REVIEW ARTICLE

Coffee and Gastrointestinal Health: A Review

Wan Syamimi Wan Kamarul Zaman[1], Su Peng Loh[1,2], Norhaizan Mohd Esa[1,2]

[1] Department of Nutrition and Dietetics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia
[2] Research Centre of Excellence, Nutrition and Non-Communicable Diseases (NNCD), Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia

ABSTRACT

Coffee is a well-known beverage being processed from coffee beans of either *Arabica* and/or *Robusta*. Observational and experimental research on coffee shows positive health impact. Coffee often relates with dyspeptic condition (i.e. Gastric release) and manifest Gastro-esophageal Reflux (GERD) and peptic ulcer (PU) diseases. Despite much contradictive results, epidemiological studies were inclined towards debunking the possible relationship between coffee and gastrointestinal diseases. Putative compounds were experimentally found to be chlorogenic acid (CQA), caffeine (CAFF), ᵝN-alkanoyl-5-hydroxytryptamide (C5HT), N-methylpyridinium (NMP), chlorogenic acid lactones (CQL) and hydroxybenzenes in coffee that leads to gastric release. The type 2 bitter taste receptors (TAS2Rs), were physiologically involve in the gastric acid secretion. These contrarily results need much considerations involving genetic, types of coffee used and the compounds in coffee that might interact causing gastrointestinal problem.

Keywords: Coffee, Gastric Acid, GERD, Peptic Ulcer, Gastrointestinal health

Corresponding Author:
Loh Su Peng, PhD
Email: sploh@upm.edu.my
Tel: +603-89472432

INTRODUCTION

Coffee is classified as the favourable thermally processed drinks due to its distinctive, pleasing aroma and stimulation of the nervous system. Historical starting of the coffee drinking was from the Africa side of the world spreading out to the Middle East before entering Europe. Coffee is one of the sought-after commodity after oil and has been a favourite drink worldwide (1). Approximately around 70 types of coffee bean existed, but only *Coffea Arabica* and *Coffea Robusta* beans are being used in coffee production for commercialization purpose. Coffee tree is classified under the plant's kingdom known as Angiosperm, belonging to the *Rubiaceae* family (2). The coffee bean is originally included as the main part of the coffee plants to be used in coffee processes. Since 1990, Asia's coffee intake has shown dynamic growth with a normal rate of 4% per year, aggregate to 4.9% starting the year of 2000 (3).

Coffee has been developed into many ranges depending on the preparation, serving, types of coffee bean used, brewing, ingredients, and processing techniques (4). This is to the extent that different country has their own way of preparing the coffee. Hence, the existence of various types of coffee such as Espresso, Latte, Instant 3-in-1 and Decaffeinated (decaf) that will affect the chemical composition of the coffee itself. To define some of the types of coffee existed, espresso coffee was known as such due to its brewing techniques by means of hot water and pressure using the conventional bar machines (5). As for decaffeinated coffee undergoes decaffeination process which is done before the roasting process to remove the caffeine using an organic solvent or water extraction method. Another type of coffee which are convenient is the instant coffee, produced by the spray-drying method at high temperature and high pressure producing small droplets to become powder (4).

Research found that different brewing methods espresso coffee could affect physicochemical characteristics of the coffee (6). The existence of milk added to the coffee could also cause the decreasing in antioxidant capacity, caffeine and chlorogenic acid compounds (7). Even the use of different coffee bean either *C. Arabica* or *C. Canephora* will affect the chemical composition of the coffee. These two coffee bean species have a different cultivating condition that affects its composition (4). These factors can cause the coffee component to vary.

The biological compounds that can be found in coffee can be classified as volatile and non-volatile compounds. The non-volatile compounds are known as phenolic compounds (i.e. caffeine and chlorogenic acid), carbohydrates, water, fiber, proteins, free amino acids,

organic acids, trigonelline, nitrogenous compounds, vitamins, lipids, minerals and alkaloid which some are potent antioxidant and anti-inflammatory compound (2,4). However, only a few of these mentioned compounds are bioactive and play role in the flavour of the coffee beverages. As for the volatile compounds are found abundant in the coffee bean such as alcohols, esters, hydrocarbons, and aldehydes (4).

Coffee drink is a complex mixture with abundance of positive health effects. Coffee was found to have an effect in lowering cholesterol, nerve diseases and mental health (8). Despite years of research on coffee, the effects of coffee on the gastrointestinal system have only been an urban story from patients and lay media. Up to this date, a sound evidence and review to support the belief of coffee effecting the gastrointestinal health are lacking. Literature evidence on the coffee and health generally were more dictated by the epidemiological data and are lacking experimental evidence. In this review, literature evidence from the epidemiological and experimental data on the coffee and its component that affects gastrointestinal health with the focus on coffee-related dyspepsia (i.e. gastric release, GERD and peptic ulcers) will be discussed.

