

# Cancer Chemoprevention and Dietary Phytochemicals in Cancer Management

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Received Dec. 09, 2017

Accepted Jan. 10, 2018

## ABSTRACT

*Cancer is a multifactorial disorder involving various steps to initiate, develop, grow and sustain in the human body. In simple words, we can say it is a disease where uncontrolled cell division affects tissue homeostasis, leading to tumour development which is capable of causing the death of an individual. As a deadly multifactorial disease, cancer affects individual's health and socioeconomic life too. Globally, millions of people are being affected by this disease every year. So, it's been the high curiosity among the scientific community to disclose more and more about causes, diagnostics, treatments, and prevention of cancer. Herein, we are putting some efforts to increase small but significant knowledge about cancer in respect of mechanistic approach of natural compound with the potential of usage in prevention and treatment of disease.*

**Keywords:** Cancer, Chemoprevention, Phytochemicals, Radiation Therapy.

## Introduction

Ancient observation of this disease was found in Egypt around 3000 BC, known as Edwin Smith papyrus which is an Egyptian textbook on trauma surgery. Hippocrates, the father of medicine coined the term carcinos and carcinoma to the non-ulcer forming and ulcer forming tumours found in breast, uterus and stomach lesions (Garrison, 1926). Aulus Celsus a Roman physician, later on, mentioned the term "cancer" in his *De Medicina*. Compilation of treatment strategies for cancer was done way back in 23-79 AD by Pliny in his *Materia Medica*. He includes major herbal compounds as therapies in advanced cancer for internal usage. Surgery was introduced by Albucasis as a cancer treatment in Europe. Heneri de Mondeville was the first to introduce the classification of cancer as per size, anatomical site and localisation of a tumour. A first printed case report for cancer was published by Antonion Benivieni in 1507 whose description narrates the incidence of gastric carcinoma, though cancer word was not used in the description. In a nearly 16<sup>th</sup> century, Paracelsus introduced the application of chemical agents as therapy for cancer, so he was the pioneer of chemotherapy. He used mercury, lead, sulfur, copper and zinc as an internal remedy with the warning that all these chemicals are potential harmful poisons, dose and concentration of it make them piousness or non-piousness. Finally, in the 1700s, first scientific report on tumours was published by Royal Society of London. All above mentioned and many more physicians had a fundamental role in recognising this deadly disease. Cancer is a leading cause of death globally with 8.2 million deaths in 2012 (Ferlay et al., 2015). Comparison of cancer incidences between 2005 and 2015, indicates 33% of overall increase globally (Fitzmaurice et al., 2017). The lung cancer and breast cancer were leading both incidences and mortality rate of men and women worldwide respectively in 2012.

In India, total incidence and mortality rates due to top ten cancers are highest among females. Overall incidences and mortality of Indian female due to breast and cervical cancer accounts for total incidences and mortality of the top three cancer for Indian male. With the highest mortality and incidence, lung cancer leads Indian male population followed by oral and stomach cancer (Fitzmaurice et al., 2017).

## Present Strategies for Cancer Management

Due to the limited treatment options, cancer can be cured if diagnosed earlier in the developing stage. Surgery is the oldest way to treat the localised solid tumour. Apart from surgery radiation therapy, chemotherapy and biologic therapy are available option to treat advanced stages of cancer and used to combat with recurrence. The surgery and radiation are considered as local treatments, and chemo and biologic therapy are systematic treatment as former one affects specific areas surrounding tumour while later one affects the entire body. Both chemoprevention and chemotherapy of cancer grow more and more with increased knowledge of molecular targets and fundamental of carcinogenesis. In the last decade of 20<sup>th</sup>-century concept of biologic therapy as a treatment of cancer was stabilised wherein viruses, bacteria, vaccines, molecular antibody, cytokines and genes were used for cancer treatment. With all lines of treatment modalities, in 1997 the mortality rate due to cancer was declined, which was all-time higher declined rate as it was doubled then the rate of decline in previous years (DeVita and Chu, 2008).

### **Tumor invasion and metastasis**

Tumors can invade locally to nearby tissues or can shed their cells into circulation through which they can reach up to distant locations, and new tumours can be formed (secondary and tertiary) these processes are known as invasion and metastasis respectively. These are the two events that result in the death of most patients from cancer. As a tumour advances the cells change their shape and become anchorage independent, they also lose their physical attachment with other cells as well as with extracellular matrix. One of the best-characterized modification by cancerous cells is loss of E-cadherin, a major transmembrane glycoprotein and cell to cell adhesion molecule. Through adjoining adjacent cells, E-cadherin assists in assembling epithelial cell sheets and keep the quiescence of the cells within these sheets. Many drugs including phytochemicals are known to increase the expression of E-cadherin in cancer cells thus inhibiting invasion and metastasis, while downregulation of E-cadherin is involved in potentiating these phenotypes. In many advanced human cancers, E-cadherin is found to be downregulated and also found to be inactive through mutations, this provides strong support for its role as a key in putting down this hallmark capability of this protein molecule (Berx and van Roy, 2009; Cavallaro and Christofori, 2004). Additionally, other molecules which are vital in preserving the basic tissue architecture by joining cell to cell and cells to extracellular matrix are also mutated or downregulated in aggressive cancers. On the contrary, adhesion molecules which are usually linked with cell migrations during embryogenesis and inflammation are frequently found to be upregulated. For example, N-cadherin is expressed in huge amounts in migrating cells such as mesenchymal and neuronal cells during the process of organogenesis. This particular protein molecule is also found to be highly expressed in various invasive carcinoma cells (Nieman et al., 1999).

