Black tea: The Future Panacea for Cancer

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Abstract: Epidemiological studies have long hinted at the possibility that what we eat greatly influence our state of health, in particular, our relative risk of developing cancer. In recent years there has been an exponential increase in the number of studies investigating how individual components of the diet interact at the molecular level to determine the fate of a cell. It is now apparent that many such molecules can preferentially inhibit the growth of tumor cells, by inducing cell cycle arrest or apoptosis. Besides, the number of signaling pathways and molecular targets involved is continually expanding. Consequently, the picture is becoming ever more complicated, not least because results often appear to be cell type-specific, dose-response relationships are critical, and any one agent appears to have multiple mechanisms of action. In addition most studies have been conducted in cell culture, often with physiologically unachievable concentrations of single agents, making extrapolation to the clinical situation difficult. In this review the mechanisms of action of the popular drink black tea and its polyphenols, theaflavins, are considered in the light of these issues. In fact, black tea and theaflavins activate an array of apoptogenic signaling events thereby ensuing reduced tumor growth. This beverage not only regresses tumor but also protects intrinsic defense machineries of the host from cancer insult. The intrinsic defense systems, e.g., immune and detoxification systems, jeopardized during cancer, are also rejuvenated by black tea. Black tea even reduces tumor-induced hepatotoxicity and protects against oxidative damage generated by the developing tumor. Therefore, acting in a multi-faceted manner, black tea and theaflavins can successfully bring about regression of the tumor and ensure survival of the host. Moreover, being a commonly consumed drink, black tea is considered safe and non-toxic and has potential as a 'natural' chemotherapeutic product to be used as an adjunct to the existing clinical procedures, making it a broad-acting and readily distributed cost-effective agent to promote public health. Thus, modern medical research seems to confirm the ancient wisdom that therapy of many diseases may reside in an inexpensive beverage in a "teapot."

Introduction

A healthy cell is continuously receiving signals from its environment through many different receptors, both membrane bound and intracellular, which eventually feed through to the nucleus to influence the activity of various transcription factors. These in turn drive gene transcription, which determines the outcome for the cell – whether to arrest, proliferate, differentiate, senesce or die. Signals in a normal, non-dividing cell are in balance between pathways that elicit proliferation and those dictating arrest. But when the first carcinogenic changes occur in preneoplasia, the balance begins to shift in favor of deregulated proliferation, until in tumors, the proliferative signals come to dominate. Thus the signaling pathways in tumor cells are very different from those in normal cells from which they are derived, affording opportunities for selective targeting in cancer treatment or prevention. Curing cancer

thus requires that all the malignant cells be removed or destroyed without killing the patient. An attractive way to achieve this would be to use such an agent that would discriminate between tumor cells and their normal counterparts and be selectively lethal to the malignant phenotypes. Since, cancer itself, as well as most of the drugs used for cancer therapy are toxic to the intrinsic defense machinery of the cancer bearer, successful cancer therapy has still remained an unfulfilled dream to scientists and medical professionals worldwide. The concept that cancer can be prevented or its onset postponed by certain diet-derived substances is currently eliciting considerable interest [1,2]. Any such natural compounds that may interfere with cancer cell growth and influence oncogenic-signaling events [3] are considered safe for the normal cells of the cancer-bearer because they are present in commonly consumed foods and beverages, having potential as 'natural' chemotherapeutic agents. Black tea is the cynosure of all researchers attempting to find an alternative cancer cure. Epidemiological studies suggest a protective effect of tea consumption on some cancer types in human [4]. In this review, cellular events induced by black tea and its polyphenols theaflavins that directly influence cancer cells or indirectly affect the intrinsic defense system of the cancer-bearer are discussed.

Targets of "targeted" therapy of cancer:

For designing any successful therapy of cancer, approaches to be adopted are:
A) Regression of tumor by (i) induction of apoptosis, (ii) inhibition of angiogenesis and (iii) retardation of metastasis
B) Correction of Immunosuppression
C) Reduction of systemic toxicity

The successful targeted therapy of cancer requires a proper understanding of each of these above-mentioned "targets".