COFFEE AND FUNCTIONAL DYSPEPSIA

Functional Dyspepsia

For years, people have been spectre to the fact that drinking coffee on an empty stomach can cause chaos to the digestive tract. Even the medical doctors restricted the coffee consumption when someone complaint of gastrointestinal problems. Stomach discomfort or scientifically known as dyspepsia was a term used for complex, heterogeneous symptoms leading to gastrointestinal complaints. In 1994, Rome criteria were developed in order to define functional dyspepsia based on a set of symptoms which includes epigastric pain, postprandial fullness, early satiation, bloating, epigastric burning, nausea, and vomiting (9). As of today, the latest Rome IV criteria was recently updated from Rome III 2006 and was used in defining functional dyspepsia. Rome IV elucidated functional dyspepsia as a pool of 4 symptoms mainly epigastric pain, postprandial fullness, early satiety and epigastric burn resulting in an acute daily interference of a minimum of 3 days in a week for over 3 months with an advance onset of symptoms of at least 6 months. Dyspepsia can be categorized as functional or previously known as non-ulcer dyspepsia and non-functional dyspepsia (10).

In Malaysia, dyspepsia problem has been reported in up to 15% of a rural and 25% of an urban population (11). The research have included the risk factor such as demographic, smoking, tea drinking, regular usage analgesia and chili intake in triggering dyspepsia among the Malaysians population (12). They concluded that high socioeconomic status, analgesic usage, and comorbidity as the main risk factors for dyspepsia among Malaysian populace. Malaysia's data on coffee-induced dyspepsia either epidemiological study or experimental study were generally scarce.

The underlying mechanism of dyspepsia conditions is hard to pinpoint specifically, as the pathophysiological explanation involves multiple mechanisms interact together resulting in dyspeptic symptoms. Three main mechanisms were used to explain this condition include psychosocial factors (i.e. stress and depression), faults in visceral sensation and dysmotility interacted together causes dyspeptic symptoms in patients (13). Decades of research have found other underlying mechanisms such as immune system, visceral hypersensitivity, acid exposure, gastrointestinal infection and food intolerance are suspected for dyspeptic pathology. Often, there is no organic cause for the problem. There is evidence that functional dyspepsia may be related to the abnormal motility of the upper gastrointestinal tract and also responding to stress situation (14).

The other question remains is what are the factors that trigger these mechanism-prompting dyspepsia. Some triggering factors such as dietary and lifestyle, even psychosocial or psychological elements have been related to functional dyspepsia cases. Dietary factors, including coffee and caffeine, are often associated with these complaints despite the much contradictory scientific evidence. Preceding research has reported dyspepsia from coffee consumption was likely due to the increase in gastric acid secretion (15). It is generally thought that coffee intake should influence this disorder probably due to gastric acid secretion induced by compounds in coffee such as chlorogenic acid and caffeine. Many speculations arise in regards to coffee consumption and gastric issues due to lack of understanding of the mechanism of coffee causing heartburn and dyspepsia (16). Previous studies on coffee causing gastric problems are mostly generated from observational studies.

Coffee and Gastric Release

Hydrochloric acid (HCL) is the main component in gastric juice being physiologically secreted by the parietal cell to support food digestion. This biological component of gastric juice plays an important role in sterilization from bacterial colonization and activation of protease pepsin. Gastric acid secretion was considered to be one of the pathophysiological mechanisms leading to dyspepsia. Through few experimental designs (i.e. *in-vitro* and HPLC analysis), few compounds in coffee were found to be responsible in causing gastric release were identified as chlorogenic acid (CQA), caffeine (CAFF), $^{\beta}$N-alkanoyl-5-hydroxytryptamide (C5HT), N-methylpyridinium (NMP), chlorogenic acid lactones (CQL) and hydroxybenzenes (17–19). Some of these putative compounds were produced when roasting the coffee beans during the coffee production.

Caffeine or scientifically known as 1, 3, 7-trimethylxanthine, is the bitter alkaloid naturally to be found abundantly in plants such as coffee beans, cocoa and tea leaves (17). Caffeine is the signature compound in coffee also contributed to the bitterness taste, and it is a well-known psychoactive drug. Famously known to stimulate the central and autonomic nervous system (20), caffeine was found to have a profound effect on gastric acid secretion (GAS) (21). The physiological mechanism as explained by Fredholm and colleague is that caffeine's bitterness property trigger the taste receptors known as type 2 bitter receptors (TAS2Rs) and involving some inhibition of enzyme leads to gastric acid secretion (GAS) (20). Further research indicates chemosensory mechanism explains the irony involvement of taste receptors in regulating gastric acid secretion by involving three important sites: (i) Excitation of oral taste cells and giving out its effect through the cephalic regulation in the gut (22)(ii) Initiate the release of gastrin and/or histamine from enteroendocrine cells and/or (iii) Attuning the gastric acid production by the parietal cells (23). The latest findings by Liszt and colleague concluded that the existence of bitter taste receptor (TAS2Rs) found at the oral and in the stomach can affect gastric acid secretion (GAS) when administered with caffeine either orally or encapsulated (24).

