbal Medicine: Biomolecular and Clinical Aspects.* 2nd edition. Boca Raton (FL): CRC Press/Taylor & Francis; 2011. Chapter 13.

3. Khan I, Samson S, Grover A. Antioxidant Supplements and Gastrointestinal Diseases: A Critical Appraisal. *Medical Principles and Practice*. 2017;26(3):201-217. doi:10.1159/000468988.

4. DiSilvestro R, Joseph E, Zhao S, Bomser J. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. *Nutr J*. 2012;11(1). doi:10.1186/1475-2891-11-79.

5. Hewlings S, Kalman D. Curcumin: A Review of Its Effects on Human Health. *Foods*. 2017;6(10):92. doi:10.3390/foods6100092.

6. Ukil A, Maity S, Karmakar S, Datta N, Vedasiromoni J, Das P. Curcumin, the major component of food flavour turmeric, reduces mucosal injury in trinitrobenzene sulphonic acid-induced colitis. *Br J Pharmacol*. 2003;139(2):209-218. doi:10.1038/sj.bjp. 070524.1

7. Otón T, Carmona L. The epidemiology of established rheumatoid arthritis. *Best Practice & Research Clinical Rheumatology*. 2019;33(5):101477. doi:10.1016/j.berh.2019.101477.

8. Daily J, Yang M, Park S. Efficacy of Turmeric Extracts and Curcumin for Alleviating the Symptoms of Joint Arthritis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *J Med Food*. 2016;19(8):717-729. doi:10.1089/jmf.2016.3705.

9. Croia C, Bursi R, Sutera D, Petrelli F, Alunno A, Puxeddu I. One year in review 2019: pathogenesis of rheumatoid arthritis. *Clin Exp Rheumatol*. 2019;37 (3):347-357.

10. Wasserman AM. Diagnosis and management of rheumatoid arthritis. *Am Fam Physician*. 2011;84 (11):1245-1252.

11. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and Managing Toxicities of High-Dose Methotrexate. *Oncologist*. 2016;21(12): 1471-1482. doi:10.1634/theoncologist.2015-0164.

12. Dai Q, Zhou D, Xu L, Song X. Curcumin alleviates rheumatoid arthritis-induced inflammation and synovial hyperplasia by targeting mTOR pathway in rats. *Drug Des Devel Ther*. 2018; Volume 12:4095-4105. doi:10.2147/dddt.s175763.

13. Sahebkar A. Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. Phytother Res. 2014 May;28(5):633-42. doi: 10.1002/ptr.5045.

14. Data and Statistics. Cdc.gov. Published 2021. Accessed January 1, 2021. https://www.cdc.gov/ibd/data-statistics.html

15. Burge K, Gunasekaran A, Eckert J, Chaaban H. Curcumin and Intestinal Inflammatory Diseases: Molecular Mechanisms of Protection. *Int J Mol Sci*. Apr 2019;20(8):1912. doi:10.3390/ijms20081912.

16. Feng W, Wang H, Zhang P, et al. Modulation of gut microbiota contributes to curcumin-mediated attenuation of hepatic steatosis in rats. *Biochim Biophys Acta Gen Subj*. 2017;1861(7):1801-1812. doi:10.1016/j.bbagen.2017.03.017.

17. Scheppach W, Weiler F. The butyrate story: old wine in new bottles? *Curr Opin Clin Nutr Metab Care*. 2004;7(5):563-567. doi:10.1097/00075197-200409000-00009.

18. Gopinath H, Karthikeyan K. Turmeric: A condiment, cosmetic and cure. *Indian J Dermatol Venereol Leprol*. Jan-Feb 2018;84(1):16-21. doi: 10.4103/ijdvl.IJDVL_1143_16. PMID: 29243674.

CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: KMK, GL

Investigation: KMK, GL

Visualization: KMK, GL

Project administration: KMK, GL

Supervision: BM

Writing – original draft: KMK, GL

Writing – review & editing: KMK, GL, BM