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REVIEW

Phytochemicals in the Fight Against Cancer

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Abstract Phytochemicals are chemical compounds from fruits, vegetables, or grains and they have been used to treat various diseases for thousands of years. More than one million people in the United States get cancer each year. Although recent advances in medicine have improved the outcomes for cancer patients, there is still a need for novel approaches in the fight against cancer. One such approach that has shown promise in recent years is the use of phytochemicals alone or as synergistic agents. In this review, we will discuss the use of phytochemicals as therapeutic agents against cancer with an emphasis on apple extract.

Keywords Phytochemicals · Apple extract · Cancer

Introduction

Cancer is a major public health concern in US and about 1, 665,540 new cases of cancer are projected to occur in USA in 2014 [1]. The prognosis of cancer has been improved significantly in recent years, however, 585,720 deaths due to cancer are projected to occur in USA in 2014. It is estimated that one in four deaths is associated with cancer [1]. It is obvious that there is still an urgent need for novel approaches in the fight against cancer. One such approach that has shown promise in recent years is the use of phytochemicals from natural plants alone and as synergistic agents. The first documented medicinal herbal literature dates back to the ancient Chinese emperor, Shen Nung, in 2800 BC [2] and natural plants and their products have been used to treat various diseases for thousands of years. Phytochemicals are chemical compounds made from fruits, vegetables, or grains and relates to any number of vitamins, minerals or bioactive compounds produced by the plant [3, 4]. These chemicals are responsible for a variety of features such as vivid colors in fruits, and vegetables, the flavors they produce, or strong aromas like those of onions and garlic. Specifically, these compounds have been shown to inhibit or attenuate the initiation, progression and spread of cancers in cell in vitro and in animals in vivo [5, 6]. This review covers the use of phytochemicals as therapeutic agents against cancer cells in the hopes to frame where their use in cancer research should go next.

Bioavailability of Phytochemicals

Upon ingestion, certain levels of phytochemicals must be achieved in the host in order for any of the apparent anticancer benefits can be utilized. As yet, a limited amount of studies have been conducted addressing the issue of the bioavailability of phytochemicals [7]. Recent studies have conducted with ileostomy patients have demonstrated that the acute consumption of 1 L of cloudy apple juice resulted in an up to 33 % recovery of the orally applied polyphenols in the ileostomy bags, indicating that the majority of the phytochemicals are absorbed in the proximal portions of the intestine and metabolized, while small amounts of unmetabolized polyphenols recovered in the ileostomy effluent would be available to the colon under physiologic circumstances [8, 9]. This tells us that there is a fairly low bioavailability for the chemicals to do their work in the host. It has been suggested

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that there may be a degree of bacterial degradation in the intestinal tract [7]. In a studies conducted by Hollman et al. [10] it was shown that quercetin derived from onions had a higher bioavailability than quercetin derived from apples. It was surmised that this may be due to the differences in quercetin conjugates in either of the two. Further study examined the same quercetin conjugates from apple peel and onion, both quercetin and quercetin-3-glucoside. The study found that there was no free quercetin in apple peel extract and very little quercetin-3-glucoside was absorbed by the treated cells. On the other hand, onion was shown to have some free quercetin and greater amounts of quercetin glucosides, and the absorption of quercetin was much great in the cells treated with onion extracts than from the apple extracts [7]. Other studies have shown that in regards to apple extracts, which most of the phytochemical bioavailability revolved around, overall, catechins and quercetin glucosides seem to be the best absorbed of the apple phytochemicals, with the procyanidins and anthocyanins (if present) being not as well absorbed [11]. Uniquely, the phytochemical lectin was shown to resist digestion resulting in high bioavailability [12]. This feature allows the cellular mechanisms of the host to utilize the full potential of the anti-cancer properties lectin has to offer. Thus, high intake of lectins can have dramatic anti-cancer benefits. Future study is needed in regards to the bioavailability of phytochemicals. Moreover, due to the extensive evidence that phytochemicals derived from apple extracts have promising anti-cancer effects, high-concentration delivery methods should be a future consideration for study.