However, none can be found in regards to chlorogenic acid alone to exert the same effect towards the bitter taste receptors leads to GAS. Chlorogenic acid was found to have the protective ability against free radicals making it the potential antioxidant compound (19). In a published work shows the chlorogenic acid effect in mice was positive by reducing the lesion area and gastric acid secretion was not stimulated (25). Similar deduction by Kang and Lee that there is a therapeutic and protective effect of chlorogenic acid (CGA) by reducing the lesion due to reflux esophagitis in rats (26). Recent years, multiple research papers approach through experimental designs in relating chlorogenic acid and some other compounds in coffee as the offenders in causing stomach irritation due to gastric release (17,27). The major chlorogenic acids (5-O caffeoylquinic acid, 3-O caffeoylquinic acid and 4-O caffeoylquinic acid) were found to thermally degraded producing bitter compounds known as (1) 5-O-caffeoyl-muco-γ-quinide (2) 3-O-caffeoyl-γ-quinide (3) 4-O-caffeoyl-muco-γ-quinide (5) 5-O-caffeoyl-epi-δ-quinide (6) 4-O-caffeoyl-γ-quinide (7) 3,4-O-dicaffeoyl-γ-quinide (8) 4,5-O- dicaffeoyl-muco-γ-quinide, and (9) 3,5-O-dicaffeoyl-epi-δ-quinide (28). Chlorogenic acids (CGAs) and its lactones were released upon roasting process through the Maillard and Strecker reaction. This is the plausible reasons for the contradiction of findings between published researches. The usage of chlorogenic acid as a drug and targeted-single compound has a different effect as compared to chlorogenic acid found in coffee biomixtures that has multiple compounds interact with one another.

Since other bitter compounds such as beer bitter acids (α-, β-, iso-α-acids,) (29), catechin and procyanidin B2 (30) were found to causes gastric acid secretion (GAS) and gastrin release, further research in regards to chlorogenic acid and its lactones to have the same effect towards the bitter taste receptors could be considered for further investigation. Interestingly, the biomixture of coffee containing multiple compounds could also be considered. The research outcomes could generate the plausible explanation for the mechanism onset of dyspepsia symptoms.

Another gastric acid-triggering compound was found at the waxy layer of coffee bean and it is the fatty acid amides of serotonin known as $^{\beta}$N-alkanoyl-5-hydroxytryptamides (C5HT). It has come into focus as another plausible compound and in recent years, it was experimentally proven to stimulate gastric acid secretion (17). Dewaxing the coffee involves the steam-treatment process, which applied before roasting to remove the chlorogenic acid content and the outer layer wax was reduced, making it into a stomach-friendly coffee (31). This compound in coffee was first researched back in the 1960s and was steadily been researched mostly on the quantitative methods. As reviewed by author Karl and Speer, this hardly researched compounds has few published papers on its presence in tree nuts (i.e. Walnut, Almond, Hazelnut and Brazil nut) (32).

Much consideration needs to be undertaken when involving coffee and gastrointestinal health. Instead of focusing only on a single compound effect, future research must focus more on the biomimetic mixture of coffee as a whole for sampling. Findings also found the N-Methylpyridinium (NMP) in the biomimetic mixture is more effective in decreasing the gastric release, suggesting that targeting-single compounds are less likely to give the same effect (27). Even the types of coffee bean used (33), roasting method (34), additional components added to the coffee brands and differences in percent dry matter of CGA can effect gastric release (35).

Coffee and Gastro-esophageal Reflux (GERD)

Gastro-esophageal reflux (GERD) is synonymously known as GORD or acid reflux is referring to the condition of the backward flow of the stomach's churned content with the gastric acid into the esophageal region connecting the stomach and throat (36). During the reflux episode of the churned food together with gastric acid, it will cause the esophageal symptoms such as heartburn, regurgitation, pain in the chest, odynophagia, and dysphagia. Typically, a frequent onset of the heartburn and regurgitation symptoms is the cardinal rules to diagnose a patient with GERD disease (37). Other signs include belching, bad breath, bloating and rumbling sound resonating in the stomach, the sour liquid taste at the back of the mouth and/or the burning sensation in the chest and swallowing problem.

