Intake of Anthocyanins and Gastric Cancer Risk: A Comprehensive Meta-Analysis on Cohort and Case-Control Studies

DeYi YANG1, Xin WANG2, WeiJie YUAN3 and ZiHua CHEN1,*

1Department of General Surgery, Xiangya Hospital, Central South University, #87 Xiangya Road, Changsha, 410008, Hunan Province, China
2Department of General Surgery, Shijitan Hospital of Capital Medical University, Beijing, China
(Received August 1, 2018)

Summary This meta-analysis aimed to explore the association between anthocyanins intake and the risk of gastric cancer. All the relative articles have been searched in the online databases, including PubMed, EMBASE, Web of Science, and the Cochrane Library until June 11th, 2018. Risk ratios (RRs) or odds ratio (ORs) and their 95% confidence intervals were calculated and pooled through the STATA 12.0. A total of 6 studies were finally selected in the meta-analysis. No significant association was found between total anthocyanins consumption and gastric cancer risk (RR=0.92, 95%CI: 0.81–1.04). Likewise, there was also no significant evidence of the relationship between anthocyanins intake and gastric cancer in tumor site (cardia: RR=0.90, 95%CI: 0.62–1.31; noncardia: RR=0.86, 95%CI: 0.69–1.07) and gender (men: RR=1.02, 95%CI: 0.73–1.40; women: RR=0.80, 95%CI: 0.52–1.23). The dose-response relationship was also not found in this meta-analysis. The Grades of Recommendations Assessment, Development and Evaluation (GRADE) quality in our study was very low. The results of our meta-analysis suggested the intake of anthocyanins had no association with the risk of gastric cancer and further studies are needed.

Key Words anthocyanins, stomach cancer, observational studies, meta-analysis

Gastric cancer is one of the most common malignant tumors in the world, ranking the 4th and 5th respectively in men and women with an estimated 951,600 new cases and also the 3rd and 5th lethal cancer cause in men and women with total 723,100 deaths worldwide in 2012 (1). It is also estimated that 26,240 new cases and 10,800 deaths will occur in the US in 2018 (2).

From the middle of the 20th century to the early of the 21st century, the incidence and mortality of gastric cancer has shown a stable decline trend in Europe and in some Asian countries where the incidence of gastric cancer was usually high (3, 4). This decline trend has been supposed to be related to several elements, such as diet, life style, and control of Helicobacter pylori infection, etc. Among those elements, eradication of Helicobacter pylori (H. pylori) and the change of diet habit and structure may play an important role (5, 6). For instance, several randomized controlled trials in Japan and some meta-analysis of RCTs revealed the effectiveness of prevention of gastric cancer by eradicating H. pylori (6). Additionally, intake of vitamin C, which is common in fruits and vegetables, has been reported to be inversely associated with gastric cancer risk in Europeans (7).

Besides vitamin C, other natural compounds also have bioactivities like polyphenols, flavonoids, anthocyanins and resveratrol, etc. (8, 9). With the increasing focus on plant-derived polyphenols, anthocyanins have been brought into the wide concern because of their potential benefits for human health (10). Anthocyanins, a subgroup of flavonoids, are a kind of water-soluble pigment and occur abundantly in fruits and vegetables, especially blueberries, sweet cherries, black currants, raspberries, strawberries, and red grapes, etc. (10, 11). Anthocyanins can be further divided into 17 types, only 6 of which are widely distributed including cyanidin, delphinidin, petunidin, peonidin, pelargonidin and malvidin (12).

Anthocyanins have a basic chemical structure named 2-phenylbenzopyrylium that has a strong capacity of donating electrons, which contributes to their antioxidant benefits (10, 13). It has been reported that anthocyanins have multiple chemopreventive and chemotherapeutic functions, such as anti-diabetic, cardioprotective, hepatoprotective, neuroprotective activities, and even anti-carcinogenic effects, especially in lung cancer, colon cancer, prostate cancer and esophageal cancer (14). Some in vivo studies in animals showed the inhibitory effect of anthocyanins on the skin cancer (15). Furthermore, there were also in vitro studies that illustrated anthocyanins could inhibit gastric cancer via antioxidant or anti-inflammation (16), induction of apoptosis (17), and blockage of cell cycle (18).

However, the association between anthocyanins intake and gastric cancer lacked sufficient epidemiological evidence to support, and the conclusions of several epidemiological studies which had been conducted in human beings did not appear completely consistent (19–21). Therefore, this meta-analysis aimed to system-
Anthocyanins and Gastric Cancer: Meta-Analysis

1. **Subjects and Methods**
   
   **Search strategy.** Our study was guided by the checklist of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (22). We performed a systematic literature search in several online databases, including PubMed, EMBASE, Web of Science and the Cochrane Library from up to June 11, 2018.

   The following searching strategy was: (anthocyanins OR anthocyanin OR anthocyanidins OR anthocyanidin OR cyanidin) AND (gastric OR stomach) AND (cancer OR carcinoma OR tumor OR neoplasm OR adenocarcinoma). Only articles having been published in English were included in our search range. We also reviewed reference lists from all included articles to identify any additional literature.