Overview of cancer development:

Tumor development is a multi-step biological phenomenon, characterized by uncontrolled cell proliferation, loss of cell differentiation, invasion of host tissue and evasion of the host immune response. Thus there has been increasing emphasis on research to develop an understanding of cancer, as well as the action of modulating factors, as the bases for prevention and therapy. The process of carcinogenesis involves the stepwise accumulation of genetic changes, ultimately leading to malignancy [5]. There are three main steps (a) Initiation, (b) Promotion and (c) Progression. To achieve full malignancy, cells must acquire certain transformation characteristics, including (a) self sufficiency in growth signaling and limitless replicative potential (b) unresponsiveness to anti-proliferative signals (c) evasion of apoptosis (d) induction and sustenance of angiogenesis and (e) acquisition of the ability to invade and metastatize [6]. This sequence of events presents many opportunities for intervention, with the aim of preventing, slowing down or reversing the transformation process. Acquired resistance toward apoptosis is a hallmark of almost all types of cancer [7]. Use of any agent that increases apoptosis in cancer cells might overcome this problem. This can be achieved by activating pro-apoptotic or suppressing anti-apoptotic activity of the cell. Suppression of tumor angiogenesis or neovascularization, results in inhibition of tumor growth, accompanied by tumor

cell apoptosis [8,9]. Malignant tumors have the ability to invade normal tissue and to spread to distant sites giving rise to metastasis, which are major factors in the morbidity and mortality of any type of cancer [10]. Signals that induce cell invasion also promote cell survival by suppressing apoptosis of the migratory cell [11].

Therefore molecular strategies that interrupt these processes may provide promising leads towards cancer pharmacogenomics.

Cancer vs. immune system of the tumor-bearer:

Another aspect of the matter is, cancer itself, as well as most of the existing anti-cancer drugs causes immunosuppression [12] Multifaceted defect in the immune capacity of patients with advanced malignancy contributes not only to an increased susceptibility to infection and disease progression but also to constitute a barrier to therapeutic interventions. Both human patients and experimental animals with advanced cancer often exhibit a poorly functioning immune system [13]. In fact, the immune system is responsible for early detection and destruction of newly transformed malignant cells. However, the genetic plasticity of cancer cells can lead to alterations that confer selective growth advantages to the tumor, some of which play a role in immune escape. There is ample evidence for the presence of tumor-associated antigens on a variety of tumors, although they are seemingly unable to elicit an adequate antitumor immune response [14]. Moreover, a number of mutations veiling tumor cells from host immune defenses have been well characterized but more recent studies suggest that a variety of tumors can also express products that are actually toxic for the immune effectors [15]. A large number of cytokines, hormones, and other molecules secreted by tumors have been demonstrated to have immunomodulating properties, of them the most extensively studied immunosuppressive molecules secreted by tumors are gangliosides, transforming growth factor-beta, interleukin 10, and prostaglandin E2 [16-19]. Chen *et al.* (2003) have implicated Fas ligand on tumor cells in evasion of immune surveillance [20]. Recent observations also implied apoptosis as the cause of tumor-induced immunosuppression [13]. Combinatorial use of any agent that can ameliorate toxicity, cancer- or drug-induced, will help the ailing host to recover its vulnerable defense system and also increase the efficacy of the drug. The ultimate cancer therapeutic agent should, therefore, be one that attends to all these factors mentioned above, concurrently. Scientists all over the world are therefore in search of any agent that may kill the cancer cells in one hand and reconstitute the intrinsic defense system of the host on the other to ultimately prevent/cure cancer.