The first ever published paper on GERD in Asian community was done by Kang and colleagues in 1993 (37). Years before the commencement of the study, common knowledge on GERD disease is uncommon among the Asian population whereby the resources on the disease are limited and possibly even none. The study causes the researcher to record the prevalence of GERD to be 3.3%. Western countries through the Canadian Digestive Health Foundation Public Impact Series have found the GERD prevalence to be 10% to 20% of the populace (38).

During the earlier investigations on GERD, it was defined with the presence of erosive esophagitis during endoscopy (39). The symptoms for GERD, Irritable bowel syndrome (IBS) and functional dyspepsia (FD) are large and often overlapping with each other, so often that it is confusing and difficult to pinpoint in a definite manner during diagnosis. The question is, what are the differences in symptoms between functional dyspepsia which has been previously discussed with GERD? Thus, does coffee affect the GERD?

The dominant symptoms and complaints presented are the nearest indication to accurately differentiate between these diseases. Hence, this must go back to the understanding of the definition of each disease presented itself. Functional dyspepsia (FD) and IBS criteria were well followed by the recent Rome III classification. Despite that, a uniform definition on GERD is still in the midst of finding a concrete and definite conclusion. Thus the existence of 30 different sets of criteria in describing GERD including the well-known Savary-Miller classification. These criteria were all lacking in proper validation, formal development and peer review making the Los Angeles classification and Montreal definition to be used widely nowadays (40).

The Savary-Miller classification indicate the presence of erythema as Grade 1 esophagitis as the indicator for the presence of GERD. Meanwhile, the Los Angeles classification required the existence of any breaching at the esophageal mucosa before any diagnosis can be made for GERD. As for Montreal definition stated '*condition that develops when the reflux of the stomach contents causes troublesome symptoms and/or complications*'. Los Angeles classification was considered to be well validated, reproducible, practical and shows consistency in predicting the outcome of the acid reflux therapy (40). After many reviews on published papers, researchers have concluded that to purposely standardize the definition of GERD are not practical for the clinicians and researchers which rather uses the definition of GERD fit to their convenience in handling the task at hand (41). Researchers would define GERD in the epidemiological study using the self-reporting of at least weekly heartburn or regurgitation or both to define GERD, increasing the possibility of overestimation. Hence, it can be said that to differentiate between the diseases is not that simple due to the overlapping and sharing of the same dominant symptoms.

Many factors can affect the GERD, it can be said that the factors can be classified as either external or internal factors. The internal factors used to study were on genetic factor (42) and obesity (43). Some even indicate racial or ethnicity to be plausible external factors leads to GERD (44). Even so, none have mentioned the possibility of this racial factors could also be affected by the dietary factors that are different from one races to another. Dietary factors specifically on the intake coffee drink have been one of the frequent risk factors to cause GERD (45). In an experimental study, heartburn effect of coffee has been proved on acid sensitivity individuals (46). However, conclusive results among studies are contradictive due to lack in understanding the aetiology of coffee leads to GERD.

Evidence through a research done in Japan known as LEGEND, the study proved that by intervening the coffee intake frequency shows an improvement in GERD symptoms even in patients developed persistent towards GERD medication known as proton pump inhibitors (PPIs) (47). The LEGEND research proved those lifestyle modifications by reducing the frequency of coffee intake show significant improvement of the GERD symptoms. To further support, the effects of PPIs were found to not always giving out the expected effect the insubstantial amount of patients that exhibit persistent symptoms of GERD (48). Researchers have linked coffee intake to be one of the plausible risk factors for GERD and found relapsing of symptoms even after the treatment of PPIs. In a recent cross-sectional study done in Saudi Arabia, it opposed the hypothesis of relating coffee and GERD whereby tea drinkers were more dominant to exhibit GERD symptoms (49). Their results further backing the other previous research been done by (50) and (51) in regards to tea consumption and GERD cases.

Several other foods other than coffee have also been put into the spotlight of having the reflux effect such as dietary fat, chocolates, onions, citrus fruits, mints and tomatoes (52,53). These postulated foods and drinks related to the relaxation mechanism of the lower oesophageal sphincter that causes the GERD problem (54). This was based on the previous data where caffeinated and decaffeinated coffee increases the pressure of lower oesophageal sphincter (21). Still, data were not sufficient and no latest clinical data to support such claims (55). Due to this, the guidelines do not include the cessation of certain food when it comes to GERD treatment (56). With all the data been published, the meta-analysis results in one conclusion that there is no significant association between coffee and GERD cases (57).

Despite substantial epidemiological studies have dominant conclusion towards negative association, it

should be noted that different varieties and processing methods of coffee have roles in affecting GERD (17). In addition to external factors, internal factors such as genetic should have fair consideration as being an important risk factor. In a study in 2002 by Cameron and colleagues have accounted heritability being 31% towards reflux disease cases (42). This stressed the importance of furthering studies relating coffee and GERD into the experimental side involving cell culture, quantification, and biomolecular techniques.