Phytochemicals in Cancer Treatment

The Role of Phytochemicals in Cancer Treatment as Synergistic Agents

Implementing the use of phytochemicals as a direct treatment against established cancer cells may seem like a relatively new concept. Modern science has repeatedly shown the efficacy of natural plant products as synergistic agents against cancer cells and, all phytochemicals tend to increase the therapeutic effect by blocking one or more targets of the signal transduction pathway by increasing the bioavailability of the other drug, or by stabilizing another drug in the system [13]. An example being the use of the phytochemical curcumin as a synergistic agent along with modern chemotherapy drugs such as tamoxifen, cisplatin, daunorubicin, and vincristine [14]. The potency of a combination such as this was witnessed in a study conducted by Li et al. [15] which showed that an apple oligogalactan enhanced the growth inhibitory effect of the COX-2 inhibitor celecoxib in colitis-associated colorectal cancer. Impressively, the study showed the phytochemicals to be effective both in vitro and in mouse models in vivo. Studies have shown that curcumin sensitizes drug-resistant cells. In one such study, curcumin actually reversed multi-drug-resistance in certain cancer cells and facilitated the accumulation of doxorubicin and mitoxantrone in those cells, thereby increasing the cells sensitivity to the chemotherapeutic drugs [14]. Correspondingly, potentially beneficial interactions between curcumin and other dietary phytochemicals such as quercetin, found in apples, onions, and citrus fruits have been found [16]. This would imply that a diet rich in phytochemical-containing foods could be used as a first line of defense, or as a compliment to traditional cancer treatments. On the other end of the spectrum, curcumin has been shown to protect DNA from chromatid breaks induced by radiation and there is also evidence that a number of other phytochemicals provide an extended window of protection against low-dose, low-dose-rate irradiation, including therapeutic potential when administered after irradiation [17, 18]. This shows that curcumin has the potential to take a pivotal role in cancer treatment in the near future.

The Role of Phytochemicals in Cancer Treatment as Stand-Alone Agents

Aside from synergistic effects, there is evidence that shows that phytochemicals are effective as stand-alone anti-cancer agents. In a recent study, extract isolated from the peel of organic Gala apples, conveyed a significant decrease in viability of a variety of cancer cell lines. Specifically, the study showed a significant decrease in growth and clonogenic survival of human prostate carcinoma CWR22Rv1 and DU 145 cells and breast carcinoma Mcf-7 and Mcf-7:Her18 cells. Furthermore, the apple peel extract exerted a G0-G1 phase arrest of prostate and breast cancer cells, as well as a marked increase in the tumor suppressor protein maspin that negatively regulates cell invasion, metastasis, and angiogenesis [19]. A study carried out by McCann et al. found similar results, indicating that a crude extract of apple phenolics inhibits carcinogenesis, as well as improves barrier function and protects DNA from damage [20]. Evidence that phytochemicals can act as stand-alone anticancer agents is a great advancement in cancer research due to the wide availability of their sources and relatively cheap price. Another mechanism under which phytochemicals have been shown to exert their anti-cancer effects is through redox reactions. In one particular situation, phenolic phytochemicals were shown to both scavenge the H2O2 utilized as signaling molecules in metastatic cancer cells to aid in survival and proliferation, as well as create the adverse situation in which they induced the formation of H2O2 to achieve intolerable levels of oxidative stress on the cancer cells, leading to cell cycle arrest and apoptosis [21]. There are other examples of phytochemicals inducing cell cycle arrest, leading to apoptosis in cancer cells from a variety of different angles. Kern et al. [22] explored the interaction

