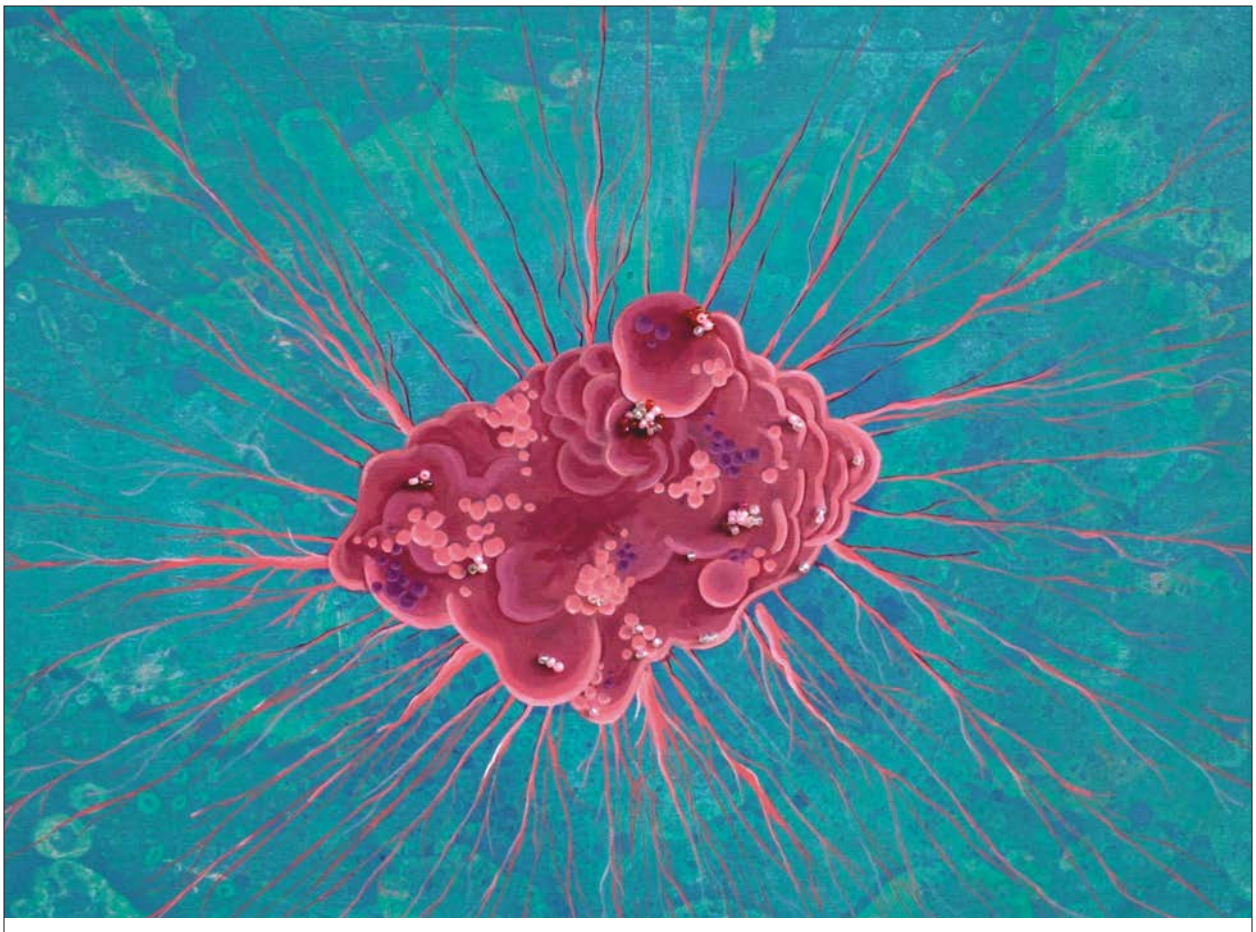

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Experimental Approach to Treatment of Colorectal Cancer by Herbs and Their Constituents: An Overview on *in vivo* and *in vitro* Protocols and Molecular Targets

