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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

mechanism for the apoptosis induction[63]. The cytotoxic and growth inhibitory potential of catechin hydrate was also reported[64].

2.5. Green tea and bladder cancer

Bladder cancer pervasiveness is increasing recently internationally. In USA, 50% increase was recorded in patients of bladder cancer during 1985 to 2006. Protein kinase B over expression causes bladder cancer development which leads to enhanced apoptosis resistance and tumor cells survival[65]. Human bladder cancer cell line (T24) study revealed that cell feasibility and repressed cellular propagation by EGCG is time and dose reliant[66]. Phosphatidyl inositol 30-kinase activation was delayed by EGCG, which leads to the inflection of Bcl-2 proteins by increasing T24 cells apoptosis. Incursion and intensification of tumor in bladder cancer infected mice is inhibited by catechins of green tea by angiogenesis regulation[67].

2.6. Green tea and oral cancer

Several clinical examinations reported different molecular mechanisms regarding green tea beneficial effects against oral cancer chemo-prevention[68]. At transcriptional level inhibition of indoleamide 2,3-dioxygenase is accomplished by EGCG via the interferon gamma-induced JAK-PKC-delta-STAT1 signaling pathway blocking[69]. EGCG plays an important role in inhibition of cell incursion via matrix metalloproteinase inhibitors demethylation. A new tumor gene (reversion-inducing-cysteine-rich protein) expression suppresses metastasis, matrix metallo-proteinases regulations and angiogenesis[70].

Table 1

Green tea constituents effect on various cancer types.

S. No	Green tea/ constituents	Cancer type	Remedial effects	Ref. No.
1	EGCG	Tumor	Apoptosis rate increased by increasing EGCG	[89]
2	Green tea	Liver, lung and colon cancer	Relative lower risk was observed for liver, lung and colon cancer, lower repetition rate (16.7%) for breast cancer	[90]
3	GTE and green tea polyphenols	Tumor cell (A427/human lungs)	Anchorage independent development, decaffeinated and GTE revealed reduced inhibition. Green tea polyphenols inhibition was significant (74%–92%)	[91]
4	Green tea	Stomach and gastric cancer	Stomach and gastric cancer goes to decreased level in smoking persons and alcoholic drinkers	[92]
5	EGCG	Transformed cells	More induced apoptosis and anticancer effect in transformed cells as compared to normal	[93]
6	EGCG	Leukemic cancerous cells	Reduction in ornithine decarboxylase (50%) and remedial potential	[94]
7	Green tea	Metastatic prostate carcinoma	Low therapeutic effect can be seen, 2%	[95]
8	Green tea	Epithelial ovarian cancer	Reduction in epithelial ovarian cancer hazard rates	[96]
9	Green tea	Prostate cancer	Decline risk of prostate cancer with duration, quantity and frequency amplification of green tea utilization	[97]
10	EGCG	LNCaP (A type of human prostate carcinoma cell)	Chemo-therapeutic drugs and EGCG mixture have remedial effects against prostate cancer	[98]
11	Green tea catechins	Prostate cancer	Cancer growth inhibition	[99]
12	Green tea	Prostate cancer	Advance prostate cancer reduced risk	[100]
13	Green tea	Breast cancer	Declined breast cancer risk with high consumption of green tea	[31]
14	EGCG	Human breast cancer cells	Inhibition of breast cancer proliferation	[101]
15	Green tea	Leukemia cells	Reduction in adult leukemia risk with green tea consumption	[102]
16	Green tea	Lung cancer	Lung cancer reduced risk	[30]
17	Green tea	A549 tumor cells	Cell motility was modulated by GTE induced lamin A/C and annexin. These contribute to the anticancer activity of green tea.	[83]
18	EGCG polyphenol	Leukemia cancerous cells	EGCG polyphenol has low relative cell proliferation of leukemia cancerous cell	[46]
19	Green tea, ascorbic acid, arginine, lysine, proline	Tumor cells	Reduction in diversity and growth of tumor	[6]
20	EGCG	Quercetin LNCaP cell	EGCG and quercetin LNCaP cell proliferation inhibition with 40 μmol/L EGCG 10 μmol/L quercetin, 48 h compared with 60% inhibition	[29]
21	Methanolic extract of *Gracilaria tenuispitata*	Tumor cells	Maximum reduction in tumor volume by higher dose of (MEGT 400 mg)	[6]
22	Green tea	Human cervical cancer cells	Methanol extract of green tea has cytotoxic towards human HeLa and potent anticancer compound with an IC_{50} of 111.9 g/mL inducing growth inhibition in the human cervical cancer cells	[6]
23	EGCG, paclitaxel and docetaxel combinations	Human head, neck, lung, breast, prostate, liver and stomach cancer cells	Synergistic increase in anticancer activity with decline in tumor (70.3%)	[71]
24	EGCG and synergistic	Human lung cancer cells	Anticancer activity of EGCG and synergistic hardware related work is a striking up-regulation of two genes, growth arrest and DNA damage-inducible gene 153 induced and p21, 12 times as and 3 PC-9 cells in the floor.	[71]
25	Jasmine green tea and catechins	Human cancer cells	Jasmine green tea has the most synergistic effects with catechins. It increases the scavenging effect	[4]

GTE: Green tea extract.