between apple extracts and Protein Kinase C (PKC) which is among the signaling elements that is known to play an important role in colon cancer carcinogenesis. Their study examined whether the apple polyphenols affected PKC activity that would lead to apoptosis in human colon carcinoma cell line HT29. Although the study showed that apple extract inhibited PKC activity in a cell-free system, the results showed minimal interaction occurred within intact cells. However, the apple extract was shown to induce apoptosis by the activation of caspase-3, DNA fragmentation, and cleavage of poly(ADP ribose) polymerase. So even though the study showed that PKC is not a primary target for phytochemicals in apple extract, it did show that they were successful in inducing apoptosis by other means [22]. Another study conducted by Li et al. [23] using the same HT29 human colon carcinoma cells, showed that an oligosaccharide (a phytochemical component) derived from apple decreased the HT29 cellular viability in a dose-dependent manner. Furthermore, it was shown that the apple oligosaccharide enhanced the expression of Bax, and decreased the levels of Bcl-2 and Bcl-xl. Ultimately the results indicated that apple oligosaccharide attenuated HT29 cell viability by inducing cell cycle arrest and apoptosis.

There are other studies that have positive results in regards to phytochemicals causing the induction of cell cycle arrest and apoptosis in carcinoma cells. One such study was conducted by Zheng et al. [24] who showed that apple polyphenols inhibited the proliferation and induced apoptosis in adenoid cystic carcinoma, a highly invasive and metastatic cancer, possibly through the downregulation of VEGFR-2 expression and the activation of caspase-3 expression. Similar results were reached in a study carried out by Sudan and Rupasinghe [25] when they treated hepatocellular carcinoma cells with flavonoids derived from the peels of Northern Spy apples. Their results also showed that the phytochemical inhibited proliferation, reduced cellular viability, and induced apoptosis via activation of the caspase-3 pathway. Along these same lines, a study that was conducted by Sun and Liu [26] suggested that phytochemicals derived from cranberry extracts possess the ability to suppress the proliferation of human breast cancer MCF-7 cells and that the suppression induced, at least in part, cell cycle arrest and apoptosis. Since the incidence of breast cancer is a burgeoning issue in the United States, breakthroughs in treatment are a welcomed event. Ray et al. [27] utilized bitter melon extract against the MCF-7 breast cancer cells, as well as MDA-MB-231 and primary human mammary cells as in vitro models to test the bitter melons efficacy as an anticancer agent. The study showed that bitter melon decreased the proliferation and induced apoptosis in the breast cancer cells. Moreover, studies have shown that phytochemicals and apple extracts can inhibit proliferation of MCF-7 breast cancer cells through the inhibition of TNF-α-induced NF- B activation of the MCF-7 cells by inhibiting the proteasomal activities [28].

There are many more mechanisms by which phytochemicals exert anti-cancer effects on established cancer cells. Some of which include: inhibition of proteasome activity leading to cancer cell death from the extract of apple, grapes, and onion [29]; inhibition of tumor promoter-induced carcinogenesis by blocking reactive oxygen species-mediated AP-1-MAPK activation by fresh apple peel extract [30]; the inhibition of transcription factors and suppression of cell adhesion and cell migration of highly invasive breast and prostate cancer by Ganoderma lucidum [31]; the inhibition of aromatase activity and proliferation of MCF-7aro cells in an aromatase-transfected breast cell line by white button mushrooms [32]; inhibition of the protein tyrosine kinase activity of epidermal growth factors receptors in intact colon cancer cells by apple juice extract [33]; the induction of apoptosis and necrosis in drug-sensitive and multidrug-resistant leukemia cells by *Annona glabra* (pond apple) seed extract [34]; the modulation of genes involved in toxicological defense against colon cancer risk factors by apple flavonoids in apple extract [35], and the inhibition of DNA methyltransferase proteins with the ability to reactivate silenced tumor suppressor genes in colorectal cancer by annurca apple extract [36]. This is only to name a few and many more examples can be found throughout the scientific literature.

