Investigating the effect of herbal antioxidants on the process of colon cancer treatment: A systematic review

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Naser Mohammad gholi Mezerji1, Abbas Moghimbeigi2*, Mostafa Eghbalian1 and Mahmoud Rafieian Kopaee3

Abstract: This study is a systematic review conducted in July, 2017. Related studies were searched in scientific databases of Biomed central, PubMed, Sciencedirect, Science of the Web, and Scopus according to the search method of Cochrane with related keywords since the creation of the desired databases. Among the studies, 4 studies did not achieve any of the outcomes, two studies had achieved all the desired outcomes and one study achieved some of the outcomes. Although, the use of antioxidants has reduced the risk of cancer or improved the patient’s condition in all the studies, these effects are not statistically significant generally.

Subjects: Bioscience; Cancer; Colorectal Surgery;

Keywords: Herbal antioxidant; colon cancer; polyp; systematic review

1. Background

Colorectal cancer is the most common cancer of the digestive tract and the fourth cause of cancer death in the world (Iacopetta, 2002). This cancer is divided into two types: hereditary and non-hereditary. Almost 80% of cancer cases are non-hereditary (Naccarati et al., 2007). Annually, more than 1,200,000 people are diagnosed with this cancer in the world and over 600,000 people die, and this number is increasing (Ferlay et al., 2015). This cancer is a highly heterogeneous disease caused by genetic and environmental factors and it progresses through the gradual accumulation of genetic and environmental changes leading to the transformation of normal mucosal cells into cancer cells (Binefa et al., 2014). Changes in the digestive tract microbiome are caused by

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PUBLIC INTEREST STATEMENT

Colorectal cancer is the most common cancer of the digestive tract and the fourth cause of cancer death in the world. More than 70% of cancer cases are related to the lifestyle and diet of individuals. Diet can affect the amount of oxidative stress in individuals and change it. Herbal antioxidants can inhibit oxidative stress by exchanging electrons with free radicals. The authors have put together the data from different articles and made a systemic review to show the effect of herbal antioxidants on the process of colon cancer treatment. They have compared different studies and concluded that although the antioxidants have reduced the risk of cancer or improved patients condition but these affects are not statistically significant in the long-term usage.
environmental changes such as infection, diet and lifestyle which could be involved in relevant cancers (Farrington et al., 2005; Gagnière et al., 2016).

More than 70% of cancer cases are related to the lifestyle and diet of the individuals (Binefa et al., 2014). Diet can affect the amount of oxidative stress in the individuals and change it. Oxidative stress is caused by the imbalance between the production of free radicals and active oxygen species (including superoxide anion, hydroxyl free radical, hydrogen peroxide, etc). There are also part of the antioxidant defense system in animals and humans (Chompoo et al., 2012). In aerobic biological systems, defense mechanisms have been designed to deal with these free radicals and active oxygen species, in order to neutralize or minimize the harmful effects of these invading factors. Some components of the defense system include enzymes (such as superoxide dismutase, glutathione peroxidase, catalase, etc) that are synthesized in the body, but some other components of this system such as vitamin E, beta-carotene and so on must be supplied through diet. Oxidative stress causes destructive effects on macromolecules, including DNA, proteins, and lipids. Herbal antioxidants which are compounds with conjugated double bonds can inhibit oxidative stress by exchanging electrons with free radicals. Some of these compounds are scavengers of free radicals and some repair the damage caused by free radicals (Panchawat et al., 2010; Rice-Evans et al., 1996). Antioxidants collectors of active oxygen species protect the cells from oxidative stress that initiate and direct carcinogenicity through the induction of gene mutation, DNA damage, genomic instability, cell differentiation, and inflammation. Carotenoids (such as beta carotene, precursor of vitamin A, and lycopene), vitamins C and E have antioxidant and anti-inflammatory properties. Therefore, these vitamins and minerals are introduced as antioxidant food that can affect cancer cells and control or treat them (Song et al., 2015).

Therefore, interventions effective on oxidative stress can probably help to prevent and treat patients. Therefore, to investigate the effects of interventions, this study was conducted with the aim of systematically reviewing previous studies and the effects of interventions made to identify the effect of herbal antioxidants on the process of colon cancer treatment.