Coffee and Peptic Ulcer Disease

Peptic ulcer (PU) has been considered to be one of the widely known esophago-gastroduodenal disorders (56). This acid-related disease commonly affected the upper gastrointestinal part (i.e. gastric and duodenal) leading to the formation of ulcer (23). Both were considered to have high possibility leading to the existence of dyspepsia cases. A group of researchers by Kurata and colleague (2002) found almost one-third of their patients in the primary care were detected with dyspepsia also positive in having the peptic ulcer (58). Eradication of the *H. pylori* among the patients has shown an improvement in dyspepsia occurrence. *H. pylori*, a gram-negative microaerophilic bacterium colonizes and may persist in the gastric mucosa of a human for a long period of time. Approximately 10% of *H. pylori* infection cases were somehow complimented together with clinical diseases such as dyspepsia and peptic ulcer (59).

In treating peptic ulcer, reducing the gastric acid secretion and *H. pylori* has become the main focus by physicians and specialist in order to increase the quality of life of the patient. Early treatment could help in preventing the condition to worsen which increase the chances of developing cancer (60). Improving peptic ulcer condition is achieved by eradicating the *H. pylori* with ways such as the short treatment method that lasted for 4-7 days as recommended by consensus guideline. This short regimen method or known as PPI-based triple therapy consists of the usage of anti-secretory and anti-microbial agent approved to be applicable in Europe countries (61).

Currently, the detection of peptic ulcer would use the endoscopy technique. However, endoscopy usage in the peptic ulcer management has its downside as being impractical, expensive and invasive (62). However, it is not necessarily to be totally omitted whereby endoscopy is still essential in ulcer management among the older patient, regular intake of NSAIDs, unusual weight loss, bleeding, infection-related factors, frequent use of Non-Steroidal Anti-inflammatory Drugs (NSAIDs). Genetic also partly involved in peptic ulcer formation. The peptic ulcer is common to be known as the acid-related disease that could be either gastric ulcer (GU) and duodenal ulcer (DU) (23). Previously, it was found to generalize that coffee contains a significant amount of caffeine leads to the gastric acid secretion resulting in peptic ulcer formation (21). Up until now, there are contradictions in proving the association between coffee and PU. It was noted that a substantial amount of previous evidence is all favoured in rejecting the possibility of coffee leads to PU and only some supported based on positive findings between PU and coffee intake leads to gastric and duodenal ulcer (63).

Notably, a multivariate analysis among healthy subjects also found no possible association which is significant enough to support the relationship between coffee intake and upper gastroduodenal ulcer diseases (64). The plausible reason behind this contradictive conclusion between researchers could be the existence of preventive effects in coffee that can offset or balance out the detrimental effect of gastric acid secretion. Chlorogenic acid compounds in coffee can be postulated to give that protective effect. This is based on the proven studies concluded chlorogenic acid to prevent diabetes, hypertension, tumor, and inflammation (65). With all the proven event has led to Shimoyama and his colleagues to finally proven gastroprotective effect by CGA treatment (25). They further explained that CGA does not help in reducing the gastric release, but it counterbalances by reducing the progression of the lesion area. Furthermore, chlorogenic acid was found to be abundance in coffee sources and daily habit in consuming coffee can provides an intake of about 300 mg to 1.0 g of GCA (66). Chlorogenic acid is found to be highly bioavailable when absorb and metabolized in humans (67).

CONCLUSION

Several shreds of experimental evidence have shown coffee to exhibit the potential to cause gastric release. Gastric acid secretion was found to cause functional dyspepsia to the happening of reflux, heartburn, epigastric pain and GERD (68).

Many of the reviewed research articles are epidemiological study that does not look further details (i.e. type of coffee used) that must be earnestly researched upon. The importance have been pointed out in one of the human observational study by Van Deventer et.al., (1992) showing different responses to coffee depending on how the green coffee has been processed (69).

Furthermore, mechanistic studies should be further probe into as conclusions resulted from questionnaire-based research are inconsistent. The urge for the experimental-based study would specifically pointed out the detail mechanism or pathway and plausible compounds affecting gastro health. This is to either further prove or rebuff the conclusions extracted from observational research data.