   **Study selection.** Eligible studies were included in the meta-analysis according to the following criteria: (1) reviews, animal or cell studies were excluded; (2) only case-control and cohort studies were included; (3) the exposure of interest was anthocyanin consumption with the outcome of gastric cancer; (4) odds ratio (ORs) or relative risks (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs) should be reported in the articles.

   **Data extraction.** The following data were extracted from each identified study by two authors (DeYi Yang and Xin Wang): the study design; last name of the first author; publication year; study location; participant characteristics; sex; age at baseline; number of cases or controls (participants for cohort studies); study period; multivariate adjusted RRs (ORs for case-control studies) with 95%CIs for each category of anthocyanin consumption, and confounders.

   **Quality assessment of study and evidence.** A 9-star system based on the Newcastle-Ottawa Quality Assessment Scale (NOQAS) was employed for quality assessment by two reviewers (DeYi Yang and Xin Wang) independently. In this system, four stars were allocated to the selection of study participants, two stars were allocated to the comparability of studies based on the design or analysis, and three stars were allocated to the evaluation of exposure in case-control studies or the ascertainment of outcomes in cohort studies. More than 6 stars can be regarded as high quality. Two reviewers (DeYi...
Table 1. Characteristics of 6 studies on anthocyanins intake and the risk of gastric cancer.

| Reference | Country and age | Design and sample size | Object or subgroup | OR or HR or RR (95%CI) | Measure of intake | Adjustments |
|-----------|-----------------|------------------------|--------------------|------------------------|-------------------|-------------|
| Lagiou, P. 2004 | Greece 60–65 y | Case-control 110 : 100 | | 1.14 (0.72–1.80) | Per 40.4 mg/d | age, gender, place of birth, body mass index, height, years of education, smoking habits and duration of smoking, alcohol consumption, total energy intake, fruit and vegetable consumption |
| Petrick, J. L. 2015 | America 30–79 y | Case-control GCA, 248 OGA, 341 Controls, 662 | Gastric cardia adenocarcinoma (GCA) | 1.00 | 0–7.21 mg/d | age (continuous), sex, race (white, other), geographic centre (Connecticut, New Jersey, Washington), cigarette smoking (ever/never), and dietary energy intake (kilocalories, continuous) |
| | | | | 0.98 (0.65–1.47) | | |
| | | | | 0.91 (0.60–1.38) | | |
| | | | | 0.71 (0.46–1.10) | | |
| | | | | 1.00 | | |
| | | | | 0.91 (0.63–1.32) | | |
| | | | | 0.89 (0.61–1.29) | | |
| | | | | 0.70 (0.47–1.03) | | |
| Rossi, M. 2010 | Italy 22–80 y | Case-control 230 : 547 | | 1.00 | 0–6.2 mg | sex, age, education, year of interview, body mass index, tobacco smoking, and total energy intake according to the residual model |
| | | | | 0.89 (0.55–1.45) | | |
| | | | | 0.78 (0.47–1.28) | | |
| | | | | 0.53 (0.31–0.91) | | |
| | | | | 0.91 (0.56–1.47) | | |
| Sun, L. 2017 | America <80 y | Cohort 12-y follow-up 469,008 1,297 gastric (625 cardia and 672 non-cardia) cancer | Cardia | 0.81–1.35 | 0–3.8 mg/d | age at baseline, sex, race, education, smoking status, BMI, alcohol intake, self-reported health, vigorous physical activity of ≥20 min, and total energy intake |
| | | | | 0.97 (0.74–1.27) | 3.9–7.0 |
| | | | | 0.99 (0.75–1.31) | 7.1–11.7 |
| | | | | 1.05 (0.80–1.39) | 11.8–20.6 |
| | | | | 1.00 | 20.7–376.6 |
| | | Noncardia | 0.91 (0.71–1.17) | 3.9–7.0 |
| | | | 0.84 (0.65–1.10) | 7.1–11.7 |
| | | | 0.84 (0.64–1.10) | 11.8–20.6 |
| | | | 0.94 (0.72–1.23) | 20.7–376.6 |
| Woo, H. D. 2014 | Korea 35–75 y | Case-control All 334 : 334 | | 1.00 | 9.4 | total energy intake, H. pylori, age, sex, education, smoking status, alcohol consumption, BMI, physical activity, and consumption of pickled vegetable and red and processed meat, fruits and vegetable consumption |
| | | | | 0.86 (0.54–1.35) | 14.7 |
| | | | | 1.06 (0.62–1.80) | 35.1 |
| | | | | 1.00 | 9.4 |
| | | | | 1.01 (0.55–1.83) | 14.7 |
| | | | | 1.16 (0.57–2.34) | 35.1 |
| | | Women | 0.80 (0.37–1.76) | 14.7 |
| | | | 1.22 (0.49–3.01) | 35.1 |
| Zamora-Ros, R. 2012 | Europe 35–70 y | Cohort 11 y 477,312 683 | Men | 1.00 | <11.7 | age, educational level, smoking status, physical activity, BMI, alcohol and energy intake, and daily consumption of fruit, vegetables, and red and processed meat |
| | | | 1.14 (0.86–1.51) | 11.7–20.3 |
| | | | 0.94 (0.69–1.29) | 20.4–32.8 |
| | | | 0.98 (0.68–1.41) | >32.8 |
| | | Women | 1.00 | <13.9 |
| | | | 0.69 (0.50–0.95) | 13.9–23.6 |
| | | | 0.79 (0.55–1.14) | 23.7–38.7 |
| | | | 0.71 (0.44–1.16) | >38.7 |
Yang and Xin Wang) evaluated the quality of evidence using the GRADE system (23) (GRADE profiler 3.6.1). In this system, the level of an observational study, which is initially regarded as low-quality, could be upgraded for three reasons: a large effect, the presentation of a dose-response gradient, and plausible confounders that would not decrease an apparent treatment effect and could also be downgraded for five reasons: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The evidence grades can be divided into four levels: 1) high, which indicates that further research is unlikely to alter the confidence in the effect estimate; 2) moderate, which indicates that further research is likely to significantly alter confidence in the effect estimate and may change the estimate; 3) low, which indicates that further research is likely to significantly alter confidence in the effect estimate and to change the estimate; and 4) very low, which indicates that any effect estimate is uncertain.