Phytochemicals in Cancer Prevention

The role of phytochemicals in biological science has been well documented. Research in the subject goes back more than 30 years, when initial research was conducted to examine the estrogenic effects of phytochemicals in the breeding of farm animals [37]. Curcumin, resveratrol, and their related derivatives are the most studied compounds in this topic so far, yet there is a multitude of evidence that other phytochemicals act as anti-invasion, anti-angiogenic, and anti-metastatic agents [38, 39]. As their use in research has expanded, it has now been shown that phytochemicals, including phenolics, express a high rate of anticancer properties. Phenolics from a large variety of plant foods, spices and beverages have been shown to inhibit or attenuate the initiation, progression and spread of cancers in cells in vitro and in animals in vivo and are becoming increasingly important sources of anticancer compounds [5, 40]. There is a capacious amount of evidence advocating that increased consumption of 5 to 10 servings of a wide range of fruits and vegetables which are high in phytochemicals significantly reduces the incidence of cancers and other chronic diseases [41, 42]. This is of particular interest to Western culture, where the common high-fat, high-protein, low-fiber diet has been shown to increase the risk of certain cancers, particularly colorectal cancer. A recent four-arm

study has shown that mice fed Annucra Apple Polyphenol Extract for 12 weeks had a significant drop in polyps when compared to mice fed a Western diet. This supports the claim that natural phytochemicals are a plausible chemopreventive agent [43]. Apples contain high levels of polyphenols and other phytochemicals, specifically in the peel [44]. Main structural classes of apple phytochemical constituents comprise hydroxycinnamic acids, dihdrochalcones, flavonols such as quercetin glycosides, catechins and oligomeric procyanidins, and triterpenoids in the peel and anthocyanins in red apples. These phytochemicals influence multiple mechanisms important to cancer prevention in in vitro studies to include: antimutagenic activity, modulation of carcinogen metabolism, antioxidant activity, anti-inflammatory mechanisms, modulation of signal transduction pathways, antiproliferative and apoptosis-inducing activity, as well as novel mechanisms on epigenetic events and innate immunity [11]. The evidence of phytochemicals as a potent inhibitor of carcinogenesis continues in further studies. One such study showed that phytochemicals inhibited the serum and growth factor-stimulated proliferation of cultured human cancer cell lines. While among animal models, phytochemicals inhibited serum prostate-specific antigens and induced p21 by a py p53-independent pathway. Furthermore, the study showed phytochemicals inhibited epidermal growth factor autophosphorylation and NF-kappa B activation [37]. In observational studies, note has been taken that populations with a diet high in phytochemicals show a marked decrease in the risk of developing cancers. An example of this was observed in certain Asian populations carrying a lower risk of breast and endometrial cancer when compared to Western-born Asian women. The American-born Asian populations under observation had as much as a 60 % higher risk of developing breast cancer relative to the women born in Asia. The link was tied to diet, where Asian-born women ate more vegetables and soy which are high in phytochemicals [45]. Along these same lines, the chemopreventive properties of phytochemicals were highlighted in a Finnish study, where apple consumption in 10,000 men and women was associated with a lower risk of lung cancer. Moreover, the results of a case-control study of 528 cases and 528 controls conducted in Hawaii found statistically significant inverse associations between lung cancer risk and onions and apples as a main food source of the phytochemical quercetin [46]. Another example of phytochemical use in cancer prevention comes from a study that utilized Indole-3-Carbinol, a metabolite from cruciferous vegetables, to hinder human mammary carcinogenesis. The experiment was conducted on reduction mammoplasty derived 184-B5 cells initiated with chemical carcinogen (184-B5/BP) or with oncogene (184-B5/HER), and on mammary-carcinoma-derived MDA-MD-231 cells to study, among other things, whether Indole-3-Carbinol inhibits proliferation in initiated transformed cels. The study concluded that the phytochemical Indole-3-Carbinol does have cancer-preventive efficacy when it showed that transformed cells treated with the substance had a 2-fold increase in cellular apoptosis, and a 54 %-61 % inhibition of growth [47]. Furthermore, a study of phytochemicals from Red Delicious apple peels showed that the isolated compounds quercetin and quercetin-3-O-β-d-glucopyranoside showed potent antiproliferative activities against HepG2 and MCF-7 cells [48]. Similarly, in a study conducted in 2014, apple extract was demonstrated to suppress rat tongue carcinogenesis through anti-inflammatory activity and apoptosis [49]. Finally, in a study of 7209 cancer patients suffering from a range of different cancers to include: 598 patients with cancers of the oral cavity and pharynx, 304 of the oesophagus, 460 of the larynx, 1953 of the colorectum, 2569 of the breast, 1031 of the ovary ad 1294 of the prostate. The cancer patients were compared to 6629 patients admitted to the same network of hospitals as cases for acute, non-neoplastic diseases using multivariate ratios allowing for demographic and biological differences. The results of the study showed that patients who reported eating one of more apples per day had a statistically significant decrease in incidence of cancer [50]. Although this study has its obvious limitations, the inverse association between apple consumption and the risk of various cancers lends credence to the hypothesis that phytochemicals help prevent multiple types of human cancers. The evidence supporting the use of phytochemicals against cancer does not stop at prevention. There is a mountain of evidence showing that phytochemicals can be used to directly treat established cancers as well. However, when considering phytochemicals as an in vivo agent against established cancers, one must consider the factors of bioavailability and metabolism.

