PJN
ISSN 1680-5194

PAKISTAN JOURNAL OF NUTRITION

ANSInet
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan
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Pakistan Journal of Nutrition 11 (9): 896-903, 2012
ISSN 1680-5194

The Role of Some Plants on Colon Cancer: A Review

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INTRODUCTION

Studies on colon cancer and its treatment by plants are the concern of medicinal investigations nowadays. There is a consensus that plants have an effect on colon cancer and this is because of their content onlignans, allium, trace minerals, antioxidant, phytoestrogens, bioactive and poly-phenolic compounds. However, it was suggested that plant consumption and colon cancer are in an inverse relationship although no ample evidence is provided (Potter *et al*., 1993; Slattery *et al*., 1997; Deneo-Pellegrini *et al*., 2002; Steinmetz *et al*., 1994; Michels *et al*., 2000; Voorrips *et al*., 2000; World Cancer Research Fund, 1997). In the US, it is estimated that the new colorectal cancer cases in 2010 will get 72.090 and 70.480 for males and females respectively, whilst the death rate will reach 26.580 and 24.790 (American Cancer Society, 2010). These statistical results refer to that the incidence of colon cancer is actually not small. Although the medical remedies of colon cancer are diverse, people afflicted with colon cancer are striving to find another therapy. Barrie *et al*. (2005) indicated that people who try complementary therapies are of better education, high socioeconomic status, young and more likely to be females.

The purpose of this review is shedding the light on many natural plants that have an anticarcinogenic factors effecting on colon cancer, but have not been practically implemented in colon cancer yet.

Wheat grass: (*Triticumaestivum* L.): Wheat grass consumption began in the western world by Charles F. Schnabel who tried to spread out the plant after the conduction of many experiments on it in 1930 (Murphy Sean, 2002). The rich content of Wheat grass in nutrients such as chlorophyll, minerals, vitamins, amino acids and enzymes made many people claim that Wheat grass has several healthy benefits. In contrast to other vegetables, Wheat grass has a high content of nutrient which is approximately equal to the other vegetables (wwwahr-kc.com). In recent years, many developed countries have processed the Wheat grass plant to be consumed in tablets and powder. This trend of changing the way the Wheat grass is consumed might indicate to that the healing properties of Wheat grass and specifically the antioxidant, could contribute to the treatment of colon cancer. It is thought that the colon cancer studies do implement and know the antioxidant effect of Wheat grass on colon cancer; however a very little attention has been paid. Peryt *et al*. (1992) reported that the extract of Wheat grass has sweeping and ferric super oxide reduction ability. In the other hand, the antioxidant activity of Wheat grass was examined by Sunil Kulkarni *et al*. (2006) in different growth level and even in both the tablet and powder forms. This study showed that the Wheat grass got the maximum antioxidant activity on the 7th day of growth. Not only did that happen, but also the commercial tablet and powder showed antioxidant power. These results suggested that patients suffering from colon cancer and looking forward to maintaining themselves from any other radical diseases, it is advisable they cultivate Wheat grass and get its benefits on weekly basis taking into account its content of antioxidant compound, such as phenolic compounds and flavonoids. Perhaps cultivating such a plant, Wheat grass, will not take too much effort as much as what we will get benefits in treating colon cancer although there is no information that supports this theory. In the implement of it on patients with breast cancer taking chemotherapy, Gil Bar-Sela *et al*. (2007) reported that Wheat grass juice may enhance hematological toxicity which is caused by FAC(5-fluoroucil- doxorubicin- cyclophosphamide) chemotherapy - based on the reduction rate result of chemotherapy toxicity during taking Wheat grass juice. "A possible alternative mode of action of Wheat grass juice happens by reducing the formation of reactive free radical intermediates which are induced by doxorubicin that can cause oxidative damage to cellular proteins that are a part of its cytotoxic effect" (Stewart and Ratain, 2005). In this sense, it can be inferred that Wheat grass has a high ability to confront the free radical intermediates which are associated with colon cancer incidence through antioxidant vitamins and the large amount of chlorophyll that may behave as an antioxidant dredging. However, narrowing down the incidence of colon cancer by dietary fiber and complex carbohydrates has been proposed by several epidemiological studies (World Cancer Research Fund, 2007; Tan and Seow-Choen, 2007). In relation to this account, a study was conducted on Wheat grass aleurone by AnkeBorowicki

