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An insight into the role of citrus bioactives in modulation of colon cancer

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ABSTRACT

Citrus fruits are important health promoting fruits rich in a number of bioactive components mainly flavonoids, limonoids, coumarins, volatile oils and carotenoids. Citrus bioactives have been found to scavenge reactive oxygen species, rejuvenate body's own antioxidant enzymes, inhibit various signalling pathways, act on extrinsic and intrinsic apoptotic pathways, suppress inflammatory mediators and arrest the cell cycle. Cancer is the second leading cause of death worldwide after cardiovascular diseases and colon cancer is the third most common cancer worldwide. Studies have suggested a positive relation between diet rich in natural phytochemicals and reduced risk of colon cancer. The present review highlights the chemopreventive action of various citrus phytochemicals in colon cancer. The studies suggest that citrus bioactives either alone or in combination with current therapeutic agents can be developed as potential drug candidates for colon cancer.

Contents

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1. Introduction

Dietary products of plant origin are a rich source of plethora of biologically active molecules usually known as secondary metabolites which are synthesised by plants as a defence mechanism against various insults. These metabolites not only protect the plants in adverse conditions but are of high medical interest as they possess a wide spectrum of biological activities such as antiinflammatory, anticarcinogenic, neuroprotective, antiallergic, oestrogenic, antithrombotic, hepatoprotective, antibiotic, antiviral, antiulcer, antilipidaemic and vasorelaxing (Heilmann, 2009). However, only a few plant-derived secondary metabolites have been directly used as drugs, majority of these phytochemicals have served themselves as lead molecules for discovery of new drug candidates. The various types of secondary metabolites based on the biosynthetic pathways in plants are polyphenols, terpenoids, steroids and alkaloids (Bourgaud, Gravot, Milesi, & Gontier, 2001).

Polyphenols, a broad class of secondary metabolites, possess aromatic moieties with variable number of hydroxyl groups on it. They can be classified into different categories on the basis of number of phenol rings and their attachment. The main classes are flavonoids, non-flavonoids (phenolic acids) and less common but highly complex molecules like stilbenes, tannins and lignins (D'Archivio et al., 2007). Terpenes are a unique group of hydrocarbon-based natural products whose structures may be derived from isoprene units (2-methyl-1,3-butadiene) (5-carbon units). Terpenes are classified by the number of 5-carbon units as Monoterpenes, sesquiterpenes, di-, tri- and tetraterpenes. Terpenoids are modified terpenes in which methyl groups are either moved, removed or substituted with oxygen. Steroids and alkaloids also constitute an important part of secondary metabolites but these are confined to specific genus and plants. Epidemiological studies have indicated that intake of dietary fruits and vegetables rich in phytochemicals can be a promising alternative approach in the prevention of cancer. These secondary metabolites not only prevent the progression but also reduce the risk of cancer initiation by modulating the molecular and cellular alterations. In this review article, our aim is to summarise the cellular and molecular chemopreventive actions of all types of bioactives present in citrus fruits against colon cancer.

2. Colon cancer

Colon cancer is one of the most prevalent and common type of cancer because of greater chances of reoccurrence, metastasis and acquired resistance to conventional chemotherapy. It has been estimated by American Cancer Society (ACS) that 136,830 people will be diagnosed with colon cancer and 50,310 people will die from this disease by the end of year 2014. Further, the number is increasing at an alarming rate as quality of life with respect to dietary intakes and physical activity is deteriorating day by day. Aetiologically, colon cancer has been associated with genetic mutations that can be inherited (germline) mutations and sporadic (somatic) mutations. Hereditary forms contribute not more than 5% of all colon cancer cases while majority of patients develop sporadic form of this disease (70–80%) and familial cases are 20% of all. Most common hereditary forms are familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC) (lynch syndrome). The FAP syndrome develops from inherited mutations in tumour suppressor gene like adenomatous polyposis coli (APC) while lynch syndrome is caused by inherited mutations in any of 5 mismatch repair (MMR) genes. The sporadic non-hereditary mutations normally occur in same genes along with kirsten-ras (K-ras), p53 and p16 as a result of exposure to environmental factors (Benson, 2007). Among the environmental factors, dietary factors alone are responsible for 70–90% chances of non-hereditary colon cancer cases (Araujo, Gonçalves, & Martel, 2011). These include low intake of fibre rich food, fruits, vegetables, vitamins and minerals, ingestion of diet rich in calories, lipids, red meat, intake of alcohol, tobacco, low physical activity and obesity (Derry, Raina, Agarwal, & Agarwal, 2013). Besides the above stated factors, individuals aged between 40 and 50 years and those with previous family history of polyps and colon cancer are at higher risk of developing colon cancer. Further, patients suffering from chronic inflammatory bowel diseases are also at a risk of progression towards oncogenecity (Benson, 2007). This risk ranges from 0.5 to 20% per year (May et al., 2010) and depends upon the duration and extent of disease.

Under normal physiological conditions, the human colon exhibits a well regulated homeostasis in proliferation (in inferior two third of colonic crypts), differentiation (in upper two-third of colonic crypts) and apoptosis (Dihal, Woutersen, Ommen, Rietjens, & Stierum, 2006). The imbalance among these cellular processes in colonic mucosa has a determinant role in the development of colon cancer. The emergence and progression of colon cancer can be divided into three stages. In the first stage of initiation, the normal cells are exposed towards genetic alterations; the second promotion phase is the longest one and is accompanied by survival and replication of damaged cells. The last phase of progression is characterised by deregulation of proliferation, differentiation and apoptosis processes (Johnson, 2007; Ramos, 2007; Surh, 2003). This results in conversion of normal colonic mucosa to aberrant crypt foci (ACF) followed by adenoma and then to a stage of adenocarcinoma. A schematic representation of steps involved in cancer progression is depicted in Fig. 1.

3. Citrus fruits

Citrus fruits, the representatives of rutaceae family, are well known for their tremendous nutritional potential. They are not