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ABSTRACT

Behind the alluring fame of established drugs in a magical cure of some types of cancers are myriad toxicities. Hence, it became imperative to search alternative approaches of treatment. Although a large number of papers are published to show that herbs, plant products and their constituents are capable to inhibit the growth of a variety of human colon carcinoma cell lines, there is a gross neglect on an impact of *in vivo* outcome which show overall effects. The present study on an experimental approach to treatment of Colorectal Cancer (CRC) by herbs, plant products and their constituents was undertaken to review the (1) adverse effects of established drugs used against CRC, (2) herbs, plant products and their constituents as alternatives to established drugs, (3) *in vivo* studies on herbs, plant products and their ingredients, (4) *in vitro* studies on herbs, plant products and their ingredients, (5) pros and cons of *in vivo* and *in vitro* studies, (6) molecular targets and (7) conclusion. The articles included were peer reviewed English language articles published up to November 2011. These were selected from Pub Med, Pub Med Central, Science Direct, Up-to-date, Med Line, Comprehensive databases, Cochrane library and the internet (Google, Yahoo). The search strategy corresponded with points, 1-6 above. The literature obtained is reviewed. It is suggested that the laboratories working on CRC with *in vitro* protocol may also undertake confirmatory *in vivo* experimentation with an application of gene expression profiling using microarray technologies.

Key words: Colorectal cancer, established drugs, toxicities, herbal treatment, molecular targets

INTRODUCTION

Notwithstanding the global efforts to find a definite and cost effective cure for CRC, it remains the third most common malignancy and the third leading cause of cancer death worldwide. The world records of CRC (both sexes) in 2008 showed 1234,000 cases diagnosed and 608,000 deaths (Globocan, 2008). The ghastly reality entails miserable saga of the fatal ailment, which attract

world-wide efforts to find a cure. Reports in the literature (Al-Anazi *et al*., 2011) do not associate gene polymorphism with colon cancer susceptibility in Saudi Arabia, however; there are a number of risk factors including diet poor in fibers and high in meat and fats (McKeown-Eyssen, 1994; Panala *et al*., 2009) in addition to physical inactivity and obesity (Gunter and Leitzmann, 2006). There are wide options of chemotherapy for treatment of CRC by established drugs, however; they are well known for their adverse effects, including hepatotoxicity, nephrotoxicity, neurotoxicity, in addition to metastasis and relapse (Taixiang *et al*., 2005). Hence, in pursuit of finding alternatives to the established drugs, there is an ongoing global search. The most suitable option remains the herbs, plant products and their ingredients. Although, a large number of papers are published to show that herbs, plant products and their constituents are capable to inhibit the growth of a variety of human colon carcinoma cell lines, there is a gross neglect on an impact of *in vivo* outcome which show overall effects. Furthermore, very few experiments performed on herbs and plant products and their ingredients involve gene expression profiling using microarray technologies. This review is an attempt to gather information on the adverse effects of synthetic drugs and the use of herbs, plant products and their constituents against treatment of CRC by both *in vivo* and *in vitro* treatment protocols, the relevance of *in vivo* experiments and application of gene expression profiling using microarray technologies. The literature obtained is discussed and concluded.

Published articles selected for inclusion in this review are based on the significance and understanding of literature search on adverse effects of synthetic drugs used in the treatment of CRC and use of herbs, plant products and their constituents in experimentation (*in vitro* and *in vivo*) against CRC, pros and cons of *in vitro* and *in vivo* protocols, application of gene expression profiling using microarray technologies. To meet this criterion, peer reviewed English language articles published up to November 2011 were selected from Pub Med, Pub Med Central, Science Direct, Up-to-date, Med Line, Comprehensive databases, Cochrane library and the internet (Google, Yahoo). The search strategy combined terms that included the title and the keywords, besides, the core of description in the review.

REVIEW OF LITERATURE

The present study is a systematic collection of literature on (1) adverse effects of established drugs used against CRC, (2) alternative approaches to established drugs, (3) *in vivo* studies (herbs and plant products, formulation and mixtures, ingredients), (4)*in vitro* studies (herbs and plant products, formulation and mixtures, ingredients), (5) pros and cons of *in vivo* and *in vitro* studies, (6) molecular targets and (7) Conclusion.

Adverse effects of established drugs: Although, the established drugs are known for their magical cure and fast relief, associated with them are innumerable toxicities, besides, resistance, metastases and relapse. Ben *et al*. (2011) reported that drugs that inhibit angiogenesis by targeting Vascular Endothelial Growth Factor (VEGF) are often used in advanced cancers including CRC. Although they are well tolerated, but cardiovascular and renal side effects may appear. Furthermore, targeting the VEGF signaling pathway are found to affect the normal function of endothelial cells in maintaining homeostasis and can cause unwanted adverse effects. The emerging experimental evidence also confirm that VEGF-targeting therapy caused less tumor cell-specific cytotoxicity, allowing residual cells to become more resistant and develop a more malignant phenotype (Chen *et al*., 2011).