Statistical analysis. Because the incidence of gastric cancer is low (1), the ORs can be approximately equal to the RRs (24). Thus, all results were reported as RRs simply.

First, we pooled the adjusted RRs/ORs with 95% CIs of gastric cancer by comparing the highest and lowest categories of anthocyanins intake and displayed the pooled RRs/ORs with 95% CIs of different subgroups. For the dose-response meta-analysis, we used the “generalized least squares for trend estimation” method provided by Greenland and Longnecker (25) to evaluate the association between log RR and the exposures.

Based on the rescaling methods of previous dose-response meta-analyses, the upper and lower boundary of anthocyanins intake was transformed into the median or mean values per category. We then assessed the heterogeneity among studies by using the Q test ($p<0.05$) (26). The Higgins $I^2$ statistic (27) was also examined. $I^2$ value $>50\%$ and $75\%$ respectively means
substantial heterogeneity and high heterogeneity existed in the trials. A random-effects model was used when significant heterogeneity was detected \( (28) \); otherwise, a fixed-effects model was preferred. We created funnel plots \( (29) \) and the Begg’s rank correlation test \( (30) \) or Egger’s regression test \( (31) \) to detect publication bias \( (p<0.10) \) \( (32) \). We carried out a sensitivity analysis to exclude one large study that tended to dominate the results. We also carried out subgroup analyses to examine potential sources of heterogeneity by sex, study design and tumor site.

All statistical analyses were performed with the STATA 12.0 statistical software package (Stata Corporation, College Station, Texas, USA). A threshold of \( p<0.05 \) was considered significant without anything special.

RESULTS

The process to screen and select the studies has been summarized in Fig. 1. Finally, a total of 6 studies were identified to evaluate the effects of anthocyanins on gastric cancer. The general features of the total 6 studies have been listed in Table 1, of which 4 studies are case-control studies \( (21, 33–35) \) and 2 are cohort studies \( (36, 37) \). The NOQAS ranged from 6 to 9, with a mean of 7.17 stars (Table 2).

Nine sets of data were included in the analysis, and no significant heterogeneity existed among the pooled results \( (p \text{ for heterogeneity}=0.597, I^2=0.00\%) \). However, the association was not significant (combined RR: 0.92, 95%CI: 0.81–1.04) (Fig. 2).

According to the study design, we separately analyzed cohort studies \( (RR=0.95, 95\%CI: 0.81–1.12, p \text{ for heterogeneity}=0.589, I^2=0.0\%) \) and case-control studies \( (OR=0.86, 95\%CI: 0.70–1.05, p \text{ for heterogeneity}=0.420, I^2=0.0\%) \); males \( (RR=1.02, 95\%CI: 0.73–1.40, p \text{ for heterogeneity}=0.678, I^2=0.0\%) \) and females \( (RR=0.80, 95\%CI: 0.52–1.23, p \text{ for heterogeneity}=0.302, I^2=6.0\%) \); cardia \( (RR=0.90, 95\%CI: 0.62–1.31, p \text{ for heterogeneity}=0.137, I^2=54.7\%) \) and noncardia \( (RR=0.86, 95\%CI: 0.69–1.07, p \text{ for heterogeneity}=0.224, I^2=32.4\%) \). We did not identify significant associations between anthocyanins intake and gastric cancer risk in these subgroups (Fig. 3).

The incidence of gastric cancer and anthocyanins intake did not exhibit dose-response relationships in the nonlinear \( (p=0.620; p \text{ for heterogeneity}=0.85, Q=16.12) \) and linear \( (1 \text{ mg/d intake of anthocyanins RR}=1.000, 95\%CI: 0.999–1.001; p \text{ for heterogeneity}=0.55, Q=23.41) \) dose-response analysis.

