

Chemoprevention of gastrointestinal cancers by natural honey

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Abstract

Gastrointestinal cancers are the most common human cancers in both men and women worldwide. Several epidemiological and experimental studies suggest a relationship between gastrointestinal cancers risk and dietary factors. Natural honey has been widely used in traditional medicine for many centuries to treat a wide range of ailments and complaints. Honey contains various components that exhibit wide activities including antibacterial, anti-inflammatory, antioxidant and anticancer properties. The anticancer effects of honey are mediated *via* diverse mechanisms,

including inhibition of proliferation, induction of apoptosis, suppression of free radicals and modulation of inflammatory signalling pathways. The present review assesses the chemopreventive effects of natural honey and its components in the modulation of gastrointestinal cancers and its modes of action in the prevention of the development of gastrointestinal tumors. Honey can be an approach as a cancer-preventive strategy which merits further experimental and clinical research in the near future.

Key words: Honey; Gastrointestinal; Cancer; Chemoprevention; Anticancer

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Core tip: Natural honey has been widely used in traditional medicine to treat a wide range of ailments and complaints. Honey contains various components that exhibit wide activities including antibacterial, anti-inflammatory, antioxidant and anticancer properties. The present review assesses the chemopreventive effects of natural honey and its components in the modulation and prevention of gastrointestinal cancers.

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GASTROINTESTINAL CANCERS

Cancer is a leading cause of death worldwide. It strikes more than one third of the world population and it's the cause of more than 20% of all deaths^[1]. Gastrointestinal cancers (cancers of the digestive

system) include cancers of the esophagus, gallbladder, liver, pancreas, stomach, small intestine, large intestine (colon) and rectum. The risk of gastrointestinal cancers varies greatly by individual ethnic group, lifestyles and risk factors^[2]. Considering the magnitude of the problem of cancer and the failure of conventional therapy of affects greatly the mortality rates for many types of cancers, new approaches to control of cancer and discovery of new agents is of great importance.

In recent years, with rising prevalence of gastrointestinal cancers by several factors such as changing lifestyle and improved screening and diagnosis, besides the obstacles of the current cancer therapy (chemotherapy and radiotherapy), there has been a great trend towards the use of dietary factors and natural products among cancer patients^[3,4]. The incidence of gastrointestinal cancers varies considerably from place to place and from time to time. It is clear that environmental factors play an important part in the development of these cancers and that many of these factors may be preventible. Oesophageal adenocarcinoma has been dramatically rising over the past decades^[5], and this rise in this cancer has been associated with an increased prevalence of gastroesophageal reflux disease and Barrett's esophagus. Fruit and vegetable consumption has been reported to have a protective effect and associated with a lower risk of oesophageal cancer. Gastric adenocarcinoma is the second leading cause of cancer worldwide^[5]. Foods that are smoked, dried, or pickled have been associated with an increased risk of gastric cancer^[6,7]. Vegetable and fruit intake has consistently been associated with a decreased incidence of gastric cancer^[8]. Pancreatic cancer is also one of the most devastating cancers, with a 5-year survival of only 6%^[9]. High dietary fiber intake, vegetable and fruit intake reduces pancreatic cancer risk^[10]. Colorectal cancer is also one of the leading cancers in both men and women in several countries^[11], and several epidemiological and experimental studies suggest a link between colon cancer risk and dietary factors^[12,13].

CANCER CHEMPREVENTION

Carcinogenesis is a multistep process induced by molecular and genetic changes that disrupt signaling pathways regulating proliferation, apoptosis and differentiation^[14]. The search for anticancer agents from natural sources for prevention and treatment of cancer is of a considerable interest in recent years. Several approaches are explored for the prevention and treatment of cancer including chemoprevention in animal models and clinical trials^[15]. Dietary supplements and natural compounds are one approach is used to reverse or prevent the development of cancer by modulating the molecular processes of initiation, promotion, and progression stages. It has been reported that diet components such as turmeric, garlic,



Figure 1 Variety of natural honey.

ginger, cruciferous vegetables and green tea play an important role in cancer prevention^[16,17]. The role of diet and prevention of gastrointestinal cancers is evolving and much data from basic science and animal models. Natural honey has been recently the focus of basic research and clinical studies for its several therapeutic benefits including cancer.

