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Review

Recent advances in complementary and replacement therapy with nutraceuticals in combating gastrointestinal illnesses

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SUMMARY

The digestive system provides nourishment to the whole body. Disorders in this system would result in many associated illnesses as the body is deprived of essential nutrients. Gastrointestinal diseases, in particular, gastric ulceration, inflammatory bowel diseases and colorectal cancer have become more prevalent in all population age groups. While this can be attributed to diet and lifestyle changes, the measures to combat these illnesses with conventional drugs is losing popularity owing to the harsh side effects, drug resistance and lack of patient compliance. The focus of this review is to endorse promising nutraceutical dietary components such as phytosterols, polyphenols, anthocyanins and polyunsaturated fatty acids and their synergistic value, in combination with conventional management of key gastrointestinal diseases. As most of these nutraceuticals are labile compounds, the need for protection and delivery using a carrier system is stressed and the methods for targeting to specific parts of the gastrointestinal tract are discussed. A section has also been devoted to perspectives on co-encapsulation methods of drugs and nutraceuticals using different particle systems. Multilayered carrier systems like double layered and core shell particles have been proposed as an exemplary system to co-encapsulate both drugs and nutrients while keeping them segregated.

1. Introduction

The GIT[3] performs the inevitable function of nutrient assimilation from food, and any ailment in this system could significantly decrease the quality of life. Among the many diseases that localize in the gastrointestinal region, gastritis of the stomach, irritable bowel diseases, Crohn's disease, ulcerative colitis and colorectal cancer have greater incidence. All these diseases are characterized by inflammation of the intestine and colon, which can range from moderate to severe. Conventional pharmacotherapy largely involves the use of anti-inflammatory drugs and chemotherapeutic agents that lack specificity impose adverse side effects and drug resistance. Such drawbacks have been a key motivator for the exploration of bioactive dietary agents as primary use and in alliance with drugs as a preventive mediator in various disorders including those associated with the mood, metabolic syndrome and Parkinson's disease [1,2]. In addition to application in preventative care, the sequential or concurrent use of drugs and nutraceuticals that provides comparable results at a reduced drug dosage and/or heightened benefits to the patient has been of particular interest [1,3]. While many definitions of the term "nutraceutical" exist, the present review refers to nutraceutical as "a food (or a part of food) that provides medical or health benefits, including the prevention and/or treatment of a disease" [4]. These compounds must be supported by sufficient scientific evidence in order to legitimately pass health claims and for approval by formal regulatory bodies of the governing country e.g. Food and Drug Administration (FDA) in the United States, Food Standards Australia New Zealand (FSANZ) in Australia and New Zealand, and European Food Safety Authority (EFSA) in Europe. The delivery system encapsulating therapeutic agents also need to comply with authority set standards.

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With these in mind, this review focuses on the advancement of proven dietary agents as collective systems and in synergistic combination with drugs for clinical maintenance of key gastrointestinal illnesses. Insights on the practical implementation of bringing forth extracted bioactive compounds and medicines to patients through current and emerging encapsulation and co-encapsulation strategies are also discussed.

2. Conventional treatments for gastrointestinal diseases

2.1. Gastritis caused by Helicobacter pylori infection

Helicobacter pylori (H. pylori) is a gram negative spiral shaped bacteria infecting more than half of the world's population with higher prevalence in developing countries. Equipped with flagella, the motile microaerophile dwells in the mucus layer of the gastric lumen in which harsh acidic conditions of the stomach normally discourage the harboring of life [5,6]. The exceptional ability of *H. pylori* to thrive is in its ability to change the environmental pH through enzymatic conversion of urea to carbon dioxide and ammonia. Infected persons may not experience deleterious symptoms but when exacerbated, includes development of peptic ulcers and gastric adenocarcinoma, which come under the broad term “gastritis”. If *H. pylori* infection is left untreated, symptoms may worsen and the class I human carcinogen can cause gastric cancer, the 3rd leading cause of cancer associated mortality [5].

The standard therapy for *H. pylori* induced gastritis typically involves a combination approach which utilizes two or three different antibiotics such as amoxicillin, clarithromycin and metronidazole [7]. The treatment must be coupled with acid blockers like Cimetidine, Ranitidine, Famotidine and Nizatidine, antacids or proton pump inhibitor such as omeprazole, and mucosa protecting agents like bismuth chelate and sucralfate [6]. The use of antibiotics imposes undesirable short term and long-term health side effects. The use of antibiotics imposes undesirable short term and long-term health side effects. While the former may comprise of nausea, vomiting, headache, diarrhea and rashes, a more challenging long-term consequence is the increased drug resistance in several bacterial species as well as changes in metabolism due to decreased acid secretion. The complete eradication of *H. pylori* is yet to be achieved and the incorporation of probiotics in treatment has been promoted as a plausible buffer [5].