REFERENCES

1. Tastan YK. From Sufi Beverage to Capitalist Commodity The Story of Coffee. J Gazi Acad View. Scientific Research Publishing; 2009;2(4):53–86.
2. Davis AP, Chester M, Maurin O, Fay MF. Searching for the relatives of Coffea (Rubiaceae, Ixoroideae): The circumscription and phylogeny of Coffeeae based on plastid sequence data and morphology. Am J Bot. 2007;94(3):313–29.
3. International Coffee Organisation. Total production of exporting countries [Internet]. 2015. Available from: http://www.ico.org/trade_statistics.asp
4. Farah A. Coffee Constituents. In: Chu YF, editor. Coffee: Emerging Health Effects and Disease Prevention. Blackwell Publishing; 2012.
5. Illy A, Viani R. Espresso coffee: the science of quality. Viani R, editor. Elsevier Academic Press. Cambridge: Elsevier Academic; 2005.
6. Parenti A, Guerrini L, Masella P, Spinelli S, Calamai L, Spugnoli P. Comparison of espresso coffee brewing techniques. J Food Eng. 2014;121(1):112–7.
7. Niseteo T, Komes D, Bel čak-Cvitanović A, Horžić D, Budeč M. Bioactive composition and antioxidant potential of different commonly consumed coffee brews affected by their preparation technique and milk addition. Food Chem. 2012;134:1870–7.
8. Higdon J V, Frei B. Coffee and health: a review of recent human research. Crit Rev Food Sci Nutr. 2006;46(2):101–23.
9. Loyd RA, McClellan DA. Update on the evaluation and management of functional dyspepsia. Am Fam Physician. 2011;83(5):546–52.
10. Stanghellini V, Chan FKL, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal Disorders. Gastroenterology. 2016;150(6):1380–92.
11. Mahadeva S, Yadav H, Rampal S, Goh K-L. Risk factors associated with dyspepsia in a rural Asian population and its impact on quality of life. Am J Gastroenterol. 2010;105(4):904–12.
12. Mahadeva S, Yadav H, Rampal S, Everett SM, Goh K-L. Ethnic variation, epidemiological factors and quality of life impairment associated with dyspepsia in urban Malaysia. Aliment Pharmacol Ther. 2010;31(10):1141–51.
13. Camilleri M. Nonulcer dyspepsia: a look into the future. Mayo Clin Proc. 1996;71(6):614–22.
14. Feinle-Bisset C, Azpiroz F. Dietary and lifestyle factors in functional dyspepsia. Nat Rev Gastroenterol Hepatol. 2013;10(3):150–7.
15. Boekema PJ, Lo B, Samsom M, Akkermans LMA, Smout AJPM. The effect of coffee on gastric emptying and oro-caecal transit time. Eur J Clin Invest. 2000;30(2):129–34.
16. Fiebich BL, Valente P, Ferrer-Montiel A, Candelario-Jalil E, Menthe J, Luecker P. Effects of coffees before and after special treatment procedure on cell membrane potentials in stomach cells. Methods Find Exp Clin Pharmacol. 2006;28(6):369.
17. Weiss C, Rubach M, Lang R, Seebach E, Blumberg S, Frank O, et al. Measurement of the intracellular ph in human stomach cells: A novel approach to evaluate the gastric acid secretory potential of coffee beverages. J Agric Food Chem. 2010;58(3):1976–85.
18. Lang R, Bardelmeier I, Weiss C, Rubach M, Somoza V, Hofmann T. Quantitation of N-alkanoyl-5-hydroxytryptamides in coffee by means of LC-MS/MS-SIDA and assessment of their gastric acid secretion potential using the HGT-1 cell assay. J Agric Food Chem. 2010;58(3):1593–602.
19. Rubach M, Lang R, Skupin C, Hofmann T, Somoza V. Activity-guided fractionation to characterize a coffee beverage that effectively down-regulates mechanisms of gastric acid secretion as compared to regular coffee. J Agric Food Chem. 2010;58:4153–61.
20. Fredholm BB, Bдttig K, Holmйn J, Nehlig a, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol Rev. 1999;51(1):83–133.
21. Cohen S, Booth GH. Gastric Acid Secretion and Lower-Esophageal-Sphincter Pressure in Response to Coffee and Caffeine. N Engl J Med. 1975;293(18):897–9.
22. Richardson CT, Walsh JH, Cooper KA, Feldman M, Fordtran JS. Studies on the role of cephalic-vagal stimulation in the acid secretory response to eating in normal human subjects. J Clin Invest. 1977;60(August):435–41.
23. Schubert ML. Gastric secretion. Curr Opin Gastroenterol. 2010;26(6):598–603.
24. Liszt KI, Ley JP, Lieder B, Behrens M, Stuger V, Reiner A, et al. Caffeine induces gastric acid secretion via bitter taste signaling in gastric parietal cells. Proc Natl Acad Sci. 2017;114(30):E6260–9.
25. Shimoyama AT, Santin JR, MacHado ID, De Oliveira E Silva AM, De Melo ILP, Mancini-Filho J, et al. Antiulcerogenic activity of chlorogenic acid in different models of gastric ulcer. Naunyn Schmiedebergs Arch Pharmacol. 2013;386(1):5–14.
26. Kang J-W, Lee S-M. Protective Effects of Chlorogenic Acid against Experimental Reflux Esophagitis in Rats. Biomol Ther (Seoul). 2014;22(5):420–5.
27. Rubach M, Lang R, Seebach E, Somoza MM, Hofmann T, Somoza V. Multi-parametric approach to identify coffee components that regulate mechanisms of gastric acid secretion. Mol Nutr Food Res. 2012;56:325–35.
28. Frank O, Zehentbauer G, Hofmann T. Bioresponse-guided decomposition of roast coffee beverage and identification of key bitter taste compounds. Eur Food Res Technol. 2006;222(5–6):492–508.
29. Walker J, Hell J, Liszt KI, Dresel M, Pignitter M,

