

Phytochemicals - An Alternative of Conventional Chemotherapy in Cancer Treatment

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Abstract

Cancer is one of the leading groups of diseases which occur due to uncontrolled cell proliferation, differentiation, metastasis, apoptosis resistance, angiogenesis, mutations, dysfunction in immunity, therefore resulting in a tumor. Conventional chemotherapy is commonly used as the first line of treatment for cancer patients with some chemotherapeutic drugs, but it shows adverse side effects, such as chemoresistance, radioresistance, stem cell property when healthy cells are exposed to these drugs. With a motive to reduce such side effects 'adjuvants' are used in combination with these chemotherapeutic drugs. 'Phytochemicals' are plant-derived compounds that are beneficial in adjuvant therapy as they show numerous properties that can control cancer expansion. They act as an epigenetic modulator; they can inhibit those enzymes which regulate cell cycle progression. Furthermore, they induce apoptosis and promote cell cycle arrest in cancerous cells. Curcumin, Emodin, Resveratrol, Nimbolide, Gingerol, EGCG, and a few other Flavonoids, Alkaloids, and Phenols are some plant-derived phytochemicals with the greater potentiality to be used in adjuvant therapy. Through studies and Research, it is visualized that these phytochemicals show chemo-preventive, anti-inflammatory, antioxidant, and anti-cancerous properties by regulating EMT and aggressiveness of cancer cells.

Keywords: Phytochemicals; Chemoresistance; Apoptosis; EMT; Conventional chemotherapy; Metastasis.

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Introduction

Carcinoma of Neoplastic Disease is one of the leading health disorders occurring to humans and the very reason for the high mortality rate all around the globe. Around 80% of people face death due to Cancer. Moreover, cancer has increased in recent few years; approximately 1,665,540 people were diagnosed with different types of cancer, and 585,720 of them died (In the United States alone) by 2014 [1]. Cancer and its types can be classified into- Breast Cancer, Lung Cancer, Colorectal Cancer, Prostate Cancer, Pancreatic Cancer, Oral Cancer, and many more. In and around our Earth, the majority of people get affected by Lung and Breast cancer. Lung and bronchus cancer, colorectal cancer are quite common in both males and females, whereas Prostate Cancer occurs in male while Breast Cancer, Uterine and Thyroid Cancer is more common in females respectively [2]. However, in the case of children, Blood cancer, and cancers related to the brain and lymph nodes, are found to be more frequent and in higher percentages as compared to other types of cancer [3,4]. Cancer mainly occurs due to consecutive mutations in the genes which leads to changes in cell functioning, thereby uncontrolled cell division, down the cell cycle. Chemical, as well as physical mutagens, are the most probable agents that cause mutation in the genes. Smoking, Tobacco, Betel quid, Alcohol also produces several carcinogenic chemical mutagens that cause lung cancer or other respiratory carcinomas [5].

Cancer generally alters the cellular composition which in response leads to dysfunction of vital genes that plays an important role in cell functioning. This alteration in the genes further affects the cell cycle and leads to uncontrolled and abnormal proliferation [6,7]. Cancerous cells spread to other healthy body parts and tissues through blood or lymph stream and vessels, which can be called (metastasis and angiogenesis). During embryonic development, the cells lose their epithelial properties and gain mesenchymal properties, this process is referred to as EMT (Epithelial-mesenchymal transition). EMT amends morphological changes which result in the translation of epithelial cells to spindle-shaped cells by the rearrangement of the actin filaments, along with the stress fibers which in turn increases the metastatic behavior of the cancer cells [8]. Increased metastasis and invasiveness of the cells bring alternation in the Bioenergetic profile. Alternation in the Bioenergetic profile is one of the major hallmarks of cancer which is characterized by the increased dependency of the cell on the aerobic glycolysis whereas less dependency