Food and Chemical Toxicology 108 (2017) 104–119

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

Antiulcer properties of fruits and vegetables: A mechanism based perspective

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ARTICLE INFO

Article history:
Received 5 July 2016
Received in revised form
19 May 2017
Accepted 10 July 2017
Available online 12 July 2017

Keywords:
Gastric ulcer
Fruits
Vegetables
Antioxidant
Inflammation

ABSTRACT

Gastric ulcer is the damage caused to mucosal layer of the stomach under the action of various factors like high levels of acid and pepsin, invasion by *Helicobacter pylori*, etc. Although most cases have been controlled and the rate of ulcer occurrence has reduced over the last few decades, gastric ulcer still holds a prime concern today. A range of palliative medicines comprising proton pump inhibitors, H2 receptor antagonists, COX-2 inhibitors (coxibs) is widely in use and patients have also been administered with acid suppression therapies. But these remedies aggravate the condition of patients causing severe side effects, or rather impart temporary relief. Therefore, it is highly imperative to develop safe and effective therapies for the treatment of gastric ulcer. Nature provides us various fruits and vegetables that can combat gastric ulcer through multiple mechanisms; predominantly via antioxidant, anti-inflammatory, antisecretory, antimicrobial, anticholinergic and cytoprotective activity, inhibition of small intestinal propulsion etc. Various phytochemicals from fruits and vegetables such as phenolics, flavonoids, tannins and saponins play a vital role in the prevention and cure of gastric ulcer. This review is a compendium of all fruits and vegetables known for their profound antiulcer effect and their underlying mechanisms of action.

Contents

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http://dx.doi.org/10.1016/j.fct.2017.07.023
0278-6915/

1. Introduction

Gastric ulcer involves the excoriation of the mucosal lining which guards the digestive organs by secreting mucus and other cytoprotective agents like prostaglandin (PG), gastrin and secretin. This disease poses a major threat to mankind affecting millions of people worldwide. Reports from Global Burden of Disease Study stated that peptic ulcer, which comprises of both gastric ulcer and duodenal ulcer, claimed the lives of 301,400 people around the world in 2013 (GBD, 2013). The high incidence of gastric ulcer is attributed to a range of predisposing factors like *Helicobacter pylori* infection, consumption of alcohol, nonsteroidal anti-inflammatory drugs (NSAIDs), etc. (Kidd and Modlin, 1998; Warren, 1983; Marshall et al., 1985). Ulcer patients infected with *H. pylori* have high chances of gastric cancer (Hwang et al., 2015). Upon *H. pylori* infection, the host generates a lot of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that lead to mucosal cytotoxicity and oxidization of the intracellular components. Approximately 10% of the individuals infected with *H. pylori* develop peptic ulcer while 1–3% individuals become victims of gastric cancer (Cirak et al., 2007). However, incidence of *H. pylori* induced peptic ulcer has decreased over the recent decades (Sung et al., 2009). Intake of excessive alcohol has also been found to be responsible for increased incidence of peptic ulcer (Chou, 1994; Vinagre et al., 2013). Alcohol disturbs the integrity of the gastric mucosal epithelium by inducing oxidative stress (Tamura et al., 2013; Das and Vasudevan, 2005). It also stimulates the release of cytokines, histamine, and leukotrienes leading to intestinal mucosal damage and blood clotting. The mucosal injury is potentiated by the decrease of prostaglandin synthesis and increased secretion of acid, under the action of alcohol (Bode and Bode, 1997). Gastric ulcer is also induced by the administration of NSAIDs (Fornai et al., 2011). NSAIDs disrupt the gastric mucosal barrier without inhibiting acid secretion. These drugs reduce prostaglandin synthesis, decrease gastric mucosal blood flow and inactivate various growth factors that aid in the defense and repair of gastric mucosa (Wallace, 2000). Besides, stress also causes ulcer and it has been reported to promote *H. pylori* infection (Levenstein, 1998; Söderholm and Perdue, 2001). Other factors that account for this disease include smoking, physical inactivity, excessive coffee drinking, improper nutrition and untimely dietary habits (Parasher and Eastwood, 2000; Roberts, 1972; Suadicani et al., 1999; Rosenstock, 2003; Nneli and Woyike, 2008).