Hofmann T, et al. Identification of beer bitter acids regulating mechanisms of gastric acid secretion. J Agric Food Chem. 2012;60(6):1405–12.
30. Lisztki, Eder R, Wendelin S, Somoza V. Identification of Catechin, Syringic Acid, and Procyanidin B2 in Wine as Stimulants of Gastric Acid Secretion. J Agric Food Chem. 2015;63(35):7775–83.
31. Farah A, Dos Santos TF. The Coffee Plant and Beans: An Introduction. In: R.Preedy V, editor. Coffee in Health and Disease Prevention. Elsevier; 2014. p. 5–10.
32. Speer K, Zahm A. Sterols and carboxylic acid-5-hydroxytrypt-amides in selected tree nuts. Lipid Technol. 2011;23(6):127–30.
33. Ky CL, Louarn J, Dussert S, Guyot B, Hamon S, Noirot M. Caffeine, trigonelline, chlorogenic acids and sucrose diversity in wild Coffea arabica L. and C. canephora P. accessions. Food Chem. 2001;75:223–30.
34. Farah A, De Paulis T, Trugo LC, Martin PR. Effect of roasting on the formation of chlorogenic acid lactones in coffee. J Agric Food Chem. 2005;53(5):1505–13.
35. Campa C, Doulbeau S, Dussert S, Hamon S, Noirot M. Qualitative relationship between caffeine and chlorogenic acid contents among wild Coffea species. Food Chem. 2005;93:135–9.
36. Vakil N, van Zanten S V., Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus. Am J Gastroenterol. 2006;101(8):1900–20.
37. Kang JY, Tay HH, Yap I, Guan R, Lim KP, Math M V. Low frequency of endoscopic esophagitis in Asian patients. J Clin Gastroenterol. 1993;16(1):70–3.
38. Fedorak RN, Vanner SJ, Paterson WG, Bridges RJ. Canadian Digestive Foundation Public Impact Series 3: Irritable bowel syndrome in Canada. Incidence, prevalence, and direct and indirect economic impact. Can J Gastroenterol. 2012;26(5):252–6.
39. Shimoyama Y, Kusano M, Sugimoto S, Kawamura O, Maeda M, Minashi K, et al. Diagnosis of gastroesophageal reflux disease using a new questionnaire. Journal of Gastroenterology and Hepatology. 2005. p. 643–7.
40. Dent J. Endoscopic grading of reflux oesophagitis: The past, present and future. Best Pract Res Clin Gastroenterol. 2008;22(4):585–99.
41. Kahrilas P, Yadlapati R, Roman S. Emerging dilemmas in the diagnosis and management of gastroesophageal reflux disease. F1000Research. 2017;6(1748):1–10.
42. Cameron AJ, Lagergren J, Henriksson C, Nyren O, Locke GR, Pedersen NL. Gastroesophageal reflux disease in monozygotic and dizygotic twins. Gastroenterology. 2002;122(1):55–9.
43. Chang P, Friedenberg F. Obesity and GERD. Gastroenterology Clinics of North America. 2014.
44. Jung H-K. Epidemiology of gastroesophageal reflux disease in Asia: a systematic review. J Neurogastroenterol Motil. 2011;17(1):14–27.
45. Nandurkar S, Locke GR, Fett S, Zinsmeister AR, Cameron AJ, Talley NJ. Relationship between body mass index, diet, exercise and gastro-oesophageal reflux symptoms in a community. Aliment Pharmacol Ther. 2004;20(5):497–505.
46. Price SF, Smithson KW, Castell DO. Food sensitivity in reflux esophagitis. Gastroenterology. 1978;75(2):240–3.
47. Haruma K, Kinoshita Y, Sakamoto S, Sanada K, Hiroi S, Miwa H. Lifestyle Factors and Efficacy of Lifestyle Interventions in Gastroesophageal Reflux Disease Patients with Functional Dyspepsia: Primary Care Perspectives from the LEGEND Study. Intern Med. 2015;54(7):695–701.
48. Lypez-Colombo A, Pacio-Quiterio MS, Jesьs-Mejenes LY, Rodrнguez-Aguilar JEG, Lypez-Guevara M, Montiel-Jarquнn AJ, et al. Factores de riesgo asociados a recanda de enfermedad por reflujo gastroesof6gico en pacientes de primer nivel de atenciyn exitosamente tratados con inhibidor de la bomba de protones. Rev Gastroenterol Mex. 2017;82(2):106–14.
49. Alkhathami AM, Alzahrani AA, Alzhrani MA, Alsuwat OB, Mahfouz MEM. Risk Factors for Gastroesophageal Reflux Disease in Saudi Arabia. Gastroenterol Res. 2017;10(5):294–300.
50. Murao T, Sakurai K, Mihara S, Marubayashi T, Murakami Y, Sasaki Y. Lifestyle change influences on GERD in Japan: A study of participants in a health examination program. Dig Dis Sci. 2011;56(10):2857–64.
51. Somi MH, Farhang S, Mirinezhad K, Jazayeri E, Nasseri-Moghaddam S, Moayeri S, et al. Prevalence and precipitating factors of gastroesophageal reflux disease in a young population of Tabriz, Northwest of Iran. Saudi Med J. 2006;27(12):1878–81.
52. Dent J, El-Serag HB, Wallander M-A, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2005;54(5):710–7.
53. Park CH, Kim KO, Baek IH, Choi MH, Jang HJ, Kae SH, et al. Differences in the risk factors of reflux esophagitis according to age in Korea. Dis Esophagus. 2014;27(2):116–21.
54. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. American Journal of Gastroenterology. 2005. p. 190–200.
55. Holtmann G, Adam B, Liebregts T. Review article: The patient with gastro-oesophageal reflux disease - Lifestyle advice and medication. Aliment Pharmacol Ther Suppl. 2004;20(8):24–7.
56. El-Serag HB, Richardson P, Pilgrim P, Gilger MA. Determinants of Gastroesophageal Reflux Disease in Adults With a History of Childhood Gastroesophageal Reflux Disease. Clin Gastroenterol Hepatol. 2007;5(6):696–701.