### **Dietary Phytochemicals- Alternative approach to cancer chemotherapy**

The term chemoprevention was initially coined by Michael Sporn. Cancer chemoprevention includes the employment of a synthetic, natural or biological agent to revert, retard or avert the incidence of malignancy. Chemoprevention may also include a variety of steps in tumour initiation, promotion and progression. The past few decades of research has increased our understanding of cancer biology that has assisted in the identification of potential targets for the intervention of the various cancers. The overall survival rate in patients with lung cancer is extremely low. It is expected that the development of adjuvant therapy might increase the survival of cancer patients. Nature provides a major source of plant molecules, phytochemicals employed in chemoprevention mostly are non-nutritive constituents in the plant-based diet that significantly possess anti-carcinogenic properties. Nearly, 250 population-based investigations indicated that people who consume nearly five servings of vegetables and fruits per day have approximately 50 % less chance of developing various cancers including of respiratory tract compared to those who either do not take or take lesser servings of fruits and vegetables per day. Vegetables and fruits possess numerous substances which have shown cancer preventive properties. The National Cancer Institute (NCI) has recognised more than 30 fruits and vegetables that have cancer-preventive properties. These comprise garlic, ginger, onion, turmeric, cruciferous vegetables, grapes, berries, etc. Several studies on cell culture and animal model have been performed to evaluate the therapeutic and preventive potential of these dietary supplements against different cancers. Flavonoids are a class of polyphenolic compounds commonly found in the plants, consisting of nearly 4000 naturally occurring compounds that are plentiful in all vascular plants. They have shown to possess numerous biological activities in model systems including antioxidant, antitumor, anti-inflammatory, antiallergic and hepatoprotective effects (Kotecha et al., 2016; Surh, 2003). Additionally, flavonoids like synthetic flavone, flavopiridol; or the common dietary flavonol, quercetin are evolving as potential anticancer drugs and few of them have already moved into clinical trials (Chahar et al., 2011; Park and Pezzuto, 2012). Flavonoids are common constituents of our diet. They are present in fruits and vegetables usually as O-glycosides with sugars at the C3 position. Nearly, 1 g/day is our daily intake of all flavonoid. Flavonoids are extensively present in the citrus (family Rutaceae) (Park and Pezzuto, 2012).

Historically, the earliest evidence for phytochemical was found as cuneiform from Mesopotamia (2600 BC). Same phytochemical is used to treat a cough, cold and inflammation (Dias et al., 2012). Another record is Ebers papyrus (2900 BC) from Egypt, which includes records of 700 plant-based drugs. Other historical evidence found from Greece, Rome, England, Ireland, France, Germany, China, and India. Ayurveda is an ancient Indian medicinal system majorly based on plant-derived substance and minerals to treat and prevent the human diseases. It is a 5000-year-old traditional medicinal system (Kohli and Kohli, 2012). Use of Ayurvedic medicines was proven to be safe and effective for many chronic diseases. There is lots of scope for identification of new drugs based on Ayurvedic traditional therapy. Most famous example of the traditional use of the plant-based compound in clinics is acetylsalicylic acid (aspirin) which found from willow barks (Dias et al., 2012). Plant-based pharmaceutical agents are recognized for their medicinal use

from history to the recent past. As a result noble prize in physiology and medicine was shared with TuYouyou for her finding of new anti-malarial agent Artemisinin. These finding broadly based on old Chinese medicinal system. Though research and use of phytochemicals experience extinction during early 21<sup>st</sup> centuries, but harsh side effects of the potent and powerful synthetic drugs put them again in the mainstream of the drug development research and industry.

### Conclusions

We are in the second decade of the 21<sup>st</sup> century with 200 years of cancer research. Still, deaths related to cancer and its incidences are high in numbers globally. In India, the consistent increase is seen in both incidence and mortality related to cancer. Women from all over the globe suffering from breast cancer, whose incidence and mortality are rising year after years in India. The available diagnostics, prognostics, and treatment option are inadequate to manage the scenario of breast cancer in Indian women. Altogether is the alarming sign for more vigorous research in demanding areas like more accurate diagnostic and prognostic tools, more treatment options. In the context of breast cancer chemotherapeutics, the available options are less with having high side effects. Phytochemicals are known for beneficial effect against cancer with lesser side effects, specifically for breast cancer. Thus, it's the thrust area, and further research is needed which might provide new breakthroughs in cancer treatment and management.

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