Cancer-induced systemic toxicity in host:

Cancer also influences detoxification activities of the host. Since the majority of detoxification occurs in the liver, it is not surprising that impairment of normal liver function due to different diseases like cancer can lead to lower detoxification activity in general [21]. The Pi (π) isoenzyme of Phase I enzymes is present in very low amounts in normal liver but its expression becomes very high with the onset of carcinogenesis [22]. As a consequence of Phase I biotransformation in detoxification, reactive molecules, which may be more toxic than the parent molecule and may cause damage to proteins, RNA and DNA within the cell, are produced and are in

turn further metabolized by Phase II conjugation. Therefore, any impairment in their activities due to cancer-induced suppression may make the situation even graver for the host. It is now also well recognized that with onset of cancer, there is a concurrent toxic manifestation in the form of oxidative stress within the host. Status of antioxidant enzymes, i.e., Superoxide dismutase (SOD), Catalase, glutathione-S-transferases (GST), peroxidases etc., which protect cells against oxidative damage, is almost invariably altered during carcinogenesis [23]. Consequently, accumulated reactive oxygen species interacts with and modifies cellular proteins, lipids and DNA, which results in altered target cell function [24]. All these finally lead to systemic toxicity in the tumor-bearer resulting in further failure of the treatment [25]. It is therefore apparent that an agent that may regress the tumor and simultaneously resurrect the intrinsic defense machinery of the tumor-bearer can provide the ultimately cure to cancer.
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Dietary Therapy:
Recently, considerable attention has been focused on identifying naturally occurring chemopreventive substances capable of inhibiting, retarding, or reversing the process of multistage carcinogenesis. Wide arrays of phenolic substances, particularly flavonoids, those present in dietary and medicinal plants, have been reported to possess substantial anti-carcinogenic and anti-mutagenic effects [26]. These flavonoids are naturally occurring low molecular weight polyphenolic compounds widely distributed in fruits, vegetables and beverages. People who eat diets rich in fruits and vegetables have lower incidences of diseases such as cancer. Numerous experimental studies have examined the role of specific flavonoids in disease prevention. For example, increased flavonoid intake was associated with decreased risk of carcinogenesis [27]. The majority of these naturally occurring phenolic compounds retain anti-oxidative and anti-inflammatory properties, which appear to contribute to their chemopreventive activity [28]. Because of their safety and the fact that they are not perceived as medicine, food derived products have high potential for development as chemopreventive and therapeutic agents that may find widespread and long-term use. Moreover *in-vitro* studies are now being conducted to identify the molecular targets within cancer cells that are modulated by these dietary constituents [29]. Tea is one of such dietary substances having diverse biomodulatory activities and therefore, may be a good candidate as a safe and potential anti-cancer agent.

Active ingredients of black tea:
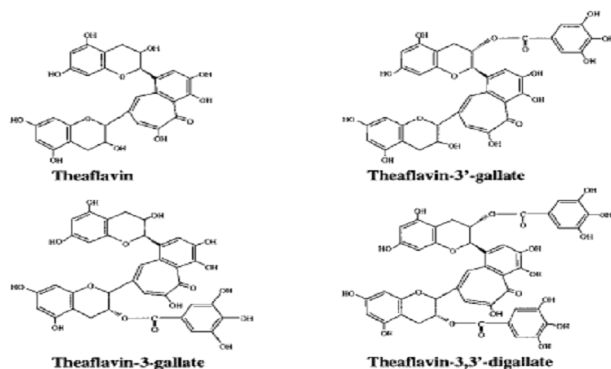Among the mixture of compounds that comprise black tea, the pharmacological

Figure 1: Structure of theaflavins

functions of theaflavins have received much attention, with identification of its properties as anti-oxidant, anti-pathogenic substance and as active cancer suppressor. Theaflavins are a mixture of theaflavin, theaflavin- 3-gallate, theaflavin-3'-gallate and theaflavin-3,3' digallate (Figure1), all having the same hydroxy-substituted benzotropolone characteristic ring. The phenolic hydroxy groups of theaflavins possess anti-oxidative activity as radical scavengers and/or metal chelaters, while the gallic acid moiety is also essential for this purpose [30].

