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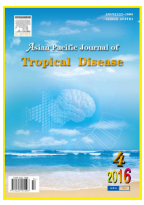

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Green tea phytocompounds as anticancer: A review

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ABSTRACT

Green tea is universally considered significant and its benefits have been experimentally explored by researchers and scientists. Anticancer potential of green tea has been completely recognized now. Green tea contains anti-cancerous constituents and nutrients that have powerful remedial effects. By using electronic data base (1998–2015), different compounds in green tea possessing anticancer activity including epigallocatechin-3-gallate, paclitaxel and docetaxel combinations, ascorbic acid, catechins, lysine, synergistic arginine, green tea extract, proline, and green tea polyphenols has been reported. Green tea extracts exhibited remedial potential against cancer of lung, colon, liver, stomach, leukemic cells, prostate, breast, human cervical cells, head, and neck. For centuries, green tea has been utilized as medicine for therapeutic purposes. It originated in China and extensively used in Asian countries for blood pressure depression and as anticancer medicine. Green tea has therapeutic potential against many diseases such as lowering of blood pressure, Parkinson's disease, weight loss, esophageal disease, skin-care, cholesterol, Alzheimer's disease and diabetes.

1. Introduction

Green tea is frequently used as a beverage universally, especially in Saudi Arabia, Japan, Morocco and China. Green tea and its constituents have been considered very valuable in the prevention and treatment of diverse diseases. Catechins of green tea has a significant role in biological activities modulation and extensively used as chemo-preventive agents[1]. Green tea catechins possess anticancer, anti-obesity, anti-hyperglycemic, and anti-hypercholesterolemic properties[2]. About 2/3 of the world's population is using tea which is the most popular beverage throughout the world and has widely been studied for its therapeutic effect against cancer[3]. Many benefits of green tea has been reported previously such as weight loss by increasing rate of metabolism, total cholesterol level reduction, enhancement of high density lipids, plague prevention, improved oral health, and fatty food digestion[4,5]. The high mortality rate of cancer was attributed to cancer cells invasive behavior which is the ultimate cause of metastasis and cancer development. Spreading of neoplastic cells from primary site to different organs is called metastasis, which is the major cause of cancer deaths. Primary cell involves tumor cell invasion, circulatory system arrest, intravasation, and extravasations. It is followed by angiogenesis and growth at remote site[6]. Several studies revealed the apoptotic mechanism and anti-proliferative properties of green tea polyphenol extract or immortalized cervical carcinoma cell line[7]. Green tea all extracts were characterized and their polyphenol composition was recorded[8,9]. Different anti-inflammatory activities of green tea and epigallocatechin-3-gallate (EGCG) were reported. Inflammation additionally has been implicated as Parkinson's disease in neurodegenerative pathologies[10-12]. A study concluded that some suggestive evidence is existed of green tea being effective against cancer but it didn't amount to a comprehensive clue of benefit[13]. Black tea consumption is also associated with significant reduction in cancer death cells[14]. Green tea utilization is related with lung cancer reduction in women, minor risk of oral cancer in Asians

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and lower risk of esophageal cancer in Chinese[15-17]. Liver cancer is considered the most common cause of death due to its poor prognosis and the sixth most familiar type of cancer[18]. Many epidemiological studies have been conducted by last 20 years to explore the relation between liver cancer risk and green tea consumption. Green tea and liver cancer risk reduction limited relation was reported by Fon Sing *et al.*[19]. A connection between green tea intake and liver cancer risk reduction has been revealed by a meta-analysis[20]. The high amount of consumption of green tea might be linked with smaller risk of liver cancer in Asian women reported in a meta-analysis of 9 potential cohort studies. While this connection was not recorded in Asian men by consumption of one cup green tea per day[21]. Green tea utilization has also been reported to have favorable effect on lung cancer risk. The strongest effect was recorded by the persons who uses more than 7 cups of green tea per day[19]. In Japanese and Chinese population, the reduced liver cancer risk was related to green tea utilization by an epidemiological study[22]. Limited evidence was found on the association of prostate and pancreatic cancer and green tea consumption[23,24]. Due to incoherent evidence, the relation between stomach cancer and green tea utilization is uncertain[25]. Some chemotherapy drugs such as bortezomib and boronic acid based proteasome inhibitors react with green tea, therefore people taking these drugs should avoid green tea consumption[26]. Phenolic acid, caffeine, theobromine, theophylline, and theanine are the catechins (poly-phenols) found in tea leaves. EGCG is the most important green tea catechin, while gallocatechin gallate, epicatechin gallate, gallocatechin, and epicatechin are considered less significant[27]. Urine excretion decrease was attributed by catechol-O-methyl transferase[28]. After 48 oz. (six cups) green tea consumption for five weeks daily, 4-O-methyl EGCG (50%) was found in human prostate tissues by prostatectomy[29,30]. Deprotonation of EGCG phonol rings hydroxyl groups was reported due to its unstable nature in neutral and alkaline conditions. Glucuronidation, methylation and sulfate formation like biotransformation reactions are also responsible for EGCG hydroxyl groups modification, consequently which can lead to the reduction of *in vivo* biological activities[31]. Green tea catechins constituent and health benefit effects have been broadly studied[32]. Green tea and catechins constituent's antioxidant effects has been mainly focused. Antioxidant potential of green tea was ascribed for the prevention and treatment of cancer and cardiovascular diseases[33]. Fresh leaves of tea was used for green tea manufacturing by steaming or drying at high temperature in order to avoid polyphenolics oxidation[6]. Tea is considered significant due to its therapeutic effect against different types of cancers[34-36]. The main cause of death and the most frequent diagnosed cancer type is lung cancer among males, which comprised 17% of total new cases of cancer and 23% of the worldwide cancer deaths[37]. Eight epidemiological studies reported the association between green tea and lung cancer risk reduction[38-45].