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et al. (2010). Anke's study reported that the fermentation of Wheat grass aleurone have anti-cancer growth properties *in vitro* by which we can get significant results if we implement it *in vivo*. In other words, fermentation of wheat aleurone adjusts the development of cancer in human colon cells. That it exists in Wheat grass in high quantity, chlorophyll is constructively similar to heme which is taken from bone marrow rapidly (Pole, 2006). Interestingly, there was a significant increase in the Hb blood level and a decrease in the frequency of blood transfusions after applying Wheat grass therapy in Thalassemia patients (Karnail *et al*., 2010). So, it was expected that these results come from either of the antioxidant effects of Wheat grass on red cell bloods (Caraciolo Fernandes, 2005), or from the supported forming of blood cells. Although this study tried to precisely determine the productive mechanism of blood cells, it took part in treating the anemia-related colon cancer. Being one of the systemic symptoms in colon cancer, lower concentration of blood cells was common as a result of blood stool. To the best of our knowledge, there has been no study conducted to investigate whether Wheat grass can prevent the anemia through incidence of colon cancer or not.

Although all the above mentioned studies accounted the antioxidant effect of Wheat grass on colon cancer, none of them investigated the relationship between Wheat grass and colon cancer deliberately. Demonstrating the effect of Wheat grass properties on colon cancer not only may add something new in the alternative remedies of colon cancer, but also may put Wheat grass in the list of chemoprotective agents against incidence of colon cancer. Hence, if any research is done on the influence of Wheat grass on colon cancer with positive results, our theory will be supported by these results.

Pomegranate (*Punicagrantum L.*): Pomegranate is one of the most known plants in our world. It was mentioned in many religions such as Islam and Christian and also in several ancient cultures in the eastern and Middle Eastern countries. Pomegranate fruit consists of seeds, juice and peel including the white internal membrane. Used as a source of traditional remedies for thousands of years, the Indian subcontinent's ancient Ayurveda system of medicine deemed that Pomegranate is very important in our lives (Sharma and Jindal, 2004). Ross *et al.* (2001) said that the dried peel of pomegranate was used as a contraceptive by Arabic countries and the decoction of pomegranate as a remedy for diarrhea in Argentina. Pomegranate has also other medicinal activities, such as analgesic, anti-amoebic, abortifacient, anti-bacterial, anti-malarial, anti-mutagenic, diuretic, hypothermic, hypoglycemic and antioxidant activities (Seeram *et al*., 2005). The antioxidant material, specifically the punicalagen, is the most active nutritional component of pomegranate. It is a rich source of vitamin C, B5, potassium and manganese. There are many of phytochemicals and polyphenols founded in pomegranate. The fat content of pomegranate is relatively centered in the seeds that can supply unsaturated fat in the form of oil.

According to many researches on the bioactive compounds of pomegranate, the health benefits of pomegranate are reasonably wide. Boateng *et al.* (2007) has demonstrated in his research that Pomegranate juice decreased the percentage of Aberrant Cryptic Foci (ACF) of colon cancer existent in F-344 male rats in approximately 91%. Instead of water, 20% of pomegranate juice in addition to AIN-93G was given to rats before and after inducing colon cancer by azoxymethane. The fed rats by pomegranate juice had shown a reduction in the number of large crypts (ACF) after 17 weeks of treatment. In addition, the number of crypts (ACF) was also less in these animals. Among other fruits juices, pomegranate has shown superiority in the inhibition of ACF in rat colon. Being one of colon cancer results, cachexia could be reduced through consuming pomegranate juice in an increased feed intake and weight gain in observed rats fed with pomegranate. In relation to the former accounts, using pomegranate juice in the development stages of colon cancer for either rats or patients is very needed to determine the capacity of this juice in shrinking and treating colon cancers.

The activity of Hepatic Glutathione S Transferase (GST) is supported by pomegranate juice intake. As a part of his study, Boateng *et al.* (2007) has measured the GST activity which was significantly high ($p<0.05$). The enzyme is common in scavenging free radicals as a result of oxidation. The productivity of enzyme activity also supports the mechanism of pomegranate's anti-oxidative efficiency in other experimental models (Rosenblat *et al*., 2006).