Our hypothesis:

We hypothesize that black tea and its active ingredients, theaflavins, may act as effective anti-cancer agents in a targeted manner by (A) directly regressing tumor *via* (i) induction of apoptosis, (ii) inhibition of angiogenesis and (iii) retardation of metastasis, and (B) correcting immunosuppression, and reducing systemic toxicity thereby rejuvenating host's intrinsic defence machineries (Figure 2). Some studies that are currently being carried out in our laboratory and others supporting this hypothesis are detailed below.
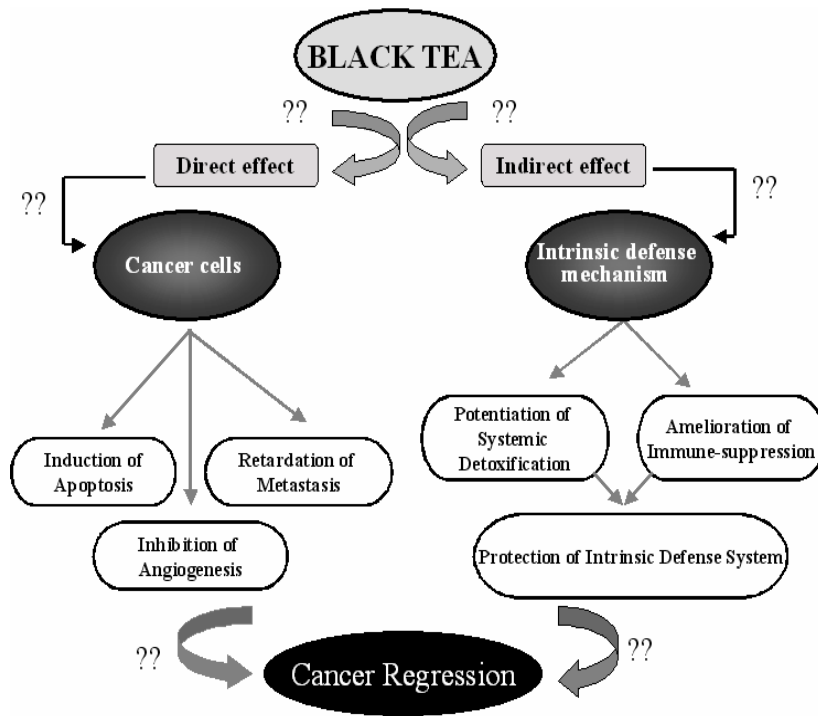

Figure 2: Our hypothesis

Direct effect of black tea and theaflavins in tumor regression:
i)   Induction of apoptosis:
Aberrant proliferation and modulated apoptosis leading to impaired cellular homeostasis represent crucial early events in the multi-step carcinogenic process. Black tea has been shown to have a direct tumor killing effect by altering the signaling cascade in tumor cells of the host without affecting the normal cells. Reports from our laboratory also revealed apoptogenic effect of black tea on tumor cells *in vivo* [31]. Several reports demonstrated that the major and most potent component of black tea polyphenols, theaflavins, strongly inhibited the kinase activity of EGF and PDGF receptors as induced by EGF or PDGF, respectively [32,33]**.** Additional studies showed that theaflavins blocked EGF from binding to its receptor [34]. The molecular mechanism of the anti-promotion activity of theaflavins involves blocking of the AP-1-dependent transcriptional activity and DNA binding activity [35]. The inhibition of AP-1 activation occurs through the inhibition of a c-Jun NH2-terminal kinase-dependent, but not an extracellular signal regulated protein kinase ErK 1-dependent or Erk2-dependent pathway. It has also been demonstrated that theaflavins inhibited TPA-induced transformation, PKC activation and AP-1 binding activities in mouse fibroblast cells in a dose-dependent manner [35,36]. These effects might have an inhibitory role on proliferation and cell cycle progression, even on apoptosis. It has been reported that black tea polyphenols strongly inhibited DNA synthesis in DS19 mouse erythroleukemia cells and HTC rat hepatoma cells [37]. The effect of theaflavins on the growth of SV-40 virally transformed WI38 human fibroblasts (WI38VA) were compared with that of normal WI38 cells [37]. Black tea polyphenols inhibit experimental colorectal carcinogenesis via Wnt/beta-catenin pathway. With associated decrease in the levels of COX-2, c-MYC and cyclin D1 proteins, which aid cell proliferation probably by regulating beta-catenin by maintaining expression of APC and decreasing inactivation of GSK3beta. Activation of MAP kinases such as ERK and JNK was also inhibited in these cases [38]. Importantly, tea polyphenols showed a pronounced growth inhibitory effect on cancerous cells but not on their normal counterparts [39]. Similar differences in growth inhibition were also observed between human colorectal (Caco-2) and breast (Hs578T) cancer cell lines and their respective normal counterparts. Moreover, it was revealed that tea polyphenols display strong growth inhibitory effects against lung tumor cell line with G2/M arrest [40,41]. It is now well recognized that whether a cell becomes committed to apoptosis partly depends upon the balance between proteins that mediate cell death, e.g., p53, p21, Bax, and proteins that promote cell viability, e.g., Bcl-2 [42]**.** A report from our laboratory has already established the relationship between p53 status, p21 induction, Bcl-2/Bax ratio, cell cycle deregulation and apoptosis in black tea-treated tumor cells [31]. The results demonstrated that black tea-induced apoptogenic signals override the growth-arresting message of p21, thereby leading the tumor cells towards death [31] by Bax translocation, loss in mitochondrial transmembrane potential, cytochrome c release and caspase activation [43]. Black tea polyphenols could also successfully inhibit proliferation of human epidermoid carcinoma and melanoma cells without adversely affecting the normal counterparts, through augmentation of Bax:Bcl2 ratio, p53 and