A patient with advanced ascending colon cancer was admitted for surgery after undergoing therapy with 15 courses of FOLFOX6 (first line), 6 courses of FOLFOX6+bevacizumab (BV) (second line) and 3 courses of FOLFIRI+BV (third line). Upon admission for surgery, she was diagnosed to have lung injury (with predominance of lymphocytes without any evidence of infection). This was expected to be caused by anticancer drugs, as treatment with steroids reversed the lung condition. The authors concluded the lung injury to be due to irinotecan. Although, chemotherapy (S-1) was continued, it proved ineffective and the patient died 27 months after operation (Komaki *et al*., 2011). Oostendorp *et al*. (2010), in a study on second-line irinotecan monotherapy for advanced CRC, found it to be beneficial to the patients, but the treatment was associated with diarrhea, nausea, vomiting and asthenia. The chemotherapy with irinotecan and oxaliplatin before resection has been associated with steatohepatitis and vascular parenchymal injury, respectively (Ryan *et al*., 2010).

Several anticancer drugs are known to cause cardiotoxicity as a major complication however, incidence of Tako-Tsubo cardiomyopathy associated with anticancer drugs is rare. Basselin *et al*. (2011) described a patient on chemotherapy regimen with 5-fluorouracil, oxaliplatin, oxaliplatin and calcium folinate (FOLFOX protocol) for colic adenocarcinoma to develop acute coronary syndrome, which was similar to Tako-Tsubo syndrome. The patient developed cardiovascular problems to the extent of cardiac arrest. Clinical limitations such as phlebitis and catheter blockages are often observed with the administration of 5-fluorouracil (5-FU) in combination with its synergistic biomodulator folinic acid in combination. These combinations are known to have reduced efficacy and/or quality of life for patients (Stutchbury *et al*., 2011). 5-Fluorouracil (5-FU) used in treatment of various solid tumors, including colorectal, head and neck cancers has been shown to cause hematological, digestive, cutaneous and neurotoxicity. Neurotoxicity included drowsiness, acute confusion, seizure, confusion and signs of metabolic encephalopathy, in addition to dysarthria and typical 5-FU-related severe toxicities (e.g., neutropenia and mucosities) (Cordier *et al*., 2011). Treatment with systemic fluorouracil is found to cause sub-acute cutaneous lupus erythematosus (Almagro *et al*., 2011).

Venous Thromboembolism (VTE), prevalent in most cancers including colon cancer is known to have serious consequences, including high rate of recurrence, long term anticoagulation and poor quality of life and death (Al-Diab, 2010). Colorectal patients treated with epidermal growth factor receptor inhibitors develop dermatologic adverse drug reactions (Andreis *et al*., 2010). Although, Oxaliplatin is known to cause hepatic sinusoidal injury, it is one of the important drugs for the treatment of CRC. The hepatic sinusoidal injury is evaluated by splenomegaly and thrombocytopenia. Many patients of CRC, who were treated by FOLFOX therapy, had severe hepatic sinusoidal injury (Toi *et al*., 2011). Burakgazi *et al*. (2011) found oxaliplatin to cause irreversible sensory and motor axon loss.

The 5-fluorouracil (5-FU) or Cisplatin treatment in murine colon carcinoma-induced BALB/c mice were found to develop severe leucopenia, bone marrow suppression and myelotoxicity (Son *et al*., 2011). In recent years, the development of new and effective management options, such as fluoro-2-deoxy-D-glucose (FDG) Positron Emission Tomography (PET), Total Mesorectal Excision (TME) and monoclonal antibody novel "targeted" therapies have led to a considerable improvement in the outcome of this disease however, these are yet to become common.

Alternative approach to established drugs: As less invasive option and cost effective measures to disrupt the tumor cell cycle or inhibition of proliferation, induction of apoptosis and improvement

of the immune system, the use of herbs, plant products and their ingredients do not lag behind in the therapeutic measures of CRC (Wang and Yuan, 2008; Li and Chi, 2011). The use of herbal medicine has tremendously increased during the last 4 decades, because of the belief that they are non-toxic and possess superior therapeutic effect as compared to established drugs.

