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Carob and its Components in the Management of Gastrointestinal Disorders

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Abstract

Plant-derived compounds have demonstrated health benefits, including cancer preventive properties, increasing bone density, improving cardiovascular functions, reducing obesity, lowering cholesterol levels and delaying aging. Plants, fruits and their medicinal products are especially known for sustaining human health and preventing diseases. Importantly, certain plant-derived purified components, and their combinations, are also effective in the treatment of human diseases. In fact, over 60% of the drugs approved today by drug-regulatory agencies worldwide, are either directly isolated from natural sources, or are derived and inspired from natural lead compounds isolated from plants. Since recent efforts to develop novel drugs using purely synthetic approaches had little success, the interest in naturally-derived medicinal components and drugs that may benefit human health has been revived. Recent scientific reports suggest that carob, the beanlike fruit of *Ceratonia siliqua*, in addition to being a health-promoting food source, it is also useful in the prevention, or even the treatment of an array of diseases. Consequently, there is a pronounced interest, from both the general public and nutritional/pharmaceutical scientists, in comprehending how carobs can be used in the improvement of human health. The active constituents found in carob, such as polyphenols, tannins, dietary fiber and sugars, along with their anti-inflammatory and antioxidant properties, have been found to be especially beneficial to the gastrointestinal tract and the digestive system. In this review we integrate findings derived from, principally, clinical studies and also *in vitro* and animal studies, focusing on the role of carob and its components in the management of gastrointestinal disorders, including gastro-esophageal reflex (GER), irritable bowel syndrome (IBS), acute diarrhea and ulcerative colitis.

Keywords: Carob fruit; Carob bean gum; Carob health benefits; Gastro-esophageal reflux; Diarrhea; Anti-reflux; Infant food formulas; Diarrhea; Irritable bowel syndrome; Ulcerative colitis

Abbreviations: CPAE: Carob Pod Aqueous Extracts; DSS: Dextran Sulfate Sodium; GI: Gastrointestinal; GER: Gastro-Esophageal Reflux; IBS: Irritable Bowel Syndrome; IL: 1β Interleukin-1 beta; LBG: Locust Bean Gum; LDL: Low Density Lipoprotein; TNF-α: Tumor Necrosis Factor alpha

Introduction

Carob (*Ceratonia siliqua L.*); is a flowering evergreen tree that belongs in the Leguminosae, also called pea family [1]. Initially carob was native only to Mediterranean regions where it has been cultivated for more than 4000 years, however it is now cultivated in other warm climate zones as well [2]. The carob tree has a mature height of about 6 to 12 meters and its branches usually extend to ground level [3]. The carob fruit, a brown pod of about 10 to 30 cm in length, contains many bioactive substances including sweet carbohydrates (sugars), dietary fiber, polyphenols and tannins [4]. The Locust bean gum (LBG), also known as carob bean gum, is a galactomannan vegetable gum extracted from the carob seed pod endosperm of the fruit. It is a natural food additive for several products including sweets, soups and ice cream (Figure 1). It has also been used in cosmetic and textile industries [5]. For instance, the LBG has been previously used in skin care creams to help with emulsion stabilizing and to control the viscosity of the formula [5]. Due to their high sugar content and low price, carob pods have been used for a long time as a feed for livestock as well as in human nutrition and in products such as sweets and processed drinks [6]. Importantly, carob is naturally gluten free, and it is commonly used as a chocolate substitute for the production of gluten free chocolate and carob snacks.

In the last two decades, several studies have shown that the crude extracts, sub-fractions and individual components of carobs can act either as disease preventive or therapeutically and promote human health. The array of diseases that the carob fruit and its products may affect include diabetes, diarrhea, hyperlipidemia and cancer. Carob pulp constituents such as fiber, polyphenols and tannins are bioactive and have been linked with its health-promoting effects [7]. Based on these findings the carob fruit has been widely used as an ingredient for the development of herbal supplements and functional foods.

The beneficial health effect of consuming phenolic-rich foods is highly associated with their antioxidant activities [8]. The antioxidant properties of carob extracts have been previously reported in both *in vivo* and *in vitro* studies [3]. In several rodent studies it was observed that carob pod and carob pulp preparations, which have a high dietary fiber content, have the ability to lower cholesterol levels and enhance excretion of cholesterol and bile acids [9,10]. A similar effect was also observed in a single arm clinical pilot study, in which a carob pulp preparation, rich in dietary fiber, caused a reduction in the levels of low-density-lipoprotein (LDL) and total cholesterol concentrations in humans [11]. Apart from lowering cholesterol levels, the dietary fiber and sugars found in carob are also essential for enhancing the viscosity of food in the stomach and therefore interfering with the reflux of acid in the esophagus [12]. It is becoming apparent that the consumption of carob fruit, or its components, is beneficial to human health, especially as it relates to gastrointestinal disorders.