2. Materials and methods
This study is a systematic review conducted to identify the randomized clinical trials interventions in investigating the effect of herbal antioxidants on the prevention and treatment of colorectal cancer. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist was used to clear how the study was conducted (Moher & Shamseer et al., 2015). The electronic search of related databases was done in July 2017.

Studies were selected using the Cochrane search strategy from the scientific databases of Web of Science (Title, Abstract, Keywords; 1983 to present), PubMed & BioMed Central (Title/Abstract; 1836 to present), Scopus (Article, Abstract, Keywords; 1836 to present), and Science Direct (Title, Abstract, Keywords; 1823 to present). The desired search strategy was developed by an expert in the field of systematic studies, using the study conducted by Myung et al. (2009). Therefore, a wide range of terminology and vocabulary related to the purpose of the study were considered for the search strategy. Also, only clinical trial studies were used since the creation of databases and searching the scientific databases was limited to English language. The following keywords were used for the combined search strategy:

“Colorectal Neoplasm” OR “Colorectal Neoplasms” OR “Colorectal cancer” AND Prevent* OR prevention OR diagnosis* OR screening OR therapy* OR therapeutics AND garcinia* OR GIE OR “garcinia indica” OR antioxidant OR “herbal antioxidant” OR “antioxidant” OR “herbal antioxidant” OR “anti-oxidant” OR carotenoid* OR flavonoid OR polyphenelie OR phenylpropanoid OR anthocyanin OR tannin OR lignin OR “vitamin C” OR “vitamin C” OR “vitamin-C” OR “ascorbic acid” OR “vitamin E” OR “tocopherol” OR “catechins” OR polyphenol* OR “phenolic acid” OR vitamin* OR phenol* OR “nonflavonoid phenolic” OR “organic antioxidant” AND effect* OR control* OR evaluation* OR program* AND “randomized controlled trial” OR “cluster-randomized controlled trial” OR
“cluster-randomized controlled trials” OR “controlled clinical trial” OR “randomized controlled trials” OR “clinical trial” OR human NOT animal.

Database search was done by only one of the researchers. First, all articles identified from different sources were collected by one of the researchers using the Endnote software. After collecting these articles, repetitive articles were eliminated and this was done by two researchers who independently reviewed all the articles obtained and excluded the articles not related to the subject using the inclusion criteria. Then, the abstracts of the remaining articles were studied independently by the two researchers. Finally, the full texts of the selected articles were investigated by two researchers until the articles that completely matched the inclusion criteria were identified. After extracting all the desired articles based on the objectives of the study, with more detailed investigation in the next step, articles which cited these remaining studies were found and all sources of the desired articles were investigated. Articles that are related to the purpose of the study were extracted and these articles were carefully investigated independently by two researchers in terms of relevance to the inclusion criteria. In all the stages, the cases of disagreements were resolved through dialogue and eventually by the third researcher’s opinion. Ethics and trust were observed in using the sources in all the research stages.

Related studies were selected using systematic search approach from scientific articles, scientific and government reports. The criterion (PICO) which includes four components of Population, Intervention, Comparator and Outcome was used for articles selection (Schardt et al., 2007).

Population: The studies were investigated to systematically review which of them had been conducted on both genders and without age and race/ethnic restrictions on the effect of herbal antioxidants on patients with at least one polyp in the rectum or colon cancer.

Types of intervention: Clinical trials and randomized controlled trials (RCT) on the effect of any herbal antioxidants on the process of colon cancer treatment were included in the study. Descriptive, qualitative, review, structured review, meta-analysis, and semi-experimental studies (before and after controlled and before and after without control) on the effect of herbal antioxidants on the process of colon cancer treatment were excluded. Also, studies investigating the effect of herbal antioxidants on other cancers were excluded. The interventions included providing dietary and pharmaceutical supplements and changes in the diet of the subjects studied.

Comparator/Control: Considering studies where the control group participated in the study in any way.

Types of Outcome: These studies were evaluated based on the results obtained from observation, self-reporting, and biological monitoring.