There was not obvious publication bias examined by either Egger’s test \( (p=0.425) \) or Begg’s test \( (p=0.917) \) (Fig. 4). The sensitivity analysis that was made by excluding one study at a time also showed a combined RR: 0.88, 95%CI: 0.76–0.99 and no obvious change.
of the overall RR for gastric cancer ranging from 0.85 (95% CI: 0.72–0.97) when excluding Sun et al. (cardia) (36) to 0.92 (95% CI: 0.79–1.04) when excluding Petrick et al. (noncardia) (33) (Fig. 5).

DISCUSSION

This meta-analysis of 2 cohort studies and 4 case-control studies including 949,226 members (patients and controls) suggested no significant association between anthocyanins intake and gastric cancer risk with no substantial heterogeneity. Furthermore, the subgroup analysis of gender and tumor site (cardia and noncardia) and even the linear and nonlinear dose-response analysis were also found no significant evidence.

Mechanisms

Anthocyanins and anthocyanidins are both subgroups of flavonoids. The basic chemical structure of anthocyanins is 2-phenylbenzopyrylium, also known as flavylium, which consists of two aromatic rings, respectively A and B, and an heterocyclic ring C containing oxygen between them. In fact, anthocyanins occur as the glycosides of polyhydroxy or polymethoxy derivatives of 2-phenylbenzopyrylium and their glycosides of the respective aglycones of anthocyanins are the anthocyanidins (10, 38, 39).

As is mentioned above, gastric cancer is in direct proportion to infection of H. pylori (6), so the effects or mechanisms aiming at eradicating H. pylori may arouse wide concern. The gastric carcinogenesis of H. pylori may be related to oxidative stress, cytotoxin-associated gene A (CagA), and cancer stem cells (CD44 + cells), etc. (40).

On the one hand, reactive oxygen species (ROS) is a high risk factor of carcinogenesis because it can cause the mutation and damage of DNA (41). The infection of H. pylori can cause chemotaxis and activation of neutrophils and the neutrophils can produce the hypochlorous anion (OCl −) that can react with the ammonia (NH3), which is produced from urea by H. pylori associated urease, to yield monochloramine (NH2 Cl), that can freely penetrate biological membranes to make intracellular components oxidized or make nucleic acids mutated (42, 43). And due to the chemical structure and properties, anthocyanins appear a capability of antioxidant (13), which can just deal with the injury of ROS. Kim et al. (16) has proved that anthocyanins from black soybean could reduce ROS generation induced by H. pylori in gastric epithelial cells. Additionally, Braunlich et al. (44) also showed anthocyanins and their derivatives could scavenge diphenylpicrylhydrazyl (DPPH) radical and inhibit 15-lipoxygenase and xanthine oxidase, which are also the sources of ROS (45, 46).

On the other hand, the CagA protein of H. pylori can be translocated into host gastric epithelial cells through type IV secretion system and then can induce gastric carcinogenesis by binding Src homology 2-containing protein tyrosine phosphatase (SHP-2) and activating the ERK-MAPK pathway (40). Moreover, chronic inflammation caused by infection of H. pylori in gastric epithelial cells can induce the expression of CD44, a cell surface marker associated with cancer stem cells (47, 48). And in these CD44-positive gastric cancer stem-like cells, it has been reported by Tsugawa et al. (47) that the autophagy of CagA, which can be induced by ROS, could be decreased by suppressing the accumulation of ROS via elevating intracellular glutathione (GSH) levels, in which case CagA maintains a relatively high level in the CD44-positive cells and can lead to their carcinogenesis more easily. Under these circumstances, anthocyanins have also been reported to have anti-microbial and anti-cancer effects. Kim et al. (49) has reported that cyanidin 3-O-glucoside (C3G), a kind of anthocyanins, could prevent secretion of CagA produced by H. pylori via suppressing the transcription of secA, a cytoplasmic protein that can assist the ATP-driven translocation of bacteria proteins out of the bacterial plasma membrane (50).

Besides, the tumor-suppressing effect of anthocyanins can also be seen in other pathways, such as interfering with cell cycle or inducing apoptosis. Wang et al. (18)
showed the proliferation of gastric cancer cells can be inhibited by a kind of anthocyanins, through upregulating the expression of the KLF6 gene, a novel tumor suppressor gene (51), which can increase the expression of p21 and decrease the expression of CDK4 and Cyclin D1 in a p53-independent manner. Moreover, there were also studies that showed the cellular apoptosis can be induced by anthocyanins through p38/p53 and p38/c-jun signaling pathways intrinsically and extrinsically or through caspase-3 related mitochondrial-mediated pathways (52).