Gastrointestinal Disorders

Gastro-esophageal reflux

Gastro-esophageal reflux (GER), which is also known as acid reflux, is a condition in which the contents of the stomach return back to the esophagus causing several complications [15]. This long-term condition of the esophagus is a common gastrointestinal disorder in infants whose lower esophageal sphincter is not fully developed. GER

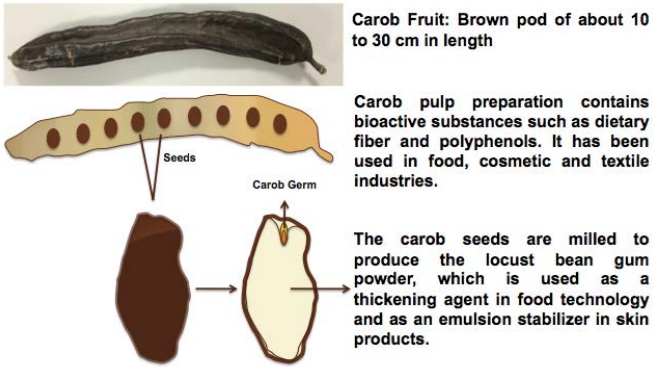

Figure 1: The different parts of carob and their commercial use.

affects up to 20% of infants and 8% of children. As the infant grows up, the angle of both the stomach and the esophagus change, leading to less frequent reflux episodes. The reflux episodes cease to exist in over 50% of infants by 10 months of age, while only 2% of two year old children present the disorder [16]. Although most of the time the episodes are mild, GER can cause severe morbidity or even mortality in rare occasions [17,18]. The conservative management of this disorder usually includes guidance on posture, the use of antacids for the neutralization of stomach's acidity and the addition of thickening substances in baby foods [19].

In infants, the thickening of formula feedings is a critical step in the therapeutic approach for GER [20]. The advantage of carob-based thickening agents, compared to other agents, is that the former are not broken down by salivary amylases and are able to maintain their thickening properties after reaching the stomach. Furthermore, the energy distribution of the infant's food formula is not altered by the carob-based thickening agents because these agents do not alter the nutritional value of the food [21]. The nutritional value refers to the energy measured in calories, the micronutrients (minerals and vitamins), the macronutrients (fats, carbohydrates and fats) and phytochemicals.

Carobel is a commercially available carob seed-based flour that, due to its thickening properties, increases food viscosity and reduces the number of acid reflux episodes [12]. In a study, carried out by Greally et al., it was observed that in 19 out of 24 infants Carobel reduced considerably the number of GER overnight [12]. GER usually occurs less frequently during sleeping state compared to wakefulness [22]. These results were confirmed in a more recent, placebo-controlled crossover study [23]. In this study 14 infants, between the age of 32 to 42 days who had at least one large regurgitation or five small regurgitations within a 72-hour period, participated. These infants were randomized into two groups and received either formula A thickened with 0.4% carob bean gum, or formula B that was un-thickened (control diet). In general, there was a significant decrease in the frequency and amount of regurgitations in infants fed with the carob-thickened food (formula A). In fact, half of the infants that received formula A did not regurgitate at all. According to the authors' conclusions, a thickened formula with carob bean gum is an efficient therapy to treat GER and regurgitation in infants [23].

LBG is chemically a galactomannan, a high molecular weight polysaccharide composed of galactose and mannose at an approximate ratio of 3:1 respectively, reaching a concentration up to 85% in the carob seed. Although LBG is indigestible, it undergoes fermentation by bacteria in the colon [21]. As a result of this fermentable characteristic, some infants react to it with colic, abdominal pain and diarrhea. However, these side effects are normal for fiber ingestion and are not specifically correlated to the use of LBG. Currently, commercially available anti-reflux formulas contain LBG galactomannans at a concentration of 0.45g/100mL. Two studies have previously described that lower concentrations of LBG, 0.35g/100mL are also effective in reducing visible reflux episodes [24,25].