The results were reported through a positive increase in the effect of herbal antioxidants, significant statistical changes in reducing the risk of polyps or colon cancer, making difference in cancer cells, reducing the number of polyps and so on. Statistical significance was considered at 0.05 for all the study results. Data were extracted from the desired articles by two researchers from September to October, 2017. The output data in the WORD software were author name/year of publication/country, participants’ characteristics, interventions, outcomes, and studies’ quality notes (Table 1).

In order to determine the quality of the desired articles, two of the trained researchers investigated the studies individually using the tools (EPHPP) related to the Institute of National Collaborating Center for Methods and Tools (National Collaborating Centre for Methods and Tools, 2010). This checklist divided the studies into three groups of powerful, moderate, and weak according to the six bias components in the selection of samples, type of study, confounding, data collection methods, and loss. An instruction was used to investigate the tool and
| Authors/Country         | Participants                                                                 | Intervention                                                                 | Outcome (s)                                      | Results                                                                 | Study quality |
|------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------|------------------------------------------------------------------------|---------------|
| McKeown-Eyssen etal. (1988)/Canada | N = 185 Patients who had at least one polyp in the colon or rectum I: n= 96 in the receive vitamins group C: n= 89 in the Placebo group | - I: Receive supplement of 400mg each of vitamins C and E, every 4 months.  
- C: Receive lactose placebo  
- Follow-up: Two years | - Relative Risks of polyp occurrence | - The percentage of subjects remaining free of polyps estimated from Kaplan-Meier survival curves was similar for those assigned to vitamin supplementation and for those assigned to placebo, and the log rank test revealed no significant difference between the groups (P > 0.30) | Strong        |
| Emmons etal. (2005)/America | N= 1247 patients with recent diagnosis of adenomatous colorectal polyps I: n= 591 patients in PREVENT intervention group C: n= 656 patients in Usual Care group | - I: The intervention was grounded in the Social Cognitive Theory, which suggests that health habits have common underpinnings.  
- C: The standard of care offered by the participating gastroenterologists served as the Usual Care (UC) intervention.  
- Follow-up: Within 4 weeks | - Risk factors for colorectal cancer | - Patients in the PREVENT condition reported significantly greater improvement than those in UC in total number of risk factors; 47% of the PREVENT group reduced their multiple risk factor score compared with 35% of the UC group (P < 0.0001).  
- Intervention condition was significant; the odds of having a positive change were 1.5 times greater for the PREVENT condition than for UC (P = 0.001). the odds of having a negative change for the PREVENT condition were 0.6 that of the UC condition (P = 0.004) | Strong        |
| Authors/Country       | Participants                  | Intervention                                                                 | Outcome (s)                                                                 | Results                                                                                                                                   | Study quality |
|-----------------------|-------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| Walfisch et al. (2007)/Israel | N = 56 colon cancer patients | I: The volunteers were given supplements of an natural source of lycopene that was administered as tomato lycopene extract and formulated into soft-gel capsules. Each capsule contains 15mg lycopene, and about 1.5mg phytoene, 1.4mg phytofluene, 0.4mg β-carotene and 5mg tocopherols. | - Blood and Plasma concentration of lycopene; IGF-I (ng/ml) IGF-II (ng/ml) IGFBP-3 (ng/ml) IGF-I/IGFBP-3 | - Plasma lycopene levels increased by two groups. - In the placebo-treated group, there was a small nonsignificant increase in lycopene plasma levels. - The plasma concentration of insulin-like growth factor-I decreased significantly by about 25% after tomato lycopene extract supplementation as compared with the placebo-treated group (P < 0.05). - No significant change was observed in insulin-like growth factor-I-binding protein-3 or insulin-like growth factor-II, whereas the insulin-like growth factor-I/insulin-like growth factor-I binding protein-3 molar ratio decreased significantly (P < 0.05). | Strong         |