However, anthocyanins did not decrease the incidence of gastric cancer in our study. And Woo et al. (21) also reported that there was no significant evidence that showed dietary anthocyanins could reduce H. pylori-positive gastric cancer both in men and women. As for H. pylori-negative subjects, the protective effects of anthocyanins on gastric cancer only in women was detected. Therefore, this inconsistency between in vitro studies and epidemiological studies needs explanations. First, the concentration of anthocyanins differs significantly between in vivo and in vitro because of the first-pass effect. Statistically, the study reported that the max plasma levels of total anthocyanins range from 1 to 100 nmol/L after having fruits in human bodies (12); however, the concentration of anthocyanins used on AGS cells in some studies can be up to dozens or hundreds micromole (17). So, the laboratory data of anthocyanins could not reflect the true concentration in human bodies. Second, the design of epidemiological studies could also underestimate the amount of intake of anthocyanins itself because of missing or insufficient data of food composition (53), not specific and comprehensive questionnaires for anthocyanins study (54, 55). Moreover, some other factors might also cause the ambiguity of the results such as the inter-individual variations in absorption and metabolism of anthocyanins (56) and dietary modification during the early pre-diagnostic period of the disease (37), etc. Finally, other elements including pH of gastric acid (57), different stability in different part of intestinal tract (10), vitamin C, salt contents of the food, gender, smoking status (21) may also account for this inconsistency. After all, humans are different from animals, so we could not depend on animal or cell studies totally and further well-designed studies should be needed.

Strengths and limitations of this review

The meta-analysis has several strengths. First, our study was the first to analyze the linear and nonlinear dose-response effects of anthocyanins on gastric cancer and also further analyzed the relatively comprehensive subgroups of the included studies. Second, the negative publication bias and sensitivity analysis both guarantee the confidence and reliability of the results. Third, the quality of studies finally identified in our study was high according to the Newcastle-Ottawa Quality Assessment Scale. Nearly all the studies considered the confounding factors such as age, sex, race, dietary energy intake, and smoking status, etc. and we chose the adjusted OR/RRs instead of the crude ones to avoid the possible interfer-
ance. Finally, we only take anthocyanins or anthocyani-
dins or their subclasses into account instead of fruits, 
vegetables or some other substances containing antho-
cyanins, in which case some variations and bias may be 
controlled and the confidence and consistency of our 
results may be strengthened to some degree.

However, some limitations were also notable in our 
study (Table 3). First, the weakest point of our study is 
the limited number of included studies. Only 6 studies 
might weaken persuasive power of our results. Similarly, 
the limited number of studies also confined the sufficient 
accessible data to make more subgroup analysis and 
more accurate dose-response analysis. Second, the esti-
mation of anthocyanins intake may produce bias. All 
the studies evaluated the intake of anthocyanins using 
the USDA database, which mainly collected data on 
American regions (33); however, the content of antho-
cyanins can be influenced by multiple variates, such as 
ripeness, climatic factors, culture types, and storage 
(58). Therefore, the data collected by different studies in 
different regions may be deviated from the true condi-
tion. Finally, there were also other remaining confound-
ing factors that could not be included although all the 
studies controlled the majority of them, which can also 
lead to bias of the overall results.

Furthermore, more studies should be conducted to 
investigate the relationship between the plasma con-
centrations of anthocyanins and gastric cancer because 
FFQs (food frequency questionnaires) which were adopted 
in all the studies could not assess the true concentrations 
in human bodies. In fact, it is the anthocya-
nins in blood or tissues that play an important role after 
absorption, metabolism, and distribution (58), and differ 
from person to person, so biomarkers are becoming the 
hot issue because they can better and more objectively 
reflect individual exposure to the targeted substances 
(59). Therefore, more epidemiological studies and more 
comprehensive and detailed designs should be needed in 
the future.

CONCLUSIONS

In summary, our meta-analysis indicated no associa-
tion between the intake of anthocyanins and the risk of 
gastric cancer. Also, no significant relationship was 
found in gender and tumor site. Therefore, further stud-
ies with better designs and more accurate measurement 
methods should be made to explore the true value and 
effects of anthocyanins on gastric tumor.

Author contributions

DeYi Yang and his advisor Professor Chen are respon-
sible for the study design, literature search, systematic 
review, data collection or analysis, the decision to pub-
lish, and manuscript preparation. Dr. Wang helped con-
duct the dose-response meta-analyses with the STATA 
program and gave meaningful suggestions. Dr. Yuan 
helped revise the manuscript and provided valuable advice. All authors made joint efforts to ensure that the 
final version of this study was reliable and integrated. 
DeYi Yang serves as a guarantor.

REFERENCES

1) Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, 
Jemal A. 2015. Global cancer statistics, 2012. CA Cancer 
J Clin 65: 87–108.

2) Siegel RL, Miller KD, Jemal A. 2018. Cancer statistics, 
2018. CA Cancer J Clin 68: 7–30.

3) Malvezzi M, Bonifazi M, Bertuccio P, Levi F, La Vecchia 
C, Decarli A, Negri E. 2010. An age-period-cohort analy-
sis of gastric cancer mortality from 1950 to 2007 in 
Europe. Ann Epidemiol 20: 898–905.