3. Therapeutic potential of green tea constituents

3.1. Green tea catechins and cancer prevention

Non-toxic anti-inflammatory catechins in green tea have been reported as cancer preventive agents. Ten Japanese cups of green tea (150 mL per cup) per day consumption results cancer prevention and colorectal adenoma recurrence in tertiary cancer prevention[71]. Much of the cancer chemopreventive properties of green tea are mediated by EGCG that induces apoptosis and promotes cell growth arrest in cancer cells (Table 1). EGCG modulates the signal transduction pathways involved in cell proliferation, transformation, inflammation, apoptosis and metastasis[72,73]. This was the significant finding showing that drinking 10 cups of green tea per day results in delay of cancer onset among the general population in primary cancer prevention. The results allowed us to think that green tea catechins in 10 cups of green tea are the cancer preventive amount of green tea for humans[74]. Recently, the combination of EGCG and anticancer compounds has been well accepted by numerous research groups. First, the authors studied whether the *in vitro* synergistic anticancer effects could be generally induced in various human cancer cell lines by treatment with combination of EGCG and a diversity of anticancer compounds. The *in vitro* experiments on 42 human cancer cell lines derived from various cancer tissues presented all synergistic anticancer effects[75,76].

3.2. Green tea EGCG and stem cells

Green tea EGCG constituent is reported being protective against CD-34 cells growth. EGCG potential against stem cells inhibition is reported recently by several studies. Inhibition of stem cells of human pancreatic cancer (CD133+/CD24+/ESA+) is achieved by green tea EGCG in primary and secondary spheroids in dose reliant manner (0–60 μmol/L). Cancer stem cells transcription factor genes (Nanog, c-Myc and Oct-4) expression is also suppressed by EGCG[77]. Stem cells of cancer self replenishment aptitude is inhibited by the treatment of CD44+ K3 cancer stem cells from head and neck squamous cell carcinoma with green tea EGCG (5 μmol/L). This inhibition is achieved by the impairment of genes (Oct-4, CD44+, Nonog, Sox2) and tumor proliferation. All the reported results revealed the targeted action of green tea EGCG constituent against stem cells of cancer in several human cancer tissues[78].

3.3. Effect of poly-phenolic constituents on cancer

In vivo and *in vitro* studies presented the suppression of the development of cancer cells by poly-phenolic constituent (EGCG) of green tea[79]. Flavan-3-ol is considered the most effective, which is 30% of total dry leaf weight[80]. EGCG prevent tumor development of both teleocidin by 12-O tetradecanoylphorbol-13-acetate (tumor promoter) and okadaic acid by inhibiting protein phosphatases 1 and 2A on mouse skin. Tumor necrosis factor were discovered in different organs as tumor promoter and studied chemokines and cytokines in tumor succession[81]. Flavonoids interaction with metal ions was accredited to green tea catechins potent effect on metabolism and absorption. Green tea elevated utilization has cytotoxic effect on liver cells. Greater reduction in tumor volume was recorded by higher dose of green tea. Hemoglobin and red blood cell level that generally goes down during progression of tumor was improved. Data pertaining to lymphocyte count with the addition of methanol extract of green tea restored. They also concluded that HeLa cells have growth inhibition in a dose dependent manner with increase in green tea extract concentration. Methanol extract of green tea has cytotoxic towards human HeLa in MTT assay and potent anti-cancer compound with an IC_{50} (potential cytotoxic substance) of 111.9 g/mL inducing growth inhibition in the human cervical cancer cells. So, *in vivo* efficacy of green tea can be resolve in animal models for cervical cancer cell lines[82].

3.4. Proteomic assessment of cancer by green tea treatment

Its protective properties on various cancer sites such as lung have been reported by laboratory studies on animals. However, green tea chemo-preventive mechanism is not fully explored. Green tea extracts having antioxidant and anticancer properties. They used proteomic approach. Alteration in tumor related proteins were recorded by green tea treatment in A549 cells. Lamin (A/C) expression was stimulated by GTE in dose dependent way. Protein was present in both nucleoplasm and cytoplasm. Cell motility was modulated by GTE induced lamin A/C and annexin. These contribute to the anticancer activity of green tea extract[83]. For early preventive intervention and cancer diagnosis, tumor associated nicotinamide adenine dinucleotide oxidase is preferably used as preventive agent. Ecto-nicotinamide adenine dinucleotide oxidase disulfide-thiol exchanger 2 (ENOX2) proteins are responsible for tumor cells development and amplification. Based on these characteristics, ENOX2 is used for early exposure and intrusion of tumor cells as targeted agent[84-87]. ENOX2 is used for the detection of cancer but presented no sign regarding the location and type of cancer. Cancer cells division is inhibited by ENOX2 blockage (48–72 h) which can ultimately undergo apoptosis[88].

4. Conclusions

Green tea is the most extensively consumed beverage and achieved significant attention due to health benefits against cancer. Green tea and its constituents have therapeutic potential against cancer. It can improve the immune system, get rid of body toxins, and provide some control over cancer. Green tea contains substances called poly-phenols and catechins. These compounds were reported to have antioxidant, anti-proliferative and anti-angiogenesis activities, which are related potentially to the prevention and treatment of cancer different forms. Green tea poly-phenolic compounds (catechins) are believed to have apoptosis inducing and anticancer properties (Table 1). Different reports showed EGCG poly-phenol the most effectual apoptosis inducing and chemo-preventive constituent of green tea. Green tea extract and EGCG have the potential to target stem cells of cancer in different cancer infected tissues. Tumor reductive activities were recorded by anticancer drugs and green tea component (EGCG) mixture. It is concluded that recent cancer handling should be allied with green tea poly-phenols (catechins). In this way, cancer patients will achieve better quality of life and health protection without suffering the painful effects of radiations and anticancer drugs. The association of anti-cancer

compounds and green tea constituents will provide more clinical benefits in cancer therapy.

Conflict of interest statement

We declare that we have no conflict of interest.

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