2.2. Inflammatory bowel diseases

IBD[4] is an autoimmune disorder that is characterized by chronic inflammation of the gastrointestinal tract [8]. Recently, cases of inflicted persons have surged – particularly in western societies – yet the etiology of the disease is far from being fully understood [9]. This disease encompasses UC[5] and CD[6], both similar in manifestation but pathophysiologically distinct: UC is associated with a Th2 immune response while CD is associated with a Th1 immune response [9]. The arising maladies attributed to UC are limited to the colon while for CD, gut inflammation can occur anywhere within the GIT, often in the ileum and colon [10]. What is agreed upon, is that the disease is an interplay of genetic, environmental and microbial factors [11]. Individuals vulnerable to the condition are likely to be genetically predisposed (especially in the case of CD), largely exposed to environmental stressors such as cigarette smoking, a diet high in refined sugars, complex carbohydrates, omega 6 fatty acids and subject to a heavy dose of medications such as NSAIDs[7] and COX-2[8] inhibitors [12]. One way in which medications lead to destructive effects is through the high production of reactive oxygen species. The generation of reactive oxygen species leads to IBD flare ups, damaging the gastric lining and increasing the risk to gastric cancer [10]. Microbial factors appear to play a large cause in the development of IBD and an abundance of literature points to the imbalance of harmful and protective bacteria in the intestine as the main cause [13]. The IBD sufferer tends to possess a lower diversity of gut microbial species and is unable to properly screen foreign and host microbiota [10].

The present management for IBD involves the use of anti-inflammatory agents like amino salicylates, corticosteroids and immunosuppressive drugs in sequence or in combination depending on the severity of the disease to revert the symptoms [14], though the disease can never be completely cured. The effectiveness of the treatment determines how rarely remission of symptoms occurs and a comprehensive review on the sequential administration of the different drugs currently available and used for the treatment of inflammatory bowel diseases like UC and CD have been outlined by Burger et al. [15]. Though some of the drugs seem to be effective in controlling disease symptoms, they need to be administered in very high dosage, and once the drug treatment is stopped, symptoms recur. Prolonged high dose administration of the drugs lead to severe side effects such as cataracts and osteoporosis, hemolytic anemia, hepatitis, renal failure and pericarditis [16].

2.3. Colorectal cancer

Colorectal cancer stems from the inflammation and uncontrolled tissue growth in the distal part of the colon and the two main reasons for a predisposition towards colorectal cancer is IBD history or the presence/history of familial adenomatous polyposis. About 20% of the people suffering from IBD are predisposed to develop colorectal cancer [17]. Based on GLOBOCAN, a report published by International Agency for Research on Cancer, colorectal cancer has been estimated to be the second most commonly diagnosed types of cancer in females and third in males globally [18].

The first line of treatment for the initial stages of colorectal cancer involves surgery to remove the polyp and in some cases, it is accompanied by radiation therapy to prevent recurrence or chemotherapy if there is a risk of metastasis or if metastasis is only to the liver. Chemotherapeutic agents used in the clinical management of the cancer are systemic first line anticancer drugs like 5-fluorouracil, Irinotecan and Oxaliplatin or localized targeted therapy with anti-angiogenesis factors or epidermal growth factor inhibitors that are monoclonal antibodies from mice. They act by blocking the epidermal growth factor receptor, in turn slowing down cell growth and metastasis [17,19]. Most of these drugs are associated with adverse side effects like diarrhea, vomiting, fatigue and hair loss.

3. Nutraceuticals of primary, adjunct and synergistic use with conventional treatment

Just as many of the gastrointestinal diseases are caused by an interplay of triggers, one may consider the treatment as a balanced cooperation of multiple factors, such as drugs coupled with a protective diet rich in fiber, or supplementation with specifically beneficial bioactive compounds, such as omega 3 fatty acids (see

[4] Inflammatory bowel disease.
[5] Ulcerative colitis.
[6] Crohn's disease.
[7] Nonsteroidal anti-inflammatory drugs.
[8] Cyclooxygenase-2.