An impressive body of data exists in support of the concept that food ingredients (turmeric, cloves, ginger, aniseed, mustard, saffron, cardamom and garlic) can be used in preventive strategies aimed at reducing the incidence and mortality of different types of cancers, including CRC, because of their antioxidative, antimutagenic and anticarcinogenic properties (Sengupta *et al*., 2004). Literature reports suggest most of the herbs, which are anti-inflammatory (Fukutake *et al*., 1998), antioxidative, antimutagenic (Sengupta *et al*., 2004), inhibit COX-1 and COX-2 activity (Fukutake *et al*., 1998; Fukuda *et al*., 1999), cause ornithine induce apoptotic activity, cytotoxicity (Kim *et al*., 2006) and are immune restorative (Plotnikov *et al*., 2005) are suspected to possess possible anticancer activity.

***In vivo* studies**

Herbs and plant products: The herbs and plant products are often used as a whole (powders, extracts, decoctions) in the treatment. Extracts of *Coptidis rhizoma* and *Scutellariae radix* significantly inhibited AOM-induced ACF formation (Fukutake *et al*., 1998). *Coptidis rhizoma* and Scutellariae radix were found to suppress experimental colon carcinogenesis and their preventive effects were attributed to their individual ingredients berberine (*Coptidis rhizoma*) and baicalien (*Scutellariae radix*) (Fukutake *et al*., 2000). Herbs Oren (*Coptidis rhizoma*) and Ogon (*Scutellariae radix*) are found to inhibit azoxymethane-induced aberrant crypt foci formation (Fukutake *et al*., 2000). Asiamah *et al*. (2011) reported *Momordica charantia* to inhibit the Azoxymethane (AOM) induced Aberrant Crypt Foci (ACF) in Fisher 344 rats.

In a study on chemopreventive efficacy of garlic in an azoxymethane induced rodent colon carcinogenesis model, Sengupta *et al*. (2004) showed protective effects on colon carcinogenesis, as revealed by significant inhibition of cell proliferation and induction of apoptosis, as well as suppression of cyclooxygenase-2 activity, associated with significant reduction in the incidence of aberrant crypt foci. Kaneshiro *et al*. (2005) found that extracts of *Hemerocallis fulva, Ipomoea batatas, Curcuma longa* and *Nasturitum officinale* caused marked dose-dependent growth inhibition. Jianpi Huoxue herbs (JPHXH) are effective in treating post-operational colonic cancer patients with Pi Deficiency Syndrome to relieve the adverse reaction of chemotherapy (Liu *et al*., 2005).

Many herbs are known to possess potent immune-modulating effects. One such is *Ganoderma lucidum* (Lingzhi), the polysaccharide functions of this herb are reported to improve functions. A study to evaluate the effects of *G. lucidum* polysaccharides on selected immune functions in patients with advanced CRC showed that *G. lucidum* may have potential immuno-modulating effect in patients with advanced CRC (Chen *et al*., 2006).

Herbal formulations and mixtures: To meet the desired therapeutic effects, sometimes the herbs, plant products and their ingredients are used as formulations or compound mixtures. Sanshishi (Gardeniae fructus) and the traditional herbal medicine Oren-Gedoku-To (OGT), composed of Ogon, Oren, Sanshishi and Obaku, have the chemopreventive potentials against colon cancer. The parameters were aberrant crypt foci (Fukutake *et al*., 2000). The authors further investigated the mechanism of action, by analyzing the influence on cyclooxygenase-1 (COX-1) and

cyclooxygenase-2 (COX-2) activities and found that both OGT and Sanshishi inhibited COX-2 but not COX-1, contributed to their suppressive effects on ACF development. The results suggest that OGT may be useful for colon cancer chemoprevention in terms of efficacy and toxicity (Fukutake *et al*., 2000).

Herbal ingredients: Herbs and plant products contain hundreds of phytoconstituents and/or ingredients, which are used against human diseases, including some types of cancers. However, here we include the literature on ingredients which are used against the treatment of CRC. Berberine and baicalin, major ingredients of *Coptidis rhizoma* and *Scutellariae radix*, inhibited ACF formation at a dose equivalent to the amount in each herbal extract (Fukutake *et al*., 1998). The authors also found berberine and baicalein to inhibit cyclooxygenase 2 and cyclooxygenase 1 activities, respectively.