| Authors/Country          | Participants | Intervention                                                                 | Outcome (s)                                                                                                                          | Results                                                                                                                                                                                                 | Study quality |
|-------------------------|--------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| Mobarhan et al. (1994)  | N= 34 polyp subjects: I: n= 16 C: n= 18 N= 24 cancer subjects: I: n= 12 C: n= 12 | - I: 90 capsules each containing 30mg β-carotene (BC)  
- C: 90 capsules of placebo  
- Follow-up: 90 days. | - Quantitation of BC and α-tocopherol concentration in tissue and serum samples                                                                                                                                                                                                                                                                 | Strong         |
| Authors/Country | Participants | Intervention | Outcome (s) | Results | Study quality |
|----------------|--------------|--------------|-------------|---------|---------------|
| Wactawski-Wende et al. (2006)/America | N= 36,282 postmenopausal women I: n= 18,176 C: n= 18,106 | I: Received 500mg of elemental calcium as calcium carbonate with 200 IU of vitamin D₃ twice daily - C: received an matching placebo - Follow-up: 7.0 years. | - Effects of supplemental calcium with vitamin D on the risk of colorectal cancer, according to selected baseline characteristics | - The incidence of invasive colorectal cancer did not differ significantly between women assigned to calcium plus vitamin D supplementation and those assigned to placebo (168 and 154 cases; hazard ratio, 1.08; 95 percent confidence interval, 0.86 to 1.34; P= 0.51), and the tumor characteristics were similar in the two groups. - The frequency of colorectal-cancer screening and abdominal symptoms was similar in the two groups. There were no significant treatment interactions with baseline characteristics. | Strong |
| Cascinu et al. (2000)/Italia | N= 77 patients with resected colorectal cancer Dukes’ stage B-C I: n= 34 C: n= 43 | I: Received daily 30,000 IU of axerophthol palmitate (vitamin A) plus 1 g ascorbic acid (vitamin C) plus 70mg of dl-alpha-tocopherol acetate (vitamin E) and 2 g natural calcium - C: received indistinguishable placebo - Follow-up: 6 months. | - Cell kinetics of normal colonic mucosa were assessed by using proliferating cell nuclear antigen (PCNA). | - Results showed that calcium and vitamin supplementation does not reduce cell kinetics of colon epithelium. - Patients treated with antioxidant vitamin and calcium supplementation did not have a better response on cell kinetic reduction compared with the placebo group (34% in the treatment group and 28% in the placebo group). | Strong |
| Authors/Country          | Participants | Intervention                                      | Outcome(s)                                                                 | Results                                                                                                                                                                                                 | Study quality |
|-------------------------|--------------|---------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| Albanes et al. (2000)/Finland | N= 29,133 male 50-69 years old and cigarette smokers |
|                         | I1: n= 7,286   | I1: α-tocopherol (50mg as dl-α-tocopherol acetate), daily |
|                         | I2: n= 7,278   | I2: β-carotene (20mg), daily                      |
|                         | I3: n= 7,282   | I3: α-tocopherol and β-carotene, daily            |
|                         | C: n= 7,287    | C: Placebo, daily                                 |
|                         |              | - Follow-up: 5-8 years.                           | - Serum concentration of α-tocopherol and β-carotene                      | - Colorectal cancer incidence was somewhat lower in the α-tocopherol arm compared to the no α-tocopherol arm, but this finding was not statistically significant (relative risk (RR) = 0.78, 95% confidence interval (CI) 0.55-1.09; log-rank test p= 0.15). |
|                         |              |                                                   | - Effects of α-tocopherol and β-carotene supplementation on the incidence of colorectal cancer | - β-carotene had no effect on colorectal cancer incidence (RR = 1.05, 95% CI 0.75-1.47; log-rank test p= 0.78). - There was no interaction between the two substances.                                      | Strong        |