NATURAL HONEY

Since ancient times, natural honey has been widely used as a conventional medicine, and is extensively used for its therapeutic effects in recent years. Ancient Egyptians, Chinese, Greeks and Romans employed honey for wounds and diseases of the intestine^[18]. In the Holy Quran, Almighty Allah mentioned the special ability of honey to heal and cure disease. Scientific research has proven the therapeutic benefits of honey in treating several human diseases. The physical properties of natural honey depend on water content, temperature, the type of flora and the proportion of its sugars. The color of the honey varies according to the floral source and its mineral content, which usually ranges from water white to dark amber (Figure 1).

TYPES OF NATURAL HONEY

A large number of natural honeys are available worldwide and are either locally produced or imported from other countries. The type of natural honey depends on which species of plants were flowering when the bees were producing the honey. Honey from a single floral source greatly varies from honey of the same floral source that obtained from different locations or seasons. The percentage of fructose, glucose, amount and type of amino acids and the organic acids vary by floral source. The floral source affects not only the physicochemical properties of the honey, but also the antimicrobial activity of honey^[19-21]. Different types of honey differ in their color, flavor and density. The antibacterial quality of honey varies among different types of honey depending on geographical locations, seasonal source, harvesting,

Table 1 Composition of natural honey^[18,31]

Component	Average (value per 100 g)
Carbohydrates	82.4 g
Fructose	38.5 g
Glucose	31 g
Sucrose	1 g
Other sugars	11.7 g
Dietary fiber	0.2 g
Fat	0 g
Protein	0.3 g
Water	17.1 g
Riboflavin (Vit. B2)	0.038 mg
Niacin (Vit. B3)	0.121 mg
Pantothenic acid (Vit. B5)	0.068 mg
Pyridoxine (Vit. B6)	0.024 mg
Folate (Vit. B9)	0.002 mg
Vitamin C	0.5 mg
Calcium	6 mg
Iron	0.42 mg
Magnesium	2 mg
Phosphorus	4 mg
Potassium	52 mg
Sodium	4 mg
Zinc	0.22 mg

purity and storage conditions^[22-24]. A survey of the antibacterial activity of 52 samples of 24 types of honey of Saudi and some international honeys revealed that the antibacterial activity of the majority of the investigated honeys did not show large variations^[25]. The equivalent phenol percent concentrations for the majority of honeys ranged between 5.5% and 7.9%. It was also noticed in this study that there was no relationship between color and antibacterial activity of honey. The antimicrobial activity of honey could be attributed to several factors like the osmotic effect of honey, acidity, the presence of hydrogen peroxide, the presence of antibacterial phytochemical components and the *in-vivo* antibacterial activity of honey^[22,26-29]. *In-vitro* antioxidant activity of Saudi Sidr honey "monofloral type of honey" revealed a strong antioxidant activity^[30]. Furthermore, pretreatment with Sidr honey prior to the administration of CCl₄ significantly prevented the increase of the serum levels of enzyme markers and reduced oxidative stress in rats.

COMPOSITION OF NATURAL HONEY

The composition of natural honey varies, depending on many factors such as the geographical areas, source of honeybee food, climate, environmental conditions and the processing it undergoes^[31-35]. Honey contains about 200 substances including fructose, glucose, amino acids, vitamins, minerals, water and enzymes^[18,31], as shown in Table 1. Natural honey uses a combination of components, including hydrogen peroxide, acidity, osmotic effect, high sugar concentration and polyphenols to prevent diseases and fight infection. All natural honey contains flavonoides, phenolic acids,