4) Bertuccio P, Chatenoud L, Levi F, Praud D, Ferlay J, Negri 
E, Malvezzi M, La Vecchia C. 2009. Recent patterns in 
gastric cancer: a global overview. Int J Cancer 125: 
666–673.

5) Yusuf AR, Bagheri Lankarani K, Bastani P, Radimaneesh 
M, Kavosi Z. 2018. Risk factors for gastric cancer: a systematic review. Asian Pac J Cancer Prev 19: 
591–603.

6) Suzuki H, Mori H. 2018. World trends for H. pylori erad-
ication therapy and gastric cancer prevention strategy by 
H. pylori test-and-treat. J Gastroenterol 53: 354–361.

7) Jemal M, Riboli E, Ferrari P, Subate J, Slimani N, Norat T, 
Friesen M, Tjonneland A, Olsen A, Overvad K, Broutron- 
Ruault MC, Clavel-Chapelon F, Touvier M, Boeing H, 
Schulze M, Linseisen J, Nagel G, Trichopoulou A, Naska 
A, Oikonomou E, Krogh V, Panico S, Masala G, Sacerdote 
C, Tumino R, Peeters PH, Nuemes M, Bueno-de-Mes-
quita HB, Buchner FL, Lund E, Pera G, Sanchez CN, San-
chez MJ, Arriola L, Barricarte A, Quiros JR, Hallmans 
G, Stenling R, Berglund G, Bingham S, Khaw KT, Key 
T, Allen N, Carneiro F, Mahlke U, De Giudice G, Palli D, 
Kaaks R, Gonzalez CA. 2006. Plasma and dietary vita-
min C levels and risk of gastric cancer in the European Prospective Investigation into Cancer and Nutrition 
(EPIC-EURGAST). Carcinogenesis 27: 2250–2257.

8) Kristo AS, Klimis-Zacas D, Sikalidis AK. 2016. Protective 
role of dietary berries in cancer. Antioxidants 5: 37.

9) Guerrero RF, Garcia-Parrilla MC, Puertas B, Cantos-Vil-
lar E. 2009. Wine, resveratrol and health: A review. Nat 
Prod Commun 4: 635–658.

10) Fang J. 2014. Bioavailability of anthocyanins. Drug 
Metab Rev 46: 508–520.

11) Wu X, Beecher GR, Holden JM, Haytowitz DB, Geb-
hardt SE, Prior RL. 2006. Concentrations of antho-
cyanins in common foods in the United States and esti-
mation of normal consumption. J Agric Food Chem 54: 
4069–4075.

12) Prior RL, Wu X. 2006. Anthocyanins: structural char-
acteristics that result in unique metabolic patterns and 
biological activities. Free Radic Res 40: 1014–1028.

13) Ali HM, Almagribi W, Al-Rashidi MN. 2016. Antiradical 
and reductive activities of anthocyanidins and antho-
cyanins, structure-activity relationship and synthesis. 
Food Chem 194: 1275–1282.

14) Putta S, Yarla NS, Peluso I, Tiwari DK, Reddy GV, Giri 
PV, Kuman N, Mallia R, Rachel V, Brammehachi PV, Reddy 
DR, Bade R, Mannaraput M, Barreto GE, Lu DY, Tarasov 
VV, Chubarev VN, Ribeiro FF, Scotti L, Scotti MT, Kamal 
MA, Ashraf GM, Aliev G, Perry G, Sarker SD, Rao CV, 
Bade R, Mannaraput M, Barreto GE, Lu DY, Tarasov 
VV, Chubarev VN, Ribeiro FF, Scotti L, Scotti MT, Kamal 
MA, Ashraf GM, Aliev G, Perry G, Sarker SD, Rao CV, 
Bade R, Mannaraput M, Barreto GE, Lu DY, Tarasov 
VV, Chubarev VN, Ribeiro FF, Scotti L, Scotti MT, Kamal 
MA, Ashraf GM, Aliev G, Perry G, Sarker SD, Rao CV, 
Bade R, Mannaraput M, Barreto GE, Lu DY, Tarasov 
VV, Chubarev VN, Ribeiro FF, Scotti L, Scotti MT, Kamal 
MA, Ashraf GM, Aliev G, Perry G, Sarker SD, Rao CV, 
Bade R, Mannaraput M, Barreto GE, Lu DY, Tarasov 
VV, Chubarev VN, Ribeiro FF, Scotti L, Scotti MT, Kamal 
MA, Ashraf GM, Aliev G, Perry G, Sarker SD, Rao CV, 
Bade R, Mannaraput M, Barreto GE, Lu DY, Tarasov 
VV, Chubarev VN, Ribeiro FF, Scotti L, Scotti MT, Kamal 
MA, Ashraf GM, Aliev G, Perry G, Sarker SD, Rao CV, 
Bade R, Mannaraput M, Barreto GE, Lu DY, Tarasov 
VV, Chubarev VN, Ribeiro FF, Scotti L, Scotti MT, Kamal 
MA, Ashraf GM, Aliev G, Perry G, Sarker SD, Rao CV, 
Bade R, Mannaraput M, Barreto GE, Lu DY, Tarasov 
VV, Chubarev VN, Ribeiro FF, Scotti L, Scotti MT, Kamal 
MA, Ashraf GM, Aliev G, Perry G, Sarker SD, Rao CV, 
Bade R, Mannaraput M, Barreto GE, Lu DY, Tarasov 
VV, Chubarev VN, Ribeiro FF, Scotti L, Scotti MT, Kamal 
MA, Ashraf GM, Aliev G, Perry G, Sarker SD, Rao CV, 
Bade R, Mannaraput M, Barreto GE, Lu DY, Tarasov 
VV, Chubarev VN, Ribeiro FF, Scotti L, Scotti MT, Kamal 
MA, Ashraf GM, Aliev G, Perry G, Sarker SD, Rao CV, 
badd
17) Shih PH, Yeh CT, Yen GC. 2005. Effects of anthocyanins on the inhibition of proliferation and induction of apoptosis in human gastric adenocarcinoma cells. *Food Chem Toxicol* **43**: 1557–1566.