Conclusion

The evidence seems to be clear that phytochemicals have promising anti-cancer properties, yet this review has only scratched the surface of what these chemical derivatives have to offer. Apple extracts appear to perhaps have one of the most promising futures in the fight against cancers. It is recommended that apple extracts be explored in other avenues of cancer treatments in the future. Furthermore, there are many medicinal plants used in foreign cultures that have not been subjected to in vitro and in vivo studies that should also be considered for future study.

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Compliance with Ethical Standards

Conflict of Interest The authors have declared no conflicts of interest.

References

1. Siegel R, Ma J, Zou Z, Jemal A (2014) Cancer statistics, 2014. CA Cancer J Clin 64(1):9–29
2. Wang H, Khor TO, Shu L, Su Z, Fuentes F, Lee J-H, Kong A-NT (2012) Plants against cancer: A review on natural phytochemicals in preventing and treating cancers and their druggability. Anti Cancer Agents Med Chem 12(10):1281
3. Halberstein RA (2005) Medicinal plants: historical and cross-cultural usage patterns. Ann Epidemiol 15(9):686–699
4. Simon JJ (2002) Phytochemicals & cancer. Journal of Chiropractic Medicine 1(3):91–96
5. Wahle KW, Brown I, Rotondo D, Heys SD (2010) Plant phenolics in the prevention and treatment of cancer. Bio-Farms for Nutraceuticals. Springer, In, pp. 36–51
6. Johnson D, Walker C (1999) Cyclins and cell cycle checkpoints. Annu Rev Pharmacol Toxicol 39(1):295–312
7. Boyer J, Liu RH (2004) Apple phytochemicals and their health benefits. Nutr J 3(5):12
8. Koch TC, Briviba K, Watzl B, Fähndrich C, Bub A, Rechkemmer G, Barth SW (2009) Prevention of colon carcinogenesis by apple juice in vivo: impact of juice constituents and obesity. Mol Nutr Food Res 53(10):1289–1302
9. Kahle K, Kraus M, Scheppach W, Richling E (2005) Colonic availability of apple polyphenols–a study in ileostomy subjects. Mol Nutr Food Res 49(12):1143–1150
10. Hollman PC, van Trijp JM, Buysman MN, van der Gaag MS, Mengelers MJ, de Vries JH, Katan MB (1997) Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man. FEBS Lett 418(1):152–156
11. Gerhauser C (2008) Cancer chemopreventive potential of apples, apple juice, and apple components. Energy (Kcal/kJ) 54:227
12. De Mejía EG, Prisecaru VI (2005) Lectins as bioactive plant proteins: a potential in cancer treatment. Crit Rev Food Sci Nutr 45(6): 425–445
13. HemaIswarya S, Doble M (2006) Potential synergism of natural products in the treatment of cancer. Phytother Res 20(4):239–249
14. Kawasaki BT, Hurt EM, Mistree T, Farrar WL (2008) Targeting cancer stem cells with phytochemicals. Mol Interv 8(4):174
15. Li Y, Niu Y, Sun Y, Mei L, Zhang B, Li Q, Liu L, Zhang R, Chen J, Mei Q (2014) An Apple Oligogalactan Potentiates the growth inhibitory effect of celecoxib on colorectal cancer. Nutr Cancer 66(1): 29–37
16. Basnet P, Skalko-Basnet N (2011) Curcumin: an anti-inflammatory molecule from a curry spice on the path to cancer treatment. Molecules 16(6):4567–4598
17. Moiseeva EP, Almeida GM, Jones GD, Manson MM (2007) Extended treatment with physiologic concentrations of dietary phytochemicals results in altered gene expression, reduced growth, and apoptosis of cancer cells. Mol Cancer Ther 6(11):3071–3079
18. Weiss JF, Landauer MR (2003) Protection against ionizing radiation by antioxidant nutrients and phytochemicals. Toxicology 189(1):1–20
19. Reagan-Shaw S, Eggert D, Mukhtar H, Ahmad N (2010) Antiproliferative effects of apple peel extract against cancer cells. Nutr Cancer 62(4):517–524
20. McCann M, Gill C, O'Brien G, Rao J, McRoberts W, Hughes P, McEntee R, Rowland I (2007) Anti-cancer properties of phenolics from apple waste on colon carcinogenesis in vitro. Food Chem Toxicol 45(7):1224–1230