57. Kim J, Oh S-W, Myung S-K, Kwon H, Lee C, Yun JM, et al. Association between coffee intake and gastroesophageal reflux disease: a meta-analysis. Dis Esophagus. 2014;27(4):311–7.
58. Kurata JH, Nogawa AN, Everhart JE. A Prospective Study of Dyspepsia in Primary Care. Dig Dis Sci. 2002;47(4):797–803.
59. Cover TL. Helicobacter pylori diversity and gastric cancer risk. MBio. 2016;7(1):1–9.
60. Bytzer P, Hansen JM o ller, Schaffalitzky de Muckadell OB. Empirical H2-blocker therapy or prompt endoscopy in management of dyspepsia. Lancet. 1994;343(8901):811–6.
61. Robinson M. Proton pump inhibitors: update on their role in acid-related gastrointestinal diseases. Int J Clin Pract. 2005;59(6):709–15.
62. Talley NJ, Vakil N. Guidelines for the Management of Dyspepsia. Am J Gastroenterol. 2005;100(10):2324–37.
63. Eisig JN, Zaterka S, Massuda HK, Bettarello A. Coffee drinking in patients with duodenal ulcer and a control population. Scand J Gastroenterol. 1989;24(7):796–8.
64. Shimamoto T, Yamamichi N, Kodashima S, Takahashi Y, Fujishiro M, Oka M, et al. No Association of Coffee Consumption with Gastric Ulcer, Duodenal Ulcer, Reflux Esophagitis, and Non-Erosive Reflux Disease: A Cross-Sectional Study of 8,013 Healthy Subjects in Japan. PLoS One. 2013;8(6):1–9.
65. Sivaraman D, Yeh H-Y, Mulchandani A, Yates M V., Chen W. Use of Flow Cytometry for Rapid, Quantitative Detection of Poliovirus-Infected Cells via TAT Peptide-Delivered Molecular Beacons. Appl Environ Microbiol. 2012;79(2):696–700.
66. Olthof MR, Hollman PC, Katan MB. Chlorogenic acid and caffeic acid are absorbed in humans. J Nutr. 2001;131(1):66–71.
67. Stalmach A, Steiling H, Williamson G, Crozier A. Bioavailability of chlorogenic acids following acute ingestion of coffee by humans with an ileostomy. Arch Biochem Biophys. 2010;501:98–105.
68. Di Mario F, Goni E. Gastric acid secretion: Changes during a century. Best Pract Res Clin Gastroenterol. 2014;28(6):953–65.
69. Van Deventer G, Kamemoto E, Kuznicki JT, Heckert DC, Schulte MC. Lower esophageal sphincter pressure, acid secretion, and blood gastrin after coffee consumption. Dig Dis Sci. 1992;37(4):558–69.