Salicylic acid, a compound present in plants functions as a hormonal mediator of the resistance response to the effect of pathogen and environmental stress. Acetylsalicylic acid (aspirin; 2-acetoxybenzoic acid) is generally used for pain relief and against inflammatory conditions and fevers. Literature reports suggest that the regular use of aspirin is associated with decreased incidence of certain cancers, particularly colon cancer (Paterson *et al*., 2006). The exact mode of action is not known, however, the authors propose that the anti-cancer effects of aspirin might be due to reduction of the transcription of prostaglandin H (2)-synthase by salicylic acid which might affect the synthesis of pro-inflammatory and potentially-neoplastic prostaglandins. Salicylic acid is present in abundant range of herbs, spices, vegetables and fruits of dietary relevance for lowering the risk of colon cancer.

Pentacyclic triterpenoid compounds, Ursolic Acid (UA) and Oleanolic Acid (OA) are found in plants in the form of aglycones or as the free acid. These compounds are used for their hepatoprotective, anti-inflammatory, antimicrobial, hypoglycemic, antimutagenic, antioxidant and antifertility activities. In a study on the formation of 1, 2-dimethyl-hydrazine (DMH)-induced Aberrant Crypt Foci (ACF) in the colon of the male Wistar rat, Furtado *et al*. (2008) found UA and OA to suppress the formation of ACF and have a protective effect against colon carcinogenesis. The major active constituents of ginseng herbs (American Ginseng and Notoginseng) are ginsenosides, which have been reported to be effective in treatment of CRC (Wang and Yuan, 2008).

Mullauer *et al*. (2011) reported the development and application of a liposome formulation of betulinic acid in mice. Liposomes were incorporated with BetA and intravenously injected into Nude mice xenografted with human colon and lung cancer tumors were effectively treated. The tumor growth was greatly reduced, almost 50% and survival was good. The oral administration of the liposomal formulation of BetA also slowed inhibition of tumor growth without any signs of systemic toxicity. Any signs of systemic toxicity caused by BetA treatment were absent. Liposomes are shown to be efficient formulation vehicle for BetA, enabling its preclinical development as a nontoxic compound for the treatment of cancers.

In vitro studies

Herbs and plant products: Kaneshiro *et al*. (2005) reported crude extracts obtained from 44 herbal plants in the Ryukyu Islands, might contain components capable of inhibiting the growth of a variety of human colon carcinoma cell lines. Dichloromethane-methanol extract of *Borassus aethiopum* Mart. is shown to induce apoptosis in human colon cancer (HT-29 cells) (Sakande *et al*., 2011). Jing *et al*. (2011) found *Boesenbergia rotunda* to induce significant inhibitions of colon cell

line (HT-29). *Solanum aculeastrum* berries are found to be anti proliferative against human colon cell line (HT-29) (Koduru *et al*., 2006). Abd Malek *et al*. (2008) showed weak cytotoxic activity of *Pereskia bleo* against human colon carcinoma cell line (HCT 116). Aqueous extract of Fructus Ligustri Lucidi (AFLL) has been shown to enhance the sensitivity of colon cancer cells (DLD-1) to doxorubicin-induced apoptosis. The expression of Tbx3 was found to be repressed by AFLL upon the activation of tumor suppressor genes (p14 and p53). These findings suggest that AFLL has a chemotherapy potential in treatment of human colorectal carcinoma (Zhang *et al*., 2011).

Herbal formulations and mixtures: PC-SPES, a mixture of eight herbs has been shown to have antitumor activity against cancer cell lines of breast, melanoma, and leukemia. The studies of the different components of this mixture showed that these components, either independently or in combination are effective against the tumor initiation and progression of colon cancer (Huerta *et al*., 2002). In an evaluation of the anti-cancer activity of an ethanol extract of Ka-Mi-Kae-Kyuk-Tang (KMKKT), a formula of ten Oriental herbs, Lee *et al*. (2006) found that the extract suppressed the invasion ability of the mouse colon 26-L5 cancer cells *in vitro* and decreased their formation of liver metastasis when intraportally inoculated in syngenic mice.

Tian-Xian liquid (TXL), a commercially available Chinese medicine decoction has been used as an anticancer dietary agent for more than 10 years without reported side effects. In a study on HT29 human colon cancer cell line and tumor-bearing nude mice, Sze *et al*. (2011) demonstrate that TXL possesses antiproliferative and antimetastatic activities and brings about reversion of MDR on HT29 cell and on xenografted tissue in tumor-implanted nude mice. The researchers also demonstrated the safety and quality of TXL extract.