21. Loo G (2003) Redox-sensitive mechanisms of phytochemical-mediated inhibition of cancer cell proliferation (review). J Nutr Biochem 14(2):64–73
22. Kern M, Pahlke G, Balavenkatraman KK, Böhmer FD, Marko D (2007) Apple polyphenols affect protein kinase C activity and the onset of apoptosis in human colon carcinoma cells. J Agric Food Chem 55(13):4999–5006
23. Li Q, Zhou S, Jing J, Yang T, Duan S, Wang Z, Mei Q, Liu L (2013) Oligosaccharide from apple induces apoptosis and cell cycle arrest in HT29 human colon cancer cells. Int J Biol Macromol 57:245–254
24. Zheng C-Q, Qiao B, Wang M, Tao Q (2013) Mechanisms of apple polyphenols-induced proliferation inhibiting and apoptosis in a metastatic oral adenoid cystic carcinoma cell line. The Kaohsiung Journal of Medical Sciences 29(5):239–245
25. Sudan S, Rupasinghe HV (2014) Flavonoid-enriched Apple Fraction AF4 induces cell cycle arrest, DNA Topoisomerase II inhibition, and apoptosis in human liver cancer HepG2 cells. Nutr Cancer 66(7):1237–1246
26. Sun J, Liu RH (2006) Cranberry phytochemical extracts induce cell cycle arrest and apoptosis in human MCF-7 breast cancer cells. Cancer Lett 241(1):124–134
27. Ray RB, Raychoudhuri A, Steele R, Nerurkar P (2010) Bitter melon (*Momordica charantia*) extract inhibits breast cancer cell proliferation by modulating cell cycle regulatory genes and promotes apoptosis. Cancer Res 70(5):1925–1931
28. Yoon H, Liu RH (2007) Effect of selected phytochemicals and apple extracts on NF-κB activation in human breast cancer MCF-7 cells. J Agric Food Chem 55(8):3167–3173
29. Chen M, Chen D, Dou Q (2004) Inhibition of proteasome activity by various fruits and vegetables is associated with cancer cell death. In vivo Athens, Greece 18(1):73
30. Ding M, Lu Y, Bowman L, Huang C, Leonard S, Wang L, Vallyathan V, Castranova V, Shi X (2004) Inhibition of AP-1 and neoplastic transformation by fresh apple peel extract. J Biol Chem 279(11):10670–10676
31. Sliva D (2003) Ganoderma lucidum (reishi) in cancer treatment. Integrative Cancer Therapies 2(4):358–364
32. Grube BJ, Eng ET, Kao Y-C, Kwon A, Chen S (2001) White button mushroom phytochemicals inhibit aromatase activity and breast cancer cell proliferation. The Journal of Nutrition 131(12):3288–3293
33. Kern M, Tjaden Z, Ngiewih Y, Puppel N, Will F, Dietrich H, Pahlke G, Marko D (2005) Inhibitors of the epidermal growth factor receptor in apple juice extract. Mol Nutr Food Res 49(4):317–328
34. Cochrane CB, Nair PR, Melnick SJ, Resek AP, Ramachandran C (2008) Anticancer effects of *Annona glabra* plant extracts in human leukemia cell lines. Anticancer Res 28(2 A):965–971
35. Veeriah S, Kautenburger T, Habermann N, Sauer J, Dietrich H, Will F, Pool-Zobel BL (2006) Apple flavonoids inhibit growth of HT29 human colon cancer cells and modulate expression of genes involved in the biotransformation of xenobiotics. Mol Carcinog 45(3):164–174
36. Fini L, Selgrad M, Fogliano V, Graziani G, Romano M, Hotchkiss E, Daoud YA, Edward B, Boland CR, Ricciardiello L (2007) Annurca apple polyphenols have potent demethylating activity and can reactivate silenced tumor suppressor genes in colorectal cancer cells. The Journal of Nutrition 137(12):2622–2628
37. Barnes S (2001) Role of phytochemicals in prevention and treatment of prostate cancer. Epidemiol Rev 23(1):102–105
38. Sagar SM, Yance D, Wong R (2006) Natural health products that inhibit angiogenesis: a potential source for investigational new agents to treat cancer—part 1. Curr Oncol 13(1):14
39. Weng C-J, Yen G-C (2012) Chemopreventive effects of dietary phytochemicals against cancer invasion and metastasis: phenolic acids, monophenol, polyphenol, and their derivatives. Cancer Treat Rev 38(1):76–87
40. Shu L, Cheung K-L, Khor TO, Chen C, Kong A-N (2010) Phytochemicals: cancer chemoprevention and suppression of tumor onset and metastasis. Cancer Metastasis Rev 29(3):483–502