18) Wang Y, Zhang X-n, Xie W-h, Zheng Y-x, Cao J-p, Cao P-r, Chen Q-j, Li X. Sun C-d. 2016. The growth of SGC-7901 tumor xenografts was suppressed by Chinese bayberry anthocyanin extract through upregulating KLF6 gene expression. *Nutrients* **8**: 599.

19) Grosso G, Godos J, Lamuela-Raventos R, Ray S, Micek A, Pajak A, Sciaccia S, D’Oranzio N, Del Rio D, Galvano F. 2017. A comprehensive meta-analysis on dietary flavonoid and lignan intake and cancer risk: Level of evidence and limitations. *Mol Nutr Food Res* **61**.

20) Woo HD, Kim J. 2013. Dietary flavonoid intake and risk of stomach and colorectal cancer. *World J Gastroenterol* **19**: 1011–1019.

21) Woo HD, Lee J, Choi IJ, Kim CG, Lee JY, Kwon O, Kim J. 2014. Dietary flavonoids and gastric cancer risk in a Korean population. *Nutrients* **6**: 4961–4973.

22) Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting, Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **283**: 2008–2012.

23) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Glasziou P, Green S, Henry D, Elurrieta P, Iglesias-Olmedo I, Jørgensen PJ, Khan M, Kralj-Hanser A, Lohr KN, M spoiler D, Nishimori I, Oxman AD, Phillips B, Schunemann HJ, Tugwell P, Vist GE, Williams JW Jr. 2011. Grading quality of evidence and strength of recommendations. *BMJ* **328**: 1490.

24) Greenland S. 1987. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev* **9**: 1–30.

25) Greenland S, Longnecker MP. 1992. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* **135**: 1301–1309.

26) DerSimonian R, Laird N. 1986. Meta-analysis in clinical trials. *Control Clin Trials* **7**: 177–188.

27) Higgins JP, Thompson SG, Deeks JJ, Altman DG. 2003. Measuring inconsistency in meta-analyses. *BMJ* **327**: 557–560.

28) Hardy RJ, Thompson SG. 1998. Detecting and describing heterogeneity in meta-analysis. *Stat Med* **17**: 841–856.

29) Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. 2008. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* **61**: 991–996.

30) Begg CB, Mazumdar M. 1994. Operating characteristics of a rank correlation test for publication bias. *Biometrics* **50**: 1088–1101.

31) Egger M, Davey Smith G, Schneider M, Minder C. 1997. Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**: 629–634.

32) Zhou JG, Tian X, Wang X, Tian JH, Wang Y, Wang F, Zhang Y, Ma H. 2015. Treatment on advanced NSCLC: platinum-based chemotherapy plus erlotinib or platinumbased chemotherapy alone? A systematic review and meta-analysis of randomised controlled trials. *Mod Oncol* **32**: 471.

33) Petrick JL, Steck SE, Bradshaw PT, Trivers KE, Abrahamson PE, Engel LS, He K, Chow WH, Mayne ST, Risch HA, Vaughan TL, Gammon MD. 2015. Dietary intake of flavonoids and oesophageal and gastric cancer: incidence and survival in the United States of America (USA). *Br J Cancer* **112**: 1291–1300.

34) Rossi M, Rosato V, Bosetti C, Lagiou P, Parpinel M, Bertuccio P, Negri E, La Vecchia C. 2010. Flavonoids, proanthocyanidins, and the risk of stomach cancer. *Cancer Causes Control* **21**: 1597–1604.

35) Lagiou P, Samoli E, Lagiou A, Peterson J, Tzonou A, Dwyer J, Trichopoulou D. 2004. Flavonoids, vitamins C and adenoscinoma of the stomach. *Cancer Causes Control* **15**: 67–72.

36) Sun L, Subiar AF, Bosire C, Dawsey SM, Kahle LL, Zimmern TP, Ahnert CC, Heller R, Graubard BI, Cook MB, Petrick JL. 2017. Dietary flavonoid intake reduces the risk of head and neck but not esophageal or gastric cancer in us men and women. *J Nutr* **147**: 1729–1738.