2. Green tea remedial effects on various cancer types

2.1. Green tea and colon cancer

Green tea activates AMPK, induced apoptotic markers (p53 and poly-ADP-ribose polymerase cleavage) and decease COX-2 expression by its mode of action[46]. By its activation, serine epidermal growth factor receptor phosphorylation shows major role of epidermal growth factor receptor down regulation in EGCG[47]. Cell cycle changes can lead to the death of EGCG-induced apoptotic cells without changing caspase activation. Human colon cancer cells (HT-29) pro-matrix metalloproteinase improved by EGCG with superoxide spontaneous generation. Cyclin D1 and beta catenin biomarkers can be decreased by green tea utilization[48]. Catechins of green tea targets the signaling pathways of activator protein elements of mitogen-activated protein kinase. It also inhibits the c-jun N-terminal kinase pathway[49]. Colorectal cancer TROP-2 biomarker suppresses by green tea[50]. Erythroid 2-related factor 2 up-regulation was reported by EGCG, which is associated with the enhanced level of uridine 5'-diphosphate-glucuronosyltransferase in cells[51,52].

2.2. Green tea and prostate cancer

Prostate cancer is the major cause of deaths in American men. This cancer is responsible for the death of more than 29 thousand deaths per annum. Several reports associated the risk of prostate cancer with green tea consumption[53,54]. Green tea is responsible for progression restrains, apoptosis, invasion and metastasis of prostate cancer reported by several studies[55]. Prostate specific antigen expression, cell propagation, and androgen receptor transcriptional activity of several sub-lines (LNCap) were suppressed by green tea EGCG constituent[56]. Catechins of green tea might be linked with methylation of DNA and enhanced levels of acetylated histones[57].

2.3. Green tea and skin cancer

Apoptosis induction is accomplished by green tea poly-phenols treatment which engendered caspases activation, enhancement in apoptotic protease activating factor, cytochrome c release and adenosine diphosphate-ribose breakdown[58]. Epigenetic dogmatic mechanism is mediated by the influence of EGCG on poly-comb group proteins. Major proteins expression is related with the alterations in poly-comb group proteins which increase development via cell cycle. Proteins expression amplification inhibits p21 and p27 cell cycle development. Green tea active constituents can be used for the treatment of DNA damage (UVB-induced)[59]. Enhancement of minimal erythema dose is accomplished by EGCG regular use, which can ultimately prevent skin damage and epidermal barrier UV induced perturbation[60].

2.4. Green tea and cervical cancer

Cervical cancer internationally is considered as the second most frequent cause of women fatalities. EGCG and green tea catechins are useful in cervical cancer inhibition. Apoptosis induction is carried out by green tea catechins, which is associated with the augmented expression of p53 and p21 apoptosis mediating proteins. Decline was recorded on the contrary in protein expression (HPV-E7)[61,62]. Cells proliferation inhibition is made by poly-phenols of green tea which is linked with G2 mitotic phase amplification. Apoptosis induction is accomplished by green tea poly-phenols in human cervical cancer cells (SiHa). Reduction in mitochondrial membrane potential and phosphatidyl serine residues of membrane enhancement is the key