In a recently published study by Georgieva et al., the efficacy of three different formulas thickened with LBG galactomannans was evaluated on reflux and tolerance in infants with GER [26]. Fifty six infants, one to six months old, were randomly divided into three groups to receive one of the following carob-thickened formulas: A, containing 0.33g/100mL of cold soluble LBG galactomannans; B, containing 0.45g/100mL of cold soluble LBG galactomannans; C, containing 0.45g/100mL of hot soluble LBG galactomannans [26]. The results showed that Formula A has the ability to reduce both esophageal acid exposure symptoms related to acid reflux, and the total daily number of refluxes. These changes were not detected in the infants fed with either Formula B or C. For infants fed with Formula A and C, a significant increase of body weight was observed, while no weight gain was observed for infants fed with Formula B, most likely due to the elevated number of diarrheal episodes and total defecations recorded in this group. The results of the study demonstrate that Formula A is more effective in decreasing GER episodes, helping in body weight gain and being well-tolerated [26].

In a randomized clinical trial, 82 male infants of median age 1.5 months were recruited in the treatment group and the control group was comprised of 84 male infants of the same age [27]. The treatment group received a formula that was thickened with LBG (Commercial name: Humana AR 1) whereas the control group received an un-thickened formula (Commercial name: Humana Plus). A clinical assessment was carried out at baseline, at four and eight weeks after treatment. The results suggested that there was a significant decrease in regurgitation both after four and eight weeks in all patients. Moreover, after eight weeks of treatment, about two-thirds of the infants were either asymptomatic or demonstrated improved symptoms. In the treatment group there was a higher frequency of asymptomatic infants (34%) compared to the control group (14%). However, 14 out of the 82 patients in the treatment group had to stop the thickened formula within the first 2 weeks due to increased episodes of diarrhea. The authors suggested that if these 14 infants are excluded from the analysis of the results, then the thickened formula is proven to be more efficient in treating regurgitation compared to the un-thickened formula. The study concluded that the use of a carob-thickened formula has the ability of increasing the number of asymptomatic infants, but it can also lead to diarrhea, thus reducing its potential benefit as a treatment for GER [27].

Although there are conflicting data on the beneficial effects of carob and diarrhea, carob products, provided either as carob flour in the milk or carob gum in processed baby foods, generally help infants with GER. Due to the lack of evidence from randomized controlled trials we cannot be certain about potential side effects of infant feedings using carob. However, according to these studies, thickening of infant feedings has the potential of increasing body weight, decreasing the frequency of regurgitation, and is well tolerated up to a concentration of 0.33g/ml [28]. Therefore, thickening of infant feedings using carob is a promising approach in the stepwise treatment of GER in infants.

Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome (IBS) is described as a chronic functional disorder of the gastrointestinal tract [29]. It is considered as the most common GI disorder having a worldwide prevalence rate of about 10-15%. IBS commonly causes abdominal discomfort or pain and changes in the frequency of bowel movements (constipation, diarrhea or both). The treatment for IBS depends on the severity of symptoms, with pain management being the most common therapeutic approach. Although the etiology is unknown, researchers have found that in IBS patients the colon muscle contracts more readily. Apparently, this is due to abnormalities in the gastrointestinal transit, which seems to be the underlying patho-physiological mechanism for IBS [30].

Gastrointestinal transit time is described as the time required for food to transit from the mouth through the gastrointestinal (GI) tract [31]. People with IBS usually have accelerated GI transit time; consequently, increasing GI transit time could be a potential therapeutic approach for IBS [32]. In a recent study, the effects of mature and immature carob pod aqueous extracts (CPAE) on GI transit were investigated [33]. Male rats after 16-hours of fasting were orally administered with either Sodium Chloride (0.9% NaCl, control group) or various doses of mature or immature CPAE (50, 100 and 200 mg kg^{-1} body weigh) for the experimental groups. The results showed that CPAE of mature carob significantly increased GI transit (by reducing transit time) in a dose-dependent manner, whereas CPAE of immature carob pods decreased considerably the GI transit, and the frequency of diarrhea (by increasing transit time) in a dose-dependent manner. Importantly, mature CPAE increased intestinal permeability while immature CPAE decreased it [33].-

These findings suggest that although CPAE of mature and immature carob pods have opposite effects on GI propulsion, immature carob has essentially laxative and anti-diarrheal properties that are attributed to its chemical composition [33]. We know for instance that there is a difference in the sugar content of mature and immature carob depending on the degree of maturity. If we were to extrapolate these results to humans, it seems that the use of immature CPAE carob could be a potential therapeutic approach for IBS as it delays the GI transit. However, prior to making this recommendation, human dietary intervention studies must be performed to determine the tolerance levels of humans to immature carobs and their extracts.