41. Liu RH (2004) Potential synergy of phytochemicals in cancer prevention: mechanism of action. The Journal of Nutrition 134(12): 3479S–3485S
42. Russo GL (2007) Ins and outs of dietary phytochemicals in cancer chemoprevention. Biochem Pharmacol 74(4):533–544
43. Fini L, Piazzi G, Daoud Y, Selgrad M, Maegawa S, Garcia M, Fogliano V, Romano M, Graziani G, Vitaglione P (2011) Chemoprevention of intestinal polyps in ApcMin/+ mice fed with western or balanced diets by drinking annurca apple polyphenol extract. Cancer Prevention Research 4(6):907–915
44. Wolfe K, Wu X, Liu RH (2003) Antioxidant activity of apple peels. J Agric Food Chem 51(3):609–614
45. Cline JM, Hughes CL Jr (1998) Phytochemicals for the prevention of breast and endometrial cancer. Biological and hormonal therapies of cancer. Springer, In, pp. 107–134
46. Zessner H, Pan L, Will F, Klimo K, Knauft J, Niewöhner R, Hümmer W, Owen R, Richling E, Frank N (2008) Fractionation of polyphenol-enriched apple juice extracts to identify constituents with cancer chemopreventive potential. Mol Nutr Food Res 52(S1): S28–S44
47. Telang NT, Katdare M, Bradlow HL, Osborne MP, Fishman J (1997) Inhibition of proliferation and modulation of estradiol metabolism: novel mechanisms for breast cancer prevention by the phytochemical indole-3-carbinol. Experimental Biology and Medicine 216(2):246–252
48. He X, Liu RH (2008) Phytochemicals of apple peels: isolation, structure elucidation, and their antiproliferative and antioxidant activities. J Agric Food Chem 56(21):9905–9910
49. Ribeiro FAP, de Moura CFG, Gollucke APB, Ferreira MS, Catharino RR, Aguiar O, Spadari RC, Barbisan LF, Ribeiro DA (2014) Chemopreventive activity of apple extract following medium-term oral carcinogenesis assay induced by 4-nitroquinoline-1-oxide. Arch Oral Biol 59(8):815–821
50. Gallus S, Talamini R, Giacosa A, Montella M, Ramazzotti V, Franceschi S, Negri E, La Vecchia C (2005) Does an apple a day keep the oncologist away? Ann Oncol 16(11):1841–1844