p21 and simultaneous inhibition of phosphorylation of cell survival protein Akt [44]. Recent work from our laboratory revealed that theaflavins induce breast cancer cell apoptosis in a p53-mediated Bax transactivation-dependent manner through mitochondrial death cascade [45].

ii) Inhibition of angiogenesis:

Angiogenesis is the neovascularization or formation of new blood vessels from the established microcirculation. The current interest in the role of neovascularization in the tumor growth and metastasis has brought about a large number of studies on angiogenesis. It is acknowledged that a greater knowledge of angiogenesis control may lead to the development of a potential therapy in cancer. In fact, many mechanisms have been proposed for the inhibition of carcinogenesis by tea, including the modulation of signal transduction pathways that leads to the inhibition of tumor invasion and angiogenesis. Black tea polyphenols have been found to inhibit angiogenesis in MNNG-induced well-differentiated squamous cell carcinomas by down-regulating VEGF production and receptor phosphorylation. [46,47]. In athymic nude mice implanted with androgen-sensitive human prostate cancer cells (CWR22Rnu1), angiogenesis was inhibited by black tea and theaflavins also *via* decrease in VEGF [48]. Preventiion of angiogenesis in DMBA-induced oral cancer [49] further provided a mechanistic basis for the chemopreventive potential of black tea polyphenols. Inhibition of tumor progression by black tea and soy phytochemical concentrate was associated with reduced tumor cell proliferation and tumor angiogenesis [50].

(iii) Retardation of metastasis :

Malignant tumors possess the ability to invade normal tissue and to spread to distant sites giving rise to metastasis, which are major factors in the morbidity and mortality of cancer. Invasion and metastasis involve attachment of tumor cells to the basement membrane, degradation of the local connective tissue, and penetration and migration through proteolyzed stroma. Metastasis involves migration and invasion into normal host tissue, dissemination via blood or lymph, and ultimately, outgrowth of new tumor masses at distant sites [51]. It is the major cause of cancer death. Cancer metastasis is a significant problem and a tremendous challenge to drug discovery relative to identifying key therapeutic targets as well as developing breakthrough medicines. Signals that induce cell invasion also promote cell survival by suppressing apoptosis of the migratory cell [52]. Black tea polyphenols could inhibit the development of metastases by inactivation of proteolytic enzymes [53]. Theaflavins were found to inhibit matrix metalloproteinases (MMPs), which are intimately associated with tumor invasion and metastasis [54]. Theaflavin and theaflavin digallate, were also found to inhibit invasion of mouse Lewis lung carcinoma LL2-Lu3 cells which are highly metastatic [55]. These two black tea compounds also inhibited the matrix metalloproteinases MMP-2 and MMP-9, which have crucial roles in tumor growth and metastasis, in these tumor cells [55]. Black tea was also found to inhibit tumor growth and prevent metastasis in the 3-methylcholanthrene (3-MC) induced solid tumor model in mice [56]. In many cancer systems like human stomach and colon carcinoma, theaflavins prevented tumor invasion and metastasis through their effect on urokinase and matrix metalloproteinases[46, 54]. We have a clear indication from the data established so far that black tea and its polyphenols have a major restrictive effect on the malignant invasion of tumor cells