1Number of individuals
2Intervention
3Control
disagreements between the researchers were resolved through discussion. Also, the internal reliability for using tools was calculated using Kappa coefficient.

3. Results

The initial search led to the finding of 3113 studies after eliminating repetitive studies. A total of 800 studies were excluded because they were not in line with the study objectives and inclusion criteria. Then, 515 abstracts of these studies were carefully investigated independently by two researchers. A total of 360 abstracts of the studies were excluded because they were not in line with the study objectives and inclusion criteria. 155 texts of the studies were carefully investigated independently by two researchers. From these 155 texts of the studies, 25 texts were from studies which are common in terms of the desired factor and response and 7 studies were completely common in terms of the type of study, the desired factor, and the response (colon cancer). 18 texts of the papers were excluded because they are semi-experimental studies, systematic reviews and studies of merely intervention on cancer cells. Finally, seven randomized trial studies were identified for evaluation in this study (Figure 1).

The results of Table 1 show that from the seven studies investigated, two were published during the last 10 years (after 2006) (Wactawski-Wende et al., 2006; Walfisch et al., 2007), three were published between 2000 and 2006 (Albanes et al., 2000; Cascinu et al., 2000; Emmons et al., 2005), and the remaining two were published before 2000 (McKeown-Eyssen et al., 1988; Mobarhan et al., 1994). From the studies obtained, three were conducted in the US (Wactawski-Wende et al., 2006; Emmons et al., 2005; Mobarhan et al., 1994), one study in Italy (Cascinu et al., 2000), one study in Israel (Walfisch et al., 2007), one study in Canada (McKeown-Eyssen et al., 1988), and one study in Finland (Albanes et al., 2000). Most of the studies had a small sample size, such that, the number of participants in 4 out of the 7 studies would be less than 200 individuals (Cascinu et al., 2000; Mobarhan et al., 1994; McKeown-Eyssen et al., 1988; Walfisch et al., 2007). The duration of follow up, regarding the impact of interventions was mainly long, such that the duration was more than 2 years in 4 studies and between 2 and 6 months in 3 studies (Cascinu et al., 2000; Mobarhan et al., 1994; Wactawski-Wende et al., 2006). From the studies obtained, three studies were conducted on patients with at least one polyp in the rectum or colon (Emmons et al., 2005; Albanes et al., 2000; McKeown-Eyssen et al., 1988) and 4 studies on patients with colon cancer (Cascinu et al., 2000; Mobarhan et al., 1994; Wactawski-Wende et al., 2006; Walfisch et al., 2007). The intervention approach used in the three studies involved the use of capsules containing herbal antioxidants (Albanes et al., 2000; Mobarhan et al., 1994; Walfisch et al., 2007). One study used pills containing vitamin Cand Eand nutritional intervention (McKeown-Eyssen et al., 1988), while another study used only calcium and vitamin Dpills (Wactawski-Wende et al., 2006). Also, only one study used pills containing vitamins C, Eand A, and calcium carbonate (Cascinu et al., 2000). In the meantime, patients were encouraged to take fruits and vegetables daily, in only one study (Emmons et al., 2005). In all studies and among the participants, subjects with at least 33 years and up to 90 years were observed. All studies included individuals older than and equal to 40 years and individuals were only in study of Cascinu et al. (2000) (with age range 33–86 years) younger than 40 years. Except in Study of Mobarhan et al. (1994) (p < 0.001), the effect of age on response was not significant in both intervention and control groups (Emmons et al., 2005; Walfisch et al., 2007). In two studies using age matching (Cascinu et al., 2000; Wactawski-Wende et al., 2006) and in two studies consider age as a confounder (Albanes et al., 2000; McKeown-Eyssen et al., 1988), effect of age to be controlled.

In evaluating papers based on race/ethnicity of participants, most studies used local communities to evaluate the antioxidant intervention (Albanes et al., 2000; Cascinu et al., 2000; McKeown-Eyssen et al., 1988; Mobarhan et al., 1994; Walfisch et al., 2007, but, in two studies enrolled participants with different races (white, black, Hispanic, etc.) (Emmons et al., 2005; Wactawski-Wende et al., 2006). The effect of the intervention in studies with local populations of Italy, Finland and Canada was not significant, but in the US study, differences were observed in the response of the
intervention and control groups without race effect. In the study of the Israeli population despite some appropriate results, however, the effect of the intervention was insignificant.

Papers assessed according to amount of antioxidant and results indicated that participates in four studies with respectively twice daily 500mg calcium with 200 IU of vitamin D, daily 30,000 IU of axerophthol palmitate (vitamin A) plus 1 g ascorbic acid (vitamin C) plus 70mg of dl-alpha-tocopherol acetate (vitamin E) and 2 g natural calcium, daily. α-tocopherol and β-carotene, and 400mg each of vitamins Cand E every 4 months did not achieve any of the desired outcomes (Albanes et al., 2000; Cascinu et al., 2000; McKeown-Eyssen et al., 1988; Wactawski-Wende et al., 2006). In two studies, that the interventions were grounded in the Social Cognitive Theory for 4 weeks and 90 capsules each containing 30mg β-carotene (BC) for 90 days, there were asignificant difference between the groups (Emmons et al., 2005; Mobarhan et al., 1994). In one study, the volunteers were given supplements of anatural source of lycopene some results are responsible between groups og intervention (Walfisch et al., 2007).