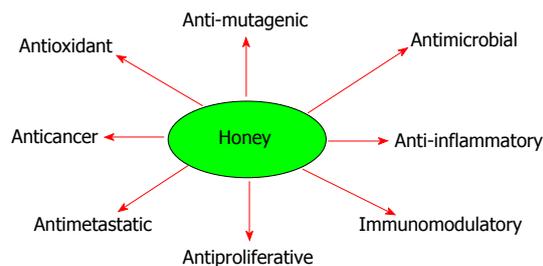


Figure 2 Actions of natural honey.

ascorbic acid, tocopherols, catalase, superoxide dismutase, reduced glutathione^[18,36]. Some of these flavonoids and phenolic compounds include chrysin, kaempferol, quercetin, pinobanksin, pinocembrin, luteolin, apigenin, genistein, naringenin, hesperetin, *P*-coumaric acid, gallic acid, ellagic acid, ferulic acid, syringic acid, caffeic acid and vanillic acid. Natural honey and its components have been shown to possess a wide range of medicinal properties such as anti-inflammatory, gastroprotective, antioxidant, antitumor and anticancer effects^[37-41]. Figure 2 depicts some of the actions of natural honey.

Potential mechanisms of honey actions were found to include regulation of cell cycle, induction of apoptosis, activation of mitochondrial pathway, inhibition of angiogenesis and modulation of oxidative stress. Honey can inhibit the development of cancer by blocking the three stages of carcinogenesis (initiation, promotion and progression). The inhibitory effect of honey on carcinogenesis can be attributed to the presence of its active components, especially flavonoids and phenolic constituents. Honey plays an important role in preventing inflammatory tissues from producing free radicals^[42]. Caffeic acid phenethyl ester (CAPE), an active component of propolis, has many biological and pharmacological activities including antioxidant, antiinflammatory, antiviral action, anti-proliferative effect, apoptosis-inducing effect and anticancer effect^[43-46]. Caffeic acid esters have been shown to have an inhibitory effect on tumor cell proliferation and transformation by the down regulation of many cellular enzymatic pathways including protein tyrosine kinase, cyclooxygenase and ornithine decarboxylase pathways^[47-50].

NATURAL HONEY AND GASTROINTESTINAL INFLAMMATION

Inflammation plays an important role in the development of several diseases including gastrointestinal diseases and cancer^[51,52]. Inflammation is recognized as a risk factor for gastric inflammation and *Helicobacter pylori* (*H. pylori*) infection and clinical intervention by natural products such as honey may provide an approach for reducing inflammation and *H. pylori*-associated diseases, particularly gastric cancer.

Honey contains many phenolic compounds such as ellagic acid, gallic acid, caffeic acid, quercetin and chrysin, which correlated to its antioxidant and anti-inflammatory activities^[36,52,53]. It was suggested that honey and its components can inhibit inflammation *via* inactivation of nuclear factor kappa-B (NF- κ B) and inhibition of transcription of genes for pro-inflammatory mediators such as COX-2, tumor necrosis factor- α (TNF- α), interleukin 6 (IL-6) and inducible nitric oxide synthase^[54,55]. Gelam honey has shown to have anti-inflammatory effects by reducing the edema size and inhibiting the production of the pro-inflammatory mediators nitric oxide, prostaglandin E2, TNF- α , and IL-6 in rats^[56]. Honey has been reported to potentiate the gastric protection effects of sucralfate against ammonia-induced gastric lesions in rats^[57]. Alagwu has reported that honey intake caused cytoprotection on the gastric mucosa of albino rats^[58]. Oral administration of honey has been reported to protect against gastrointestinal infection such as gastritis, duodenitis and gastric ulcer caused by bacteria^[59-61]. Nasutia *et al*^[62] demonstrated that oral pretreatment of honey prevented indomethacin-induced gastric lesions in rats. Perfusion of the stomach with isotonic honey resulted in a marked reduction of the lesions caused by ethanol and indomethacin in rats^[38,63].