In studying the effect of pomegranate seed oil, Kohno *et al.* (2004a) has reported an important diminution in the occurrence and multiplicity of colon cancer in azoxymethane induced rats. In an experiment, pomegranate seed oil was merged with AIN-76 diet in three raised concentration 0.01%, 0.1% and 1% (w/w), individually. Anti-carcinogenic effect was noticed in all doses despite of the non-studied effect of exposure response. The period of this study was 32 weeks.

Pomegranate seed oil has more than 70 % cis 9, trans 11, trans 13 Conjugated Linolenic Acids (CLN) which were metabolized to Conjugated Linoleic Acid (CLA) in liver. A clinical trial conducted by Kohno *et al.* (2004b) demonstrated many results related to colon cancer and CLN of the Pomegranate seed oil. The CLA was increased in a dose-dependant manner in lipid tissue but the analysis of this tissue flopped to detect any CLN. Unsurely, some enzymes have role in catalyzing the saturation step occurred *in vivo*. Giving pomegranate

seed oil in different concentrations to AOM-induced colon cancer in male F344 rats inhibited the occurrence and the multiplicity of colonic adenocarcinomas even though a clear dose-response was not studied. Spontaneously, increased level of CLA (c9,t11-18:2) in the lipid of colon mucosa and liver came from giving pomegranate seed oil which lead to inhibit the colonic tumors and increase the expression of Peroxisome Proliferator-Activated Receptor (PPAR) γ protein in the non-tumor mucosa.

Considered as one of the anti-proliferative components, punicalagin, elegiac acid and total pomegranate tannin inhibited the proliferation of different colon cancer cells (SW480, HT29, HCT116, SW620) with using pomegranate juice (Seeram *et al*., 2005). The suppress of cell cycle in $CaCo_2$ cells, a kind of colon cancer cell, has been shown as a result of using punicalagin and elegiac acid (Larossa *et al*., 2006). These ingredients organize two of cyclic class of regulatory protein, cyclic A and cyclic B. They are responsible for transit through S-phase and organization of mitosis. Inducing apoptosis in HT29 and HCT116 cells by elegiac acid, punicalagin and total pomegranate tannin was failed when treated at doses in equal to find in pomegranate juice (Seeram *et al*., 2005). They just affected those cells when manipulated at 100 μg/ml doses. It is proposed that the synergism among the components of pomegranate juice demonstrate greater effect and response than individually isolated ingredients.

In separate study conducted by Sashi Kasimsetty *et al*. (2010), pomegranate juice derived ellagitannins and their intestinal bacterial metabolites, Urolithins, intercepted TCDD-induced CYP1-mediated EROD activity *in vitro* with IC_{50} value varying from 56.7 μM to 74.8 μM involving seven kinds of urolithins. These compounds showed time- and dose-dependent decreases in cell proliferation and clonogenic capacity of HT-29 cells. Inhibition of cell proliferation was mediated through cell cycle arrest in G_0/G_1 and G_2/M stages of the cell cycle followed by induction of apoptosis. Even though the precise amount of urolithins that is manipulated in colon cancer is not known, providing a sufficient concentration of urolithins through the continuous consumption of pomegranate juice could play significant role in inhibiting progression of colon cancer.

In the mechanistic side of pomegranate on inducing apoptosis of colon cancer cells, punicalagin and elegiac acid have significant impact in this operation (Larossa *et al*., 2006). Oozing of mitochondrial cytochrome c in the cytosol by elegiac acid and punicalagin proposed a substantial pathway of apoptosis. Anti-apoptotic bcl-XL protein was down regulated with 30 μM elegiac acid and 100 μM punicalagine, respectively. Member of caspase family of proteases, caspase 9 and procaspase 3 were induced by punicalagine and elegiac acid. Both compounds cannot activate caspase 8 included in caspase family and associated with extrinsic pathways of apoptosis. Similarly, no inhibitory effect takes place on apoptosis when elegiac acid and punicalagine are incubated with anti-Fas ZB4 antibody. These results boost the role of pomegranate in inducing apoptosis in colon carcinogenesis.