The findings of these studies were mainly determined by laboratory measurements (Cascinu et al., 2000; McKeown-Eyssen et al., 1988; Mobarhan et al., 1994; Walfisch et al., 2007). Outcomes were measured based on self-reporting in astudy (Emmons et al., 2005). The two methods of self-reporting and laboratory measurements were used to investigate the outcomes in two studies (Albanes et al., 2000; Wactawski-Wende et al., 2006). From the papers investigated, four studies did not achieve any of the desired outcomes and as such no statistically significant difference was observed between the control and intervention groups (Albanes et al., 2000; Cascinu et al., 2000; McKeown-Eyssen et al., 1988; Wactawski-Wende et al., 2006). Only two studies had achieved all the desired outcomes and as such there was asigsignificant difference between the groups (Emmons et al., 2005; Mobarhan et al., 1994). But only one study achieved some of the outcomes (Walfisch et al., 2007).

In terms of investigating the quality of studies and bias, none of the studies had poor or moderate quality, but all were powerful in terms of investigating quality (Albanes et al., 2000; Cascinu et al., 2000; Emmons et al., 2005; McKeown-Eyssen et al., 1988; Mobarhan et al., 1994; Wactawski-Wende et al., 2006; Walfisch et al., 2007). Kappa coefficient was calculated to investigate the internal consistency between the two evaluators of the EPHPP components. Kappa coefficient was in good agreement for withdrawals and selection bias (k = 0.60 to 0.80) and was in very good agreement for others (k = 0.80 to 1.00) (Table 2).

4. Discussion

This systematic review investigated randomized clinical trials interventions which had investigated the effect of herbal antioxidants on the prevention and treatment of colorectal cancer. After reviewing the studies by the researchers, finally seven studies were identified for evaluation in this study. The seven studies were randomized trials. The sample size of most of the studies was

| Component ratings                  | Kappa value (SE) | P-value | Interpretation          |
|------------------------------------|------------------|---------|-------------------------|
| Selection bias                     | 0.666 (0.87)     | 0.001>  | good agreement          |
| Study design                       | 1.000 (0.00)     | 0.001>  | Very good agreement     |
| Confounders                        | 0.892 (0.73)     | 0.001>  | Very good agreement     |
| Blinding                           | 1.000 (0.00)     | 0.001>  | Very good agreement     |
| Data collection methods            | 1.000 (0.00)     | 0.001>  | Very good agreement     |
| Withdrawals and drop-outs          | 0.665 (0.96)     | 0.001>  | Good agreement          |

Table 2. Inter-rater agreement for component ratings
small and the duration of follow up, regarding the impact of interventions, was mainly long. The results of these studies were mainly determined using two methods, such as laboratory measurements and self-reporting in two studies and self-reporting in one study. The intervention approach used in all the studies was by using capsules or pills containing herbal antioxidants or combining drug with herbal diet. From the studies investigated, four studies did not achieve any of the desired outcomes, two achieved all the desired outcomes, and one achieved some of the outcomes. All the studies were powerful in terms of the quality of the investigation.

According to the systematic review conducted by Bjelakovic et al. (Bjelakovic et al., 2008) to investigate the effects of antioxidants used in preventing gastrointestinal cancers, finally, 20 studies were achieved and all of them were randomized trials. Also in another study, the results showed that all the studies that investigated antioxidants to prevent gastrointestinal cancer were studies that used randomized trials (Bjelakovic et al., 2004). Therefore, the results of the two studies mentioned were consistent with the results of this study. From the studies investigated, most of them were published after 2000. In the meta-analysis study of Liu et al., which was conducted to evaluate the relationship between the consumption of multivitamins and the incidence of colon cancer, most of these studies were published after 2000, and as such were consistent with the results of this study (Liu et al., 2015). In this work, most of the studies reviewed were conducted in developed countries such as the United States, and this is clear from the previously reviewed studies on the effect of antioxidants consumption in preventing and treating colon cancer (Bjelakovic et al., 2008, 2004; Liu et al., 2015). This can be considered probably due to the access of these populations to a sufficient and effective level of vitamins and herbal antioxidants and paying attention to the health problems of this population is also an important research priority in these countries. But the situation in developing countries is that this population is given less consideration by the researchers, because of the health problems in other groups.