NATURAL HONEY AND *H. PYLORI* INFECTION

H. pylori infection represents the most common risk factor underlying chronic inflammation and gastric cancer^[64,65]. *H. pylori* can lead to mucosal inflammation and cancer development through several mechanisms including *H. pylori* virulence factors such as CagA and VacA genotypes and inflammatory mediators that induce cellular signalling alterations in gastric cells^[65]. The intake of honey also helps treat *H. pylori* infection^[66]. Natural honey from New Zealand and Saudi Arabia at concentrations 20% (v/v) inhibited the growth of *H. pylori in vitro*^[67,68]. Honey had an inhibitory effect on *H. pylori in vitro* at solutions of both 10% and 20% honey^[67]. al Somal *et al*^[59] also found that Manuka honey from New Zealand, at concentrations as low as 5% v/v, completely inhibit the growth of *H. pylori*, and that 2.5% v/v partially inhibits the growth of *H. pylori*^[68]. Osmotic effects were shown to be the most important parameter for killing *H. pylori* as all carbohydrate solutions \geq 15% (v/v) inhibited 100% of the *H. pylori*. The therapeutic effect of honey was attributed to the antibacterial properties^[68,69]. Osato *et al*^[70] also reported that commercial honeys and the artificial solution were effective as Manuka honey in inhibiting growth of all *H. pylori* isolates at concentrations 15% v/v. It has also been reported that the use of honey with triple therapy regimen may help shorten the time required to eliminate *H. pylori* from stomach lining of patients

with gastritis or duodenal ulcer caused by *H. pylori* infection^[71].

H. pylori has been shown to activate mitogen-activated protein kinases and transcription factors such as AP-1 and NF- κ B that regulate cell proliferation and differentiation in gastric epithelial cells using several different bacterial components and host signaling pathways^[72,73]. NF- κ B and activator protein-1 (AP-1) are key regulators of inflammation and signaling cascades that lead to carcinogenesis. There are numerous agents including honey have been reported to suppress NF- κ B activation and act as potential chemopreventive agents for inflammation and cancer^[74]. CAPE blocked *H. pylori*-induced NF- κ B and AP-1 expression in gastric cancer cells, and CAPE also suppressed *H. pylori*-induced cell proliferation and production of the cytokines TNF- α and IL-8 and COX-2 expression^[55]. Therefore, the inhibition of these molecules by CAPE could result in suppression of many genes during *H. pylori*-induced inflammation. Wu *et al*^[75] demonstrated that the activity of NF- κ B and the expression of matrix metalloproteinase-9, IL-1beta, and IL-8 in gastric cancer cells by *H. pylori* significantly reversed by CAPE treatment, which suggested that CAPE could be promising adjuvant agent against gastric cancer. In Mongolian gerbils, CAPE treatment elicited anti-inflammatory effects on *H. pylori*-induced chronic gastritis. CAPE significantly inhibited *H. pylori*-stimulated NF- κ B activation and mRNA expression of several inflammatory factors in a dose-dependent manner, and prevented degradation of I κ B-alpha and phosphorylation of p65 in gastric cancer cells^[76].

NATURAL HONEY AND GASTROINTESTINAL CANCERS

There are many research studies support the use of natural honey for cancer prevention and treatment, especially cancers of the gastrointestinal tract. Nutritional studies have indicated that consumption of honey modulates the risk of the development of gastric cancer, and also honey induced apoptosis in gastric mucosa^[77]. It was postulated that CAPE may be a promising adjuvant treatment in gastric cancer^[78]. The chemopreventive actions of honey and its components have been also studied in various colon cancer models. Gelam and Nenas honeys suppressed the growth of HT 29 colon cancer cells by inducing DNA damage and apoptosis and suppressing inflammation^[79]. Jaganathan also demonstrated the anti-proliferative effect of Caffeic acid, one of the phenolic constituents of honey, inhibited in the colon cancer cells HCT15 and HT29^[80]. Honey induced apoptosis by causing the depletion of intracellular non-protein thiols and reduced the mitochondrial membrane potential and increased generation of reactive oxygen species. Furthermore, honey constituents induced apoptosis in colon cancer cells^[81]. Orsolić *et al*^[82] showed that honey exerted anti-metastatic effect in a murine