In another study, tumor necrosis factor-alpha (TNF-α) was suppressed by pomegranate juice, elegiac acid and punicalagine in mediated expression of COX-2. Increased expression of COX-2 has been implicated in inflammation of the colon and COX-2 suppression by chemical antagonists reduces the incidence of colon cancer in animal and in vitro models (Marnett and DuBois, 2002). The maximum inhibitory effect of COX-2 protein, as Western Blot data indicated, was elicited by pomegranate juice, total pomegranate tannin and punicalagine, respectively. The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/nuclear factor kappa-B (NFκB) pathway is significant in COX-2 activation. Not only pomegranate juice restrained the activation of NFκB by suppressing TNF but also the NFκB phosphorylation (Adams *et al*., 2006). Despite of these studies in the apoptotic effect of pomegranate via intrinsic pathway, the COX-2 role in inducing apoptosis is not completely demonstrated (Larossa *et al*., 2006).

To best of our knowledge, there is no clinical study conducted on humans having colon cancer and proves the previous results attained in either *vitro* or *vivo*. On the other hand, many of nutritional supplementations containing pomegranatic compounds are available in pharmaceutical markets. The importance of manufacturing such these formulations are being considered by several scientists, suggesting capability of pomegranatic compounds namely, punicallagine, elegiac acid, total pomegranate tannin and the others in supporting the alternative therapy of colon cancer and increasing the anti-oxidative potency of colon against carcinogenic potential of many substances.

Olive oil: Olive oil is an oil obtained from the olive (*Oleaeuropaea*; family Oleaceae), a traditional tree crop of the Mediterranean Basin. The oil is produced by grinding whole olives and extracting the oil by mechanical or chemical means. It is commonly used in cooking, cosmetics, pharmaceuticals and soaps and as a fuel for traditional oil lamps. Olive oil is used throughout the world, but especially in the Mediterranean countries. Olive oil has been medicinal, magical, an endless source of fascination and wonder and the fountain of great wealth and power. It is worth mentioning that olive oil is an essential element in Mediterranean diet which demonstrated a protective effect against cancer incidence in several studies. In addition, the Mediterranean diet areas have relatively low cases of colonic tumor (Weisburger, 1991; Esteve *et al*.,

1993). Many continuous processes for extracting olive oil divide it into seven kinds namely, oil of extra virgin olive, virgin olive, pure olive, olive, olive pomace, lampante, refined olive, etc. Each one has different characteristics such as acidity rate. In the last years, various studies have shown the nutritional value of olive oil. In nutrition terms, the major vitamins in olive oil are vitamin K and vitamin E. In addition, the oil contains trace amounts of minerals, including calcium, iron and potassium. Olive oil contains other antioxidant components called polyphenols, such as tyrosol, hydrotyrosol, protocatechuic acid and oleuropein. The compounds chlorophyll and carotenoids are other beneficial components found in olive oil. There is an increasing proof that olive oil may be correlated with a decreased risk factor of some cancers such as colon cancer.