The sample size of most of the studies was small and the number of participants in four out of seven studies was less than 200 individuals. Also, the duration of follow up, the impact of interventions was mainly long. In other studies, similar results were obtained (Bjelakovic et al., 2008, 2004). The reason for this can be the nature of design and follow up in the randomized trial studies which dealt with the real patients and required long-term follow-up in order to achieve minimum effectiveness in intervention.

Outcomes in the studies were determined using laboratory measurements. The measurement of outcomes was based on self-reporting in a study, and two methods of self-reporting and laboratory measurements were used to investigate the outcomes in two studies. From the papers investigated, four studies did not achieve any of the desired outcomes, thus, no statistically significant difference was observed between the control and intervention groups. Two studies achieved all the desired outcomes, therefore, there was a significant difference between the groups. But only one study achieved some of the outcomes. Similar review studies reported similar results (Bjelakovic et al., 2008, 2004). The different effects of antioxidants in the groups with different risks can be considered as the reason why antioxidants are reported effective in some populations and ineffective in some others.

In all studies, effect of intervention between groups assessed by controlling on some confounder such as the age, race, and amount of antioxidant.

The intervention approach used in all the studies was by using capsules or pills containing herbal antioxidants or combining drug with herbal diet. The reason for the greater use of pills and capsules in interventions can be considered by matching and controlling the amount of intervention in the individuals as compared to the dietary intervention. Also, in dietary interventions, there is greater probability that the subjects of the study will not observe the study protocol. Only few studies had used other approaches and it can be argued that these interventions were not well received due to the cost,
time-consuming, and long-term outcomes. In similar studies, the intervention approach was often similar to the approach of this study (Bjelokovic et al., 2008, 2004; Liu et al., 2015).

The findings of the studies were determined by laboratory measurements. The measurement of the outcomes was done based on self-reporting only in a study and two methods of self-reporting and laboratory measurements were used to investigate the outcomes in two studies. Self-reporting requires less time, cost, and facilities than the laboratory methods. But the accuracy of the conclusions in the laboratory method is more than the self-reporting methods. Also, most studies that have used the laboratory methods had been conducted in developed countries and the reason can be the high cost of these experiments and the need for expert force.

The strengths of this study can be considered by looking at a particular outcome, colorectal cancer, instead of considering several outcomes. Also, more relevant databases were investigated using comprehensive search strategy than other studies. The weaknesses of this study were considered as investigating only English-language studies and the lack of use of other language studies.

5. Conclusions
There are significant differences in the study for using self-expression method to investigate the outcomes, but no significant difference was observed in most of the studies that have used the laboratory method. Although consuming antioxidants has reduced the risk of cancer or improved the patient’s condition in all the studies, but these effects are not significant in most studies. Due to the accuracy of the laboratory methods as compared to the self-expression method, it can be concluded that consuming antioxidants reduces the risk of colon cancer among healthy people and increases the probability of improvement in the community of patients with colon cancer, but there is no statistically significant difference between these interventions and the control group (without treatment) in the long term.

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Competing interests
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Cover Image
Source: Author

Abbreviations
EPHPP: Effective Public Health Practice Project

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PICO: Population Intervention Comparison Outcome
RCT: Clinical trials and randomized controlled trials
CI: Confidence Interval
RR: Relative Risk
OR: Odds Ratio

Authors’ Contributions
All research was done by the authors. All authors contributed to the design and concept, performed the literature searches, wrote the manuscript, and approved the final manuscript.

Availability of Data and Materials
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Ethics Approval and Consent to Participate
This article does not contain any studies with human or animal subjects performed by any of the authors. No ethical approval or informed consent statement was required for this review article.

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