tumor model with colon carcinoma. Supplementation of diet with honey and *Nigella sativa* had a protective effect against methylnitrosourea-induced oxidative stress, inflammatory response and carcinogenesis in Sprague Dawley rats^[83]. Caffeic acid esters derivatives inhibited azoxymethane-induced colonic colonic pre-neoplastic lesions, ornithine decarboxylase, tyrosine protein kinase, and lipoxygenase activities and aberrant crypt foci formation, which are relevant to colon carcinogenesis in rat colon^[50]. Caffeic acid and its ester are potent inhibitors of human colon adenocarcinoma cell growth^[84]. Dietary administration of phenylethyl-3-methylcaffeate significantly inhibited the incidence and multiplicity of invasive, noninvasive adenocarcinomas of the colon, and also suppressed the colon tumor volume by 43% compared to the control diet, and also inhibited the formation in colonic tumors by 15%-30% in the animals^[48]. Gribel' *et al*^[85] indicated that honey possessed moderate antitumor effect and pronounced antitumor activity of 5-fluorouracil and cyclophosphamide against five different strains of rat and mouse tumors. Furthermore, honey potentiated the antitumor activity of the chemotherapeutic drugs 5-fluorouracil and cyclophosphamide in colorectal cancer cells^[86,87].

The anticancer effects of natural honey and its components on liver cancer cells have been investigated in a number of studies^[88-90]. Treatment of hepatocellular carcinoma HepG2 cells with bee honey and *Nigella sativa* led to a significant decrease in both the number of viable HepG2 cells and the levels of nitric oxide and improved the total antioxidant status and caspase-3 activity, especially in HepG2 cells treated with higher doses of bee honey *Nigella sativa* (20% and 5000 µg/mL)^[88]. It has been reported that Spanish honeys were most effective in protecting against food mutagen-induced DNA damage in HepG2 cells, which was attributed to its antioxidant and free radical scavenging properties^[89]. Gelam honey was selectively cytotoxic to liver cancer cells and found that the IC₅₀ value of gelam honey towards HepG2 was 25% whereas it was 70% for normal human hepatocytes (WRL-68)^[90]. Abdel Aziz *et al*^[91] reported that honey extracts exerted cytotoxic, antimetastatic and anti-angiogenic effects in HepG2 cells. Treatment with diethylnitrosamine induced hepatic cancer in rats and the neoplastic hepatic cells were reduced in the liver of honey-treated DEN-induced rats^[92]. These studies indicate that honey has an anticancer effect on various types of cancer cells and exerts its protective effect against the development of cancer by modulating the molecular and cellular mechanisms of carcinogenesis stages. Some of the mechanisms by which honey may exert its anticancer effects are cell cycle arrest, activation of mitochondrial pathway, induction of mitochondrial outer membrane permeabilization, induction of apoptosis, modulation of oxidative stress, amelioration of inflammation, modulation of insulin signaling, and inhibition of angiogenesis^[37].

The effect of honey was also investigated in pancreatic cancer. Caffeic acid phenethyl ester induced apoptosis in

human pancreatic cancer cells by activation of caspase-3/ caspase-7 and mitochondrial dysfunction^[93]. Treatment with CAPE slightly restored the expression of E-cadherin and markedly reversed the transforming growth factor-β-induced overexpression of vimentin at 24 h in Human pancreatic cancer cells (PANC-1) cells. CAPE suppressed the expression of Twist 2 and growth of PANC-1 xenografts without significant toxicity in an orthotopic pancreatic cancer model. These data suggest that CAPE could suppress the epithelial-mesenchymal transition in pancreatic cancer^[94].

CONCLUSION

Natural honey has many therapeutic benefits and medical uses. The different effects of natural honey including anti-inflammatory antioxidants and anticancer effects highlight its importance in the prevention of gastrointestinal cancers and improvement of cancer therapies. Some evidence of the anticancer effects of honey has been reported from *in-vitro* and *in-vivo* studies in gastrointestinal cancers, however, further investigation of anticancer effects of honey in animal and clinical studies are required to prove its therapeutic efficacy in chemoprevention strategies.

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