Herbal ingredients: Monoterpenes, including geraniol found in essential oils of herbs and fruits are suggested to be effective in cancer chemoprevention. There was a 50% decrease of ornithine decarboxylase activity (a key enzyme of polyamine biosynthesis, which is enhanced in cancer growth). There was a 40% reduction of the intracellular pool of putrescine. Geraniol also activated the intracellular catabolism of polyamines, indicated by enhanced polyamine acetylation. These observations indicate that polyamine metabolism is presumably a target in the antiproliferative properties of geraniol. There were no signs of cytotoxicity or apoptosis detected (Chen *et al*., 2006).

The anticarcinogenic effects of eight flavanones (flavanone, 2'-OH flavanone, 4'-OH flavanone, 6-OH flavanone, 7-OH flavanone, naringenin, nargin and taxifolin) were investigated in colorectal carcinoma cells (HT29, COLO205 and COLO320HSR). Investigation on MTT assay showed 2'-OH flavanone to have the most potent cytotoxic effect on these three cells, both *in vivo* and *in vitro* (Shen *et al*., 2004). In a study on parallel treatment of Huangqi compounds and chemotherapy, Taixiang *et al*. (2005) found that the compounds of herbs may stimulate immune-competent cells and decrease side effects in patients treated with chemotherapy.

Betulinic acid (BetA) is a plant-derived pentacyclic triterpenoid which is known to have effective *in vitro* activity against several cancers, including colorectal, prostate, lung, cervix and breast cancer, melanomas, neuroblastomas and leukemias. There are no cytotoxic effects of the compound against healthy cells which projects BetA a promising candidate against cancer treatment. Nevertheless, due to the solubility problems, it was difficult to study this compound *in vivo* (Mullauer *et al*., 2011).

Polyphenols in herbs, fruits, soybean and vegetables are known to act as bioactive components related with prevention of cancer by inducing apoptotic activity. In a study on apoptotic effects of

red wine polyphenols on human colon cancer cells (SNU-C4), Kim *et al.* (2006) found increase in the apoptotic activity, as revealed by different relevant parameters. The Caspase-3 activity was significantly increased suggesting that polyphenols have a strong potential for development as an anti-colon cancer agent. Beta-elemene, a natural compound extracted from over 50 different Chinese medicinal herbs and plants, has been effective in the treatment of brain, breast, cervical, colon and lung carcinoma cells (Li *et al.*, 2010).

Pros and cons of *in vivo* and *in vitro* studies: There are a large number of papers published on herbal products and their ingredients to show their capability to inhibit the growth of a variety of human colon carcinoma cell lines (Kaneshiro *et al.*, 2005). However, the studies on *in vivo* effect are neglected. Literature reports suggest similarity of *in vivo* protocol to clinical trials, in addition to its superiority to *in vitro* investigations (Jeffrey, 2007). The experiments involved in the discovery of new drugs cannot rely on *in vitro* test methods, because these methods do not resemble the drug biotransformation *in vivo* in liver. In past few decades, several *in vitro* human liver models (supersomes, microsomes, cytosol, S9 fraction, cell lines, transgenic cell lines, primary hepatocytes, liver slices and perfused liver) have been developed, but each model has several or specific drawbacks, which prevent their widespread use and acceptance by regulatory authorities as an alternative for *in vivo* screening (Brandon *et al.*, 2003).

In vivo is an experimentation that employs a whole living organism as opposed to a partial or an *in vitro* in a controlled environment. Animal testing and clinical trials remains the ultimate two forms of *in vivo* research. *In vivo* testing is often preferred over *in vitro* protocol because it is better suited for observing the overall effects of an experiment on a living subject (Jeffrey, 2007) however, *in vivo* experimentation is losing a common application. However, the experiments conducted on *in vivo* studies have their own demerits. They involve cumbersome methods to obtain the colorectal tissue and sacrifice of many animals at different stages of progression. Nevertheless, during the early part of the third millennium, visual colonoscopy was developed in mice with a traditional pediatric cytoscope (2 mm diameter, rigid) to identify raised tumors by surface topology. With this discovery, the method of serial sacrifice of animals can be substituted by the method of Murine colonoscopy that can allow time to time evaluation and mucosal biopsies of the same animal (Huang *et al.*, 2002).

