

Gastrointestinal Diseases and Curcumin: Developments and Challenges

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INTRODUCTION

Gastrointestinal (GI) diseases are substantial clinical and economic burdens accounting for extensive morbidity and mortality among humans worldwide. The incidence of many GI conditions, such as inflammatory bowel disease (IBD) and gastrointestinal infections, has increased dramatically in western countries over the past few decades. Solely in the USA, of the 122 million emergency department visits in 2007, 15 million (12%) were diagnosed with GI diseases¹. This influx of GI patients has led to the total spending on GI diseases estimated at \$142 billion per year with \$27.9 billion spent on emergency department billings². Apart from being a substantial economic burden, GI diseases also worsen the quality of life and significantly impair work and daily activity of the patients. It is now increasingly recognized that certain dietary and lifestyle modifications that occurred during the last few decades synchronize with a surge in GI diseases. Therefore, change in dietary habits and incorporation of micronutrients, such as antioxidants may be beneficial in prevention and/or treatment of GI disorders.

One of such antioxidant molecules is curcumin, the major constituent of turmeric that has been consumed as a part of the human diet for centuries. It has long been viewed as a key therapeutic biomolecule with armamentarium of

health benefits. It is the center of modern clinical curiosity since its isolation in the early 19th century followed by crystalline purification in the 1870s, and structural elucidation in early 20th century. Its wide spectrum of therapeutic potential has sparked interest in its clinical application for several GI disorders. This interest is also backed by the fact that curcumin preferentially accumulates in the intestine, colon and liver leading to its higher bioavailability in the gastrointestinal tract than other organs³. In two clinical studies of curcumin, IBD patients have achieved encouraging results showing potent therapeutic effects^{4,5}. However, the further rigorous randomized controlled trials needed to validate these studies have not been undertaken yet. Likewise, curcumin extended significant therapeutic effects in irritable bowel syndrome and exhibited potential to increase bowel motility and to activate hydrogen-producing bacterial flora in the colon^{6,7}. In colorectal cancer (CRC) trials, curcumin was well tolerated and no dose-limiting toxicity was detected. Interestingly, curcumin intake attenuated the amplified levels of prostaglandin E₂, M₁G and a daily dose of 3.60 g of curcumin was found to be pharmacologically effective in CRC patients^{8,9}. Likewise, observations were made in the familial adenomatous polyposis (FAP) patients, where curcumin suppressed adenomas¹⁰. Furthermore, clinical trials have also confirmed the therapeutic efficacy of curcumin in peptic ulcers and *Helicobacter pylori* infection¹¹. Although several clinical trials have been concluded, various trials

are still evaluating the efficacy of curcumin against GI ailments. A search on www.clinicaltrials.gov (accessed in November 2014) indicated that about 25 clinical trials with curcumin are ongoing in GI disorders. These include trials evaluating efficacy of curcumin in FAP, CRC, IBD and ulcerative colitis.

Since, the landmark study published by Schraufstatter and Bernt in 1949¹² unveiled the therapeutic effect of curcumin, a copious amount of research has strengthened the curcumin's candidacy as a silver bullet medication, however, its low bioavailability has plagued its clinical use. Therefore, strategies such as structural modification, microencapsulation and nanoparticles have been undertaken to improve the bioavailability of curcumin. A few clinical trials have also been conducted to access the improved bioavailability of modified curcumin or its combination with other bioactives. A clinical trial addressing the effect of oral administration of curcumin and piperine in human patients with tropical pancreatitis resulted in reduced oxidative stress markers along with a surge in glutathione levels¹³. Recently, two clinical trials (NCT01982734, NCT01925287) reported that

incorporation of curcumin into micelles improved the bioavailability of curcumin. It is essential to understand that the strategies to increase the bioavailability of curcumin should be followed by its effectiveness in GI diseases. Even though multiple clinical studies have not reported toxicity by curcumin even at doses up to 8.00 g per day; but the encapsulated/modified curcumin must be assessed for its physiological safety. Comparative studies are also required to investigate the parent molecule and encapsulated/formulated curcumin to ultimately advance to large clinical trials focused on GI disorders. This will also unveil important insights into metabolomics and pharmacokinetics of the novel formulations or modifications of curcumin. These are the imperative steps which must be undertaken before curcumin or its modified/formulated version can be translated to the clinic for the treatment of various GI disorders.

List of abbreviations

CRC- colorectal cancer; FAP- familial adenomatous polyposis; GI- Gastrointestinal; IBD- inflammatory bowel disease;

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