A variety of drugs with different modes of action are commercially available for the treatment of gastric ulcer. Since cyclooxygenase-2 (COX-2) is responsible for inflammation and ulcer (Vane et al., 1998), its inhibitors (coxibs) such as celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib and lumiracoxib have been designed that selectively inhibit COX-2 without interfering with the protection induced by COX-1 (Dubois et al., 2004). Drugs like licofelone with dual cyclooxygenase (COX)/5-lipoxygenase (5-LOX) inhibitory effect are used to block the synthesis of both prostaglandins and leukotrienes to reduce inflammation in the gastric mucosa (Martel-Pelletier et al., 2003; Singh et al., 2005). Besides coxibs, a number of novel therapeutics including proton pump inhibitors, H2 receptor antagonists and acid suppression therapy for *H. pylori* have been developed. Proton pump inhibitors like omeprazole or synthetic prostaglandins, specifically misoprostol inhibit gastric acid secretion. The secretory effect is also reduced by antacids, H2-blockers like ranitidine, cimetidine, famotidine, and nizatidine (Mejia and Kraft, 2009). A combination of antibiotics is also found to promote gastric ulcer healing by potentially eradicating the harmful parasite *H. pylori* (O'Connor et al., 2015). Despite the development of a number of drugs for the prevention and treatment of gastric ulcer, a huge incidence of gastric ulcer is still evidenced worldwide. Thus, the crisis for effective healing and prevention has urged scientists to seek out natural therapies for the prevention and treatment of gastric ulcer.

2. Fruits and vegetables in the treatment of gastric ulcer

The World Health Organization (WHO) has ranked low consumption of fruits and vegetables among the top 10 risk factors leading to mortality (Guilbert, 2003). These agents have been reported to reduce the risk of cancer, cardiovascular diseases, diabetes, Alzheimer's disease, cataract and age-related functional decline (Kunnumakkara, 2015; Kunnumakkara et al., 2008). These agents and their active components have also been reported to prevent gastric ulcer in various *in vitro*, *in vivo* and clinical ulcer models through different mechanisms of action. (Tables 1–3, Fig. 1). Based on their mechanism of action, these

Table 1
Antiulcer activity of various fruits and vegetables and their mechanism of action (*In vitro*).

Fruits and vegetables	Model	Mechanism of action	References
Allium ascalonicum (Shallot)	*H. pylori* strains	↑antibacterial activity	Adeniyi & Aniyam, 2004
Allium sativum (Garlic)	AGS cell line	↑Nrf2, ↑HO-1, ↑NQO1	Kim et al., 2014
Citrus bergamia (Bergamot orange)	ATCC 43504 and ATCC 49503	↑antibacterial activity	Filocamo et al., 2015
Citrus lemon (Lemon)	*H. pylori* strains	↑antibacterial activity	Rozza et al., 2011
Poncirus trifoliate (Trifoliate orange)	AGS cell line	↑antioxidant activity	Lee et al., 2009
	SNU638 cell line	↑antioxidant activity	Lee et al., 2009
Rubus fruticosus (Blackberry)	TNF-α & IL-1β induced AGS cells	↓NF-κB driven transcription, ↓NF-κB translocation, ↓release of IL-8	Sangiovanni et al., 2013
	EtOH induced AGS cells	↓release of IL-8	Sangiovanni et al., 2013
	H_2O_2 induced AGS cells	↓release of IL-8	Sangiovanni et al., 2013
Rubus idaeus (European red raspberry)	TNF-α & IL-1β induced AGS cells	↓NF-κB driven transcription, ↓NF-κB translocation, ↓release of IL-8	Sangiovanni et al., 2013
	EtOH induced AGS cells	↓release of IL-8	Sangiovanni et al., 2013
	H_2O_2 induced AGS cells	↓release of IL-8	Sangiovanni et al., 2013
Vaccinium oxycoccos (Small cranberry)	*H. pylori* strains	↑antibacterial activity	Burger et al., 2002
Solanum tuberosum (Potato)	*H. pylori* strains	↑antibacterial activity	Badanavalu Chandrashekar and Dharmesh, 2016

Note: ↑: Upregulation, ↓: Downregulation, EtOH: Ethanol, *H. pylori*: *Helicobacter pylori*, HO-1: Heme oxygenase-1, H_2O_2: Hydrogen peroxide, IL: Interleukin, NF-κB: Nuclear factor kappa B, Nrf2: Nuclear factor-erythroid-2-related factor-2, NQO1: NAD(P)H:quinone oxidoreductase-1, TNF: Tumor necrosis factor.