There are two main parts in olive oil that have an impact on healthy status of colon namely, fatty acids and natural constituents. The amount of fatty acid in olive oil, according to the Recommended International Standard for olive oil, is respectively abdicable: oleic acid, palmitic acid, linoleic acid, stearic acid, palmitoleic acid, linolenic acid, myristic acid and other fatty acids in precise amount. The different structure of compositional fatty acids could be a more significant influence in the genesis of colon cancer (Reddy, 1992) than the total amount of fat intake. Epidemiologically, dietary fat intake has received a considerable attention by many researchers as a factor in causing colon cancer for over 20 years (Cohen and Wynder, 1990). In trying to achieve a relationship between fatty acids and colon cancer, as in breast cancer studies, all efforts have failed. To be more precise, a collected analysis of 13 case-control studies reported that the intake of total, saturated, monounsaturated or polyunsaturated fats was not associated with the potential incidence of colon carcinogenesis (Howe *et al*., 1997). During the last years, the effect of long chain n-3 PUFA (20:5n-3, eicosapentaenoic acid; 22:6n-3, docoshahexaenoic acid) as the main fat in the diet containing high amount of fish is so as to inhibit not only colorectal cancer but also coronal disease, aside from the olive oil (Woutersen *et al*., 1999; Hong *et al*., 2000). Empirically, no differences have been found between n-3 and n-6 PUFA (polyunsaturated fatty acid) on creating bile acid *in vitro* (Dommels *et al*., 2002), while in the other hand several animal studies, *in vivo*, show n-3 PUFA as a preserver against incidence of colorectal cancer and n-6 PUFA as an incitement for colonic tumor. Bartoli *et al*. (2000) found in his research that aberrant crypt foci and cancer formation were decreased at the early phase of tumor progression in AOM-injected rats as a result of olive oil consumption (5% fat diet containing olive oil). In that research, n-6, n-3, n-9 fat diet were examined on colonic tumor of the rats. n-3, n-9 fat eaten rats have aberrant crypt foci less than rats on n-6 fat diet. Suggested by the researchers, the alteration of arachidonic acid metabolism and the local synthesis of PGE_2 may be associated with these results. In relation to that results, a question can be posed in the literature: Is there a direct preventive effect from the olive oil on colon tumorigenesis? In attempting to evaluate the impact of olive oil, oleic acid and linoleic acid on essential mechanisms involved in colorectal tumor and its relation to COX-2 and Bcl-2 expression, Llor and Pons their colleagues (2003) supplemented the $CaCo_2$ and HT-29 colonic tumor cells with various fats and their effect on apoptosis stimulation, cell proliferation and differentiation was tested. Oleic acid and olive oil have induced apoptotic influence on both cell line in shorter time than linoleic acid which taken 72 h after supplementation. The difference of time in inducing apoptosis may be related to anti-oxidative strengthen from olive oil and oleic acid and still need more investigation. On the other hand, linoleic acid has shown a significantly inhibitory action of proliferation, just, in HT-29 cell line putting a question mark about this solo effect, whereas neither olive oil nor oleic acid have proved any proliferative impact on both cell line. All mentioned fats above have same response for differentiation. Down-regulated apoptosis of Bcl-2 and COX-2 was demonstrated by olive oil, while the others have no same result. Hereafter this result, the anti-cancer compounds in olive oil and the synergism among of them may have a relatively important part.

Un-nutritional dietary micro-compounds presented in the skin of olive oil (*Oleaeuropea*), triterpenoids are well-known as antimicrobial agents (Bianchi, 2003). Maslinic acid (2α,3β-dihidroxyolean-12ene-28oic) and oleanolic acid (3β-hydroxyolean-12-ene-28-oic) are the main teriterpene (Bianchi *et al*., 1994). Emilia Juan *et al*. (2006) extracted maslinic acid and oleanolic acid from the waxy outer layer of olive oil fruits in order to study their effect on inhibiting proliferation and apoptotic induce in HT-29 cells. The anti-proliferative impact without marks of cytotoxicity was demonstrated at an EC50 amount of 75 μmol/L and 25 μmol/L of maslinic acid and oleanolic acid respectively. Apoptosis was stimulated by 55.5 and 150 μmol/L of oleanolic and maslinic acid through the intrinsic pathways or mitochondrial-mediated stimulus mechanism. Caspase-3 was increased to 6-fold that of control cells by adding 200 μmol/L and 74 μmol/L of maslinic acid and oleanolic acid, respectively, after 24-h incubation. Our concern is whether the daily intake of table olive oil supports enough amount of the tested compounds above toward protecting colon health against tumor mutations. Another factor may have an effect which is the bioavailability of these constituents namely, the percentage of absorbed compounds in small intestine. There is a thought that bile salts could have effect in causing colon cancer (Nagengast *et al*., 1995). Diamine

Oxidase (DAO) has been suggested relatively that play a role in colonic activity (Kusche *et al*., 1988) and cancer (Stoneham, 1997). To elucidate more, the high consumption of meat leads to high levels of faecal bile acid namely, deoxycholic acid which is associated with colonic adenoma and high rate of proliferative colon cells (Moorehead *et al*., 1987; Terpstra *et al*., 1987; Stadler *et al*., 1988). Speculating relationship between DAO and deoxycholic acid, DAO was inhibited by glycochenodeoxycholic acid *in vitro* (Stoneham, 1997). Botham and Boyd (1983) demonstrated a reduction in the cholic acid and chenodeoxycholic acid in olive oil diet-given rats. As result from above, it can be expected that olive oil may have a protective or supportive action on DAO which could reflect decreasing in colonic tumor incidence.