It is interesting to note that extensive investigations have been undertaken on the transplantable tumors during the last 2 to 3 decades. The goal of these studies was to improve techniques in cancer therapy that can combine both *in vitro* and *in vivo* evaluation, simultaneously (Ozaslan *et al.*, 2011). While experimental tumors have great significance for the purposes of modeling, Ehrlich Ascites Carcinoma (EAC) is one of the commonest (Ozaslan *et al.*, 2011). The peritoneal cavity of the animal serves as the most sterilized natural incubator for the growth of the malignant cells allowing almost all the studies, including chemotherapy, survival time, body weight changes, total ascitic volume, cytotoxicity of the EAC cells, impact of preventive agents on biochemical, molecular and genetic changes and toxicity (Qureshi *et al.*, 2000, 2001; Asiri, 2009; El-Naggar *et al.*, 2011). Literature reports suggest positive indication of the anti-carcinogenic potentials of a number of herbs, plant products and their ingredients including, *Commiphora molmol* (Qureshi *et al.*, 1993; Al-Harbi *et al.*, 1994), *Macrosolen parasiticus* (Sodde *et al.*, 2011), *Ocimum sanctum* (Islam *et al.*, 2011) and anethole (Al-Harbi *et al.*, 1995).

Although, the prognosis for patients with early stage colon cancer is good, but majority of these cancers are diagnosed at later stages. Most drug development strategies use transplantation of human tumor cells into genetically engineered mouse models, which make them a suitable platform for biomarker discovery, study of cancer biology and preclinical therapeutic trials (Hung *et al*., 2010). There are many animal models for different cancers in humans which can be used for *in vivo* experiments. Mice and rat models for the study of colonic aberrant crypt foci induced by azoxymethane (Panala *et al*., 2009) is one such example, which can analyze quite a lot of preventive agents against CRC (Adhami *et al*., 2009).

Molecular targets: Many techniques (X-ray, imaging, computed tomography scan, magnetic resonance imaging, auto-fluorescence) have been employed in early detection, diagnosis and prognosis of the malignant diseases (Masilamani *et al*., 2004, 2011). However, the significance of genetic changes has not been realized. The knowledge of genetic changes that cause colorectal cancer has important ramifications for prevention, detection and treatment of this disease (Fahy and Bold, 1998). The techniques of gene array and proteomics have been used to investigate the response of colo-rectal cancer cells to chemotherapeutic agents, including butyrate (Williams *et al*., 2003). Mariadason *et al*. (2004) reported use of gene expression profiling as a tool to customize chemotherapy in colon cancer is an attainable goal in the foreseeable future. The regulation of gene expression in a post-transcriptional manner can be regulated by non-coding RNAs called MicroRNAs. These MicroRNAs play a major role in regulation of cell proliferation, differentiation, apoptosis and immunity. Their link with cancer progression, angiogenesis, metastasis and chemotherapy resistance of tumors has become vital issues in epigenetics of cancer (Liu and Chen, 2010). The application of MicroRNAs techniques as biomarkers in diagnosis and prognosis and treatment of cancer will be a boon to researches in development of novel therapeutic agents against CRC. Taken together, the innovations in researches on CRC can be used in improvement in the prevention, detection and treatment of the disease, however, these ramifications are yet to reach the common laboratory.

CONCLUSION

The established drugs used in the treatment of CRC are well known for their adverse effects, hence; there has been always a pursuit for safe alternatives. In view of their most publicized non-toxic nature, the herbs and their ingredients are given priority. Currently, there is a wide range experimentation on their therapeutic potentials by *in vitro* protocol, while the *in vivo* method is grossly neglected, despite of the fact that the *in vitro* experiments do not resemble the drug biotransformation *in vivo*. Nevertheless, the experiments conducted on *in vivo* studies involve burdensome and time consuming methods to obtain the colonic tissue with sacrificing many animals at different stages of progression of the disease. Although, the more sophisticated methods of colonoscopy in rodents do exist, but they are yet to become common. Furthermore, the post-genomic technology has revolutionized our ability to characterize and recognize the molecular profiles to identify more effective and better tolerated preventive agents, however; very few experiments performed on herbs, plant products and their ingredients involve gene expression profiling using microarray technologies. It is suggested that the laboratories working on *in vitro* protocol may also undertake confirmatory *in vivo* experimentation with an application of gene expression profiling using microarray technologies.

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