37) Zamora-Ros R, Agudo A, Lujan-Barroso L, Romieu I, Ferrari P, Kneaze V, Bueno-de-Mesquita HB, Leenders M, Travis RC, Navarro C, Sanchez-Cantalejo E, Slimani N, Scalbert A, Fedirko V, Hjaltaker A, Engeset D, Skeie G, Boeing H, Forster J, Li K, Teucher B, Agnoli C, Tumino R, Mattiello A, Saieva C, Johansson I, Sterling R, Redondo ML, Wallstrom P, Ericson U, Khaw KT, Mulligan AA, Trichopoulou A, Dils V, Katsoulis M, Peeters PH, Igali L, Tjonneland A, Halkjaer J, Touilaud M, Perquier F, Faghfrazz G, Amiano P, Ardanaz E, Bredsdorff L, Overvard K, Rici T, Riboli E, Gonzalez CA. 2012. Dietary flavonoid and lignan intake and gastric adenocarcinoma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Am J Clin Nutr* **96**: 1398–1408.

38) Kamiohlu S, Capanoglu E, Grootaert C, Vann Camp J. 2015. Anthocyanin absorption and metabolism by human intestinal Caco-2 cells—A review. *Int J Mol Sci* **16**: 21555–21574.

39) Ignat I, Voit I, Popa VI. 2011. A critical review of methods for characterisation of polyphenolic compounds in fruits and vegetables. *Food Chem* **126**: 1821–1835.

40) Nishizawa T, Suzuki H. 2015. Gastric carcinogenesis and underlying molecular mechanisms: Helicobacter pylori and novel targeted therapy. *Biomed Res Int* **2015**: 794378.

41) Meira LB, Bugnj MJ, Green SL, Lee CW, Pang B, Borenstein D, Rickman BH, Rogers AB, Morosiski-Erkul CA, McFalone JL, Schauer DB, Dedon PC, Fox JG, Samson LD. 2008. DNA damage induced by chronic inflammation contributes to colon carcinogenesis in mice. *J Clin Invest* **118**: 2516–2525.

42) Suzuki H, Nishizawa T, Tsugawa H, Mogami S, Hibi T. 2012. Roles of oxidative stress in stomach disorders. *J Clin Biochem Nutr* **50**: 35–39.

43) Suzuki M, Miura S, Suematsu M, Fukushima D, Kurose I, Suzuki H, Kao A, Kodoh Y, Ohashi M, Tsuchiya M. 1992. Helicobacter pylori-associated ammonia production enhances neutrophil-dependent gastric mucosal cell injury. *Am J Physiol* **263**: G719–725.

44) Braunlich M, Slimestad R, Wangensteen H, Brede C, Malterud KE, Barsett H. 2013. Extracts, anthocyanins and proanthocyanidins from Aronia melanocarpa as radical scavengers and enzyme inhibitors. *Nutrients* **5**:...
Anthocyanins and Gastric Cancer: Meta-Analysis

663–678.

45) Dobrian AD, Lieb DC, Cole BK, Taylor-Fishwick DA, Chakrabarti SK, Nadler JL. 2011. Functional and pathological roles of the 12- and 15-lipoxygenases. *Prog Lipid Res* **50**:115–131.

46) Pacher P, Nivorozhkin A, Szabo C. 2006. Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol. *Pharmacol Rev* **58**:87–114.

47) Tsuchiya H, Suzuki H, Saya H, Hatakeyama M, Hirayama T, Hirata K, Nagano O, Matsuzaki J, Hibi T. 2012. Reactive oxygen species-induced autophagic degradation of Helicobacter pylori CagA is specifically suppressed in cancer stem-like cells. *Cell Host Microbe* **12**:764–777.

48) Ishimoto T, Oshima H, Oshima M, Kai K, Torii R, Masuko T, Baba H, Saya H, Nagano O. 2010. CD44 slow-cycling tumor cell expansion is triggered by cooperative actions of Wnt and prostaglandin E2 in gastric tumorigenesis. *Cancer Sci* **101**:673–678.

49) Narla G, Heath KE, Reeves HL, Li D, Giono LE, Kimmelman AC, Glucksman MJ, Narla J, Eng FJ, Chan AM, Ferrari AC, Martignetti JA, Friedman SL. 2001. KLF6, a candidate tumor suppressor gene mutated in prostate cancer. *Science* **294**:2563–2566.

50) D'Archivio M, Filesi C, Di Benedetto R, Gargiulo R, Giovannini C, Masella R. 2007. Polyphenols, dietary sources and bioavailability. *Ann Ist Super Sanita* **43**:348–361.

51) Zamora-Ros R, Touillaud M, Rothwell JA, Romieu I, Scalbert A. 2014. Measuring exposure to the polyphenol metabolome in observational epidemiologic studies: current tools and applications and their limits. *Am J Clin Nutr* **100**:11–26.