It is well-understood by previous studies that chronic inflammation is considered a potential key factor to colon cancer in Inflammatory Bowel Disease (IBD). It has been mentioned above about the practices factor of COX-2 which up-regulate the oncology of colon. Extra Virgin Olive Oil (EVOO) has been shown as an important effect on that inflammation. A clinical study conducted by Sanchez-Fidalgo *et al*. (2010) explained the effect of extra virgin olive oil-enriched diet in altering the inflammation oncology carcinoma-consequence of colon cancer progression. 84 C57BL/6 female mice were divided into two groups according to the diet. Dextran sodium sulfate-induced chronic ulcerative colitis in rats which was fed through the time period of experiment on 10 g/100 g diet EVOO and the same amount of Sunflower Oil (SFO) was given to the other group. In the end of the trial, Diseases Activity Index (DAI) was importantly lower in EVOO-diet comparing with SFO-diet. EVOO-fed mice demonstrated a decrease in occurrence and multiplicity of tumors and the opposite happened in SFO-fed mice. Being important in the early incidence of human colorectal cancer, translocation of β-catenin from cell membrane to nucleus was limited in animals group fed with EVOO comparing with the other animal group. Cytokines production (TNF-α, IL-6 and IFN-γ) was not importantly enhanced in EVOO-fed mice while this production was noticed clearly in SFO-fed mice. No significant modification in P53 expression was existed in all animal groups while inducible Nitric Oxidase (iNOS) and Cyclooxigenase-2 (COX-2) were less expressive in animal group fed with EVOO than in SFO-fed group. These results could support extra virgin olive oil more than the other kinds of olive oil in preventing/protecting patients with ulcerative colitis from developing colon cancer by many mechanisms. On the other hand, studying the effect of extra virgin olive oil on P53 is very important because of its role in prohibition of colon-generation. The previous research did not show any effect coming from EVOO on P53 while Lucia Fini *et al*. (2008) found in his research various results regarding EVOO and P53. In that research, the phenolic content of extra virgin olive oil, pinoresinol forming the majority of phenols in EVOO, was tested on four kind of human colon cancer cell lines (RKO, SW489, HCT116 and $HCT116_{p53-1}$) comparing with purified pinoresinol. As expected, the viability of cells was significantly affected during cell cycle by activating P53 axis through inducing apoptosis at a concentration 200 n/M of total phenolic compound of extra virgin olive oil. To explain more, this result may encourage the consumption of extra virgin olive oil naturally because of the synergism of polyphenol in EVOO against colon cancer generation by stimulating P53 cascade that inducing apoptosis.

It is noteworthy that olive oil has a lot of natural components which is considered as antioxidant agents. Unsaturated fatty acids and phytochemical components such as tyrosol, sterols, carotenoids, α-tocopherols and phenolic compounds are beneficial micronutrients in the olive oil with pro-healthy properties. Few studies have been conducted *in vivo* namely, in human for discovering the effect of olive oil on colon cancer comparing with *in vitro* studies. For more precise results, there are different results regarding the effect of olive oil on P53 pathway so that more investigation on that topic is very needed. Probably, olive oil has impact on anti- or pro-colonic carcinogenesis through APC gene and K-ras. Any research investigating toward showing the anti-cancer impact of olive oil will support not only its use but also the Mediterranean diet that is recommended by many scientific researches.

Conclusion: In our nature, there are many plants having antioxidant effect on colon cancer. Of those are not discovered or needed to be directly investigated on colonic tumor *in vitro* and *in vivo* such as Wheat grass although its anti-oxidative impact has been proven. Reducing the amount of blood transfusion in Thalassemia patients by administrating Wheat grass juice could be preferably significant not only in contribution of treating colonic tumor but also in reducing the development of anemia-related to colon cancer. On the other hand, pomegranate was profoundly tested in multi-studies associated with colorectal cancer either *in vitro* or *in vivo* and there were positive results which in turn support administrating pomegranate in order to study its effect on patients having colonic tumor. Being a major constitute in Mediterranean diet, using olive oil supports decreasing the incidence and mortality of colon cancer (Francesco Sofi *et al*., 2008). We suppose from this review that those plants might have implications in the treatment and prevention of colonic tumor on human beings and specifically by Wheat grass because of its benefits that were mentioned for the first time. To the best of our knowledge, the synergism effect of the above mentioned plants on the prevention and treatment of colon cancer, as well as the synergistic inhibition of 5-

fluorouracil simultaneously or singly have not been studied yet.

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