Acute Diarrhea

Acute diarrhea is defined as the passage of three or more watery stools in a 24-hour period [34]. In adults, acute diarrhea is one of the most frequently diagnosed diseases and it is considered as one of the leading causes of morbidity [35,36]. Diarrheal disease is the second leading cause of death in children. Specifically, about 760,000 children under the age of five die worldwide every year due to diarrhea and its complications. Other vulnerable groups to diarrhea are travelers, adults who are in contact with children and people with immunocompromised responses [37].

Carobs are a rich source of sugars and tannins. The sugars of LBG (galactose and mannose) act as a thickener for the absorption of water and aid in binding together watery stools. When loose, watery stools pass through the bowel too fast causing diarrhea [13]. Therefore, the locust bean gum is essential for keeping the loose stools together and prevent diarrhea.

Roasted carob powder has been previously reported to be useful as an additional dietary intervention for the treatment of acute diarrhea in infants [13]. In both adults and children, oral rehydration and quick re-feeding are part of the suggested treatment for acute diarrhea [38]. Although there are many reports describing that decoctions of roasted carob powder can reduce the incidence of diarrhea when administered preventively, it has been found to be more effective for the treatment of acute diarrhea [39,40]. Several reports have suggested that the carob powder is well tolerated without producing any side effects even when administered for a long period of time [38-40].

Besides dietary fiber and sugars, ripe carob pods contain tannins. The tannins found in carob have the unusual property of being only partially soluble [41]. The insoluble nature of tannins present in carob extracts have been found to bind bile acids and bacterial toxins, inhibiting in this manner, the growth of bacteria [42,43]. The efficacy of insoluble tannin-rich carob pod was investigated, in a double blind clinical trial, in infants and children 3-21 months of age with acute diarrhea of either viral or bacterial origin [13]. The infants were treated with oral rehydration fluid and received randomly a tannin-rich carob pod powder or placebo for up to six days. The results showed a significant decrease in the duration of diarrhea in the treatment group compared to the control group (2.0 +/- 0.27 days in the treatment group compared to 3.75 +/- 0.30 days in the control group) [13]. Furthermore, the patients in the treatment group gained weight and had reached faster normalized defecation, body temperature and cessation of vomiting compared to the patients in the control group. Overall, the study demonstrated that the test substance was well tolerated and accepted by the patients in the test group [13]. In a double blind study the water-insoluble carob fraction was found to be helpful for adults with traveler's diarrhea (positive trend) but without significant differences in efficacy [14].

The administration of tannin-rich carob pod could be suitable for infants suffering from acute-onset diarrhea for an extended period of time, as the results of the aforementioned study demonstrated not only a significant reduction in the duration of diarrhea but also an improved weight gain [13]. The efficacy and safety of tannin-rich carob pod, proven by its extensive use throughout the world, for many years, make it a valuable and low-cost solution for the treatment of acute diarrhea, especially in infants.

Ulcerative Colitis

Oxidative stress and chronic inflammation are considered common mechanisms of ulcerative colitis and other gastrointestinal diseases. Ulcerative colitis is an inflammatory disease of the bowel that causes long-term inflammation and ulcers in the digestive tract [44]. Approximately, one million people are affected, worldwide, with ulcerative colitis. The annual incidence reaches 10.4 to 12 cases per 100,000 people whereas the prevalence rate is about 35 to 100 cases per 100,000 people. This disease also causes the appearance of colonic lesions as a result of severe histopathological damage in the mucosa of the colon.

Micronutrients and polyphenols in carob pods have been previously reported to play an important role in the prevention of intestinal inflammation due to their anti-inflammatory and antioxidant properties [3]. Ulcerative colitis is usually correlated with the production of pro-inflammatory cytokines by cells of the immune system such as Interleukin-1 beta (IL-1β) and Tumor Necrosis Factor alpha (TNF-α) [45]. These cytokines are known to mediate the migration of neutrophils, which is observed in many experimental models as well as in human inflammatory diseases [46].

In a recent study carried out by Rtibi et al., the effect of carob pods aqueous extracts (CPAE) was investigated against dextran sulfate sodium (DSS)-induced ulcerative colitis in a rat model [47]. The results demonstrated that treatment with CPAE for 21 days (50 and 100 mg kg^{-1} body weight) restored body weight gain in a dose-dependent manner, decreased the severity of colonic lesions and prevented associated biochemical changes [47].