Indirect effect of black tea and theaflavins in tumor regression:

(i)   *Amelioration of tumor-induced immunosuppression***:**

The tumor microenvironment influences the functional potential of immune cells. Escape from immune surveillance prefigures the rapid progression of cancers [57]. Various immune escape mechanisms in cancer have been proposed [58]. Studies from our laboratories have shown that in tumor bearing mice there is an increased incidence of apoptosis of the immunocytes. Black tea treatment restored tumor-induced immunosuppression by inhibiting apoptosis. A search for the molecular mechanism revealed that tumor burden increased the expression of the pro-apoptotic proteins p53 and Bax in splenic lymphocytes although it did not change the level of pro-proliferative protein Bcl-2. Interestingly, black tea down-regulated p53, decreased Bax while augmenting Bcl-2 in these cells. As a result, Bcl-2/Bax ratio was increased and the immunocytes were protected from tumor-induced apoptosis. [59]. Certain cancer cells may secrete immunosuppressive factors to modify the host immune responses [59,60]. Studies from our laboratory have reported that that in tumor-bearing mice, the tumor cells secrete immunosuppressive cytokines, transforming growth factor beta (TGF-beta) and interleukin-10 (IL-10) that induce a general T helper cells type 2 (Th2) dominance dampening the T cytotoxic cells type 1 (Tc1) population. Interestingly, black tea at the antitumor dose of 2.5% significantly reduced TGF-beta and IL-10 in tumor cells in vivo, thereby preventing Th2 dominance in the tumor bearers and initiating a Th1/Tc1 response [61]. Oral administration of black tea also significantly reduced depletion of CD4+ and CD8+ cells in peripheral blood and protected the thymus considerably from tumor onslaught [62]. Black tea treatment to tumor bearers inhibited tumor-induced thymic apoptosis and ensured proper functioning of this organ by preventing IL-7 receptor alpha (IL-7R alpha) down-regulation and restoration of the JAK-STAT signaling cascade [62].

All this information leads us to conclude that by potentiating the host's immune system, tea helps in regressing tumor.

(ii)   Reduction of systemic toxicity :

Tea and its polyphenols have been found to possess anti-oxidative properties and thereby possibly prevent a normal cell from becoming malignant [63]. The antioxidant properties of various tea polyphenols have been extensively investigated [64]. Reports from a study showed that 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging ability of various black tea polyphenols was in the order of TF-2 > TF-1 > TF. The DPPH radical- scavenging activity was proportional to the number of –OH groups in the catechins or theaflavins. However all the theaflavins exhibited the same ability to inhibit the production of superoxide. Both green and black teas were shown to block the production of oxygen free radicals in the presence of NADPH-cytochrome P450 reductase [65]. Tea polyphenols could also decrease the peroxynitrite-induced nitration of tyrosine and protect apolipoprotein B-100 of LDL from peroxynitrite induced modification of critical amino acids, which contribute to its surface charge [66].

Recently, it has been observed that both black and green tea offered protection against oxidative damage to red blood cells induced by a variety of reagents, e.g.,

H$_2$O$_2$, primaquine, 2,2'-azo-bis(2-amidinopropane) dihydrochloride (AAPH), henylhydrazine (PHx), Cu2+-ascorbic acid, and the xanthine/ xanthine oxidase system [67-69]. Oral administration of green or black tea leaf powder inhibited the lipid peroxidation of liver induced by tert-butyl hydroperoxide in rats [70]. The antioxidant effect of green and black tea on plasma antioxidant potential in man has been demonstrated [71]. Their results showed that intake of tea produced a significant increase of human plasma antioxidant capacity. It has been shown that (+)-catechin prevented human plasma from undergoing oxidation induced by [2,2'-azobis-(2-amidinopropane) clorhidrate] (AAPH) or [2,2'-azobis-(2,4-valeronitrile)] (AMVN) [72]. Tea has also been shown to effectively inhibit tumorigenesis induced by various carcinogens in the skin, lung, fore-stomach, pancreas liver and esophagus of rodents by activating the detoxification systems of the host [73]. Reports indicate that treatment of rats with green and black tea for 4 or 6 weeks caused significant induction of cytochrome P450 enzymes [74,75].