Furthermore, it was observed that the high levels of IL-1β and TNF-α in colon were significantly decreased after treatment with CPAE. The beneficial effects of carob were attributed to its high polyphenol content as it was previously reported that polyphenols reduce the levels of the pro-inflammatory cytokines IL-1β and TNF-α in several murine models of colitis [48]. All parameters measured in the study indicated that CPAE inhibit the presence of inflammation and injury caused by oxidative stress, suggesting the beneficial anti-inflammatory effects of carob on inflamed colonic tissues and plasma [47].

Chronic inflammation is highly associated with malignancy and it is considered to be a major contributor in the development of various types of cancer [49]. Consequently, chronic colonic inflammation, due to ulcerative colitis, is associated with an elevated risk of colon cancer [50]. Gallic acid and other carob ingredients, have demonstrated anti-proliferative properties in human colon adenocarcinoma cells [51]. It has been recently reported that the, rich in fiber, water-soluble fraction of carob, has the ability to significantly reduce the number of colon carcinoma and adenoma cells [52,53]. It has also been suggested that the protective effects of carob extracts on colon adenoma cells provide potential mechanisms of cellular protection against factors that contribute to oxidative stress [53]. This protection mechanism against oxidative stress in colon cancer cells could significantly slow down the process of carcinogenesis [53]. It has been concluded that the ability of carob extracts to inhibit cell proliferation in the colon carcinoma and adenoma cells, also provides a key mechanism of cancer chemoprevention [53]. However, additional evidence from clinical trials and human dietary intervention studies are required in order to identify the exact mechanisms through which carob demonstrates its presumed chemopreventive properties.

Conclusions

This review highlights the optimism presently surrounding the use of carob to improve gastrointestinal health. Traditionally, carob has

Table 1: The beneficial effects of carob components on gastrointestinal disorders according to *in vitro*, animal and human studies.

Type of Study	Carob Component	Beneficial Effect	Reference
In vivo, Human nutritional intervention studies / Randomized clinical trials	Carob Seed Flour (Locust Bean Gum)	Reduction of GOR episodes in infants, Helped infants in gaining weight	Greally et al. [12] Wenz et al. [23] Georgieva et al. [26] Iacono et al. [27]
In vivo, Randomized clinical trial	Insoluble Tannin-rich Carob Pod	Decreased duration of diarrhea in infants, Helped infants to reach faster normalised defecation and body temperature, Helped infants to gain weight and to stop vomiting	Loeb et al. [13]
In vivo, Rats	Carob Pod Aqueous Extracts (CPAE)	Restored body weight gain, Decreased the severity of colonic lesions	Rtibi et al. [47]
In vivo, Male rats	Immature Carob Pod Aqueous Extracts (CPAE)	Decreased GI transit time, Lower frequency of diarrhea	Rtibi et al. [33]

been used for the treatment and management of several gastrointestinal conditions as it contains a large number of bioactive substances such as polyphenols, sugars, tannins and fiber. The carob bean gum, extracted from the seeds of carob, has been proven to be effective in decreasing the regurgitation frequency in infants, and it is therefore considered beneficial for the treatment and monitoring of GER. Furthermore, results obtained from animal studies have shown that immature CPAE might be a promising therapeutic approach for delaying the GI transit time and thus help people with IBS. The unusual properties of tannins found in carob have also been proven valuable for gastrointestinal health. Administration of tannin-rich carob pod was found to decrease significantly the duration of acute diarrhea and improve weight gain in infants. Finally, according to a study performed on rats, the antioxidant and anti-inflammatory properties of polyphenols found in CPAE have the aptitude of reducing colonic damage and eventually prevent ulcerative colitis and colon cancer.

Regardless, due to the limited number of clinical or human intervention studies, there are still safety and efficacy concerns. Only few epidemiological and observational studies have been performed, and the active substances of carob are largely unknown or insufficiently characterized. Properly conducted clinical trials for carobs, as well as other dietary supplements, are obstructed by strict regulatory requirements. Consequently, the recommended dosages of several marketed supplements are often without scientific basis [54]. Safety questions that remain unanswered concerning the use of carobs and their constituents for the treatment of gastrointestinal disorders include toxicity, possible interaction with other drugs and potential inhibition of the beneficial effects of other nutrients [54]. Although there are no reports referring to serious adverse effects by the consumption of carob in its native form, unexpected toxicity could arise due to commercial production methods [54].

Overall, carob has demonstrated promising results in a number of *in vitro*, animal studies and in few human studies (Summarized in Table 1), suggesting its beneficial properties in the treatment of several gastrointestinal disorders. However, there is a need for a more thorough characterization of all the active constituents of carob and the conduction of additional randomized clinical trials or human intervention studies.

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