It is recognized that during cancer, the disease itself as well as many of the anticancer drugs in use produce undesirable side effects including oxidative stress and liver damage in the tumor bearer. Reports from our laboratory demonstrate tumor-induced hepatotoxicity and its protection by oral administration of black tea in mice [76]. Hepatotoxicity was adjudged by liver histopathology and by measurement of plasma level of alkaline phosphatase (ALP). Exploration of the underlying mechanisms revealed tumor-induced generation of reactive oxygen species (ROS) on one hand and depression in the level of antioxidants that neutralize ROS, i.e., superoxide dismutase (SOD), catalase, reduced glutathione (GSH), and glutathione-S-transferase (GST), on the other. As a result, lipid peroxidation, which leads to damage of host cell components, was increased. Treatment with antitumor dose of black tea could replenish the host's antioxidant system and regress cancer-induced ROS significantly, thereby protecting the host's liver from lipid peroxidation and subsequent degeneration [76].

Conclusion

Based on the results of numerous laboratory studies, including ours, it can be said that tea consumption might reduce the risk of certain cancers. This review leads us to conclude that tea, the popular beverage, may directly act as an anti-cancer agent by killing tumor cells, or it may act as a "rescue drink" that strengthens the defense mechanism of the host, which otherwise may get suppressed due to the developing cancer. (Figure 3).
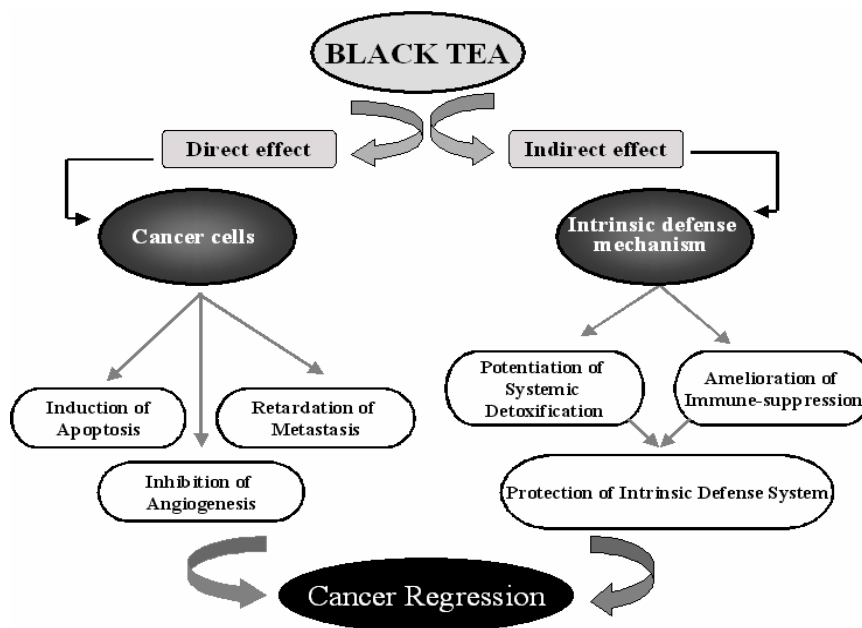
Figure 3. Black tea regresses cancer by (i) directly killing cancer cells and (ii) rejuvenating host's suppressed defense machinery

The knowledge of tea and its polyphenols adds a new dimension to our understanding of the use of dietary constituents either during therapy of cancer patients or as a preventive measure in high-risk individuals who work in a polluted environment containing carcinogenic/toxic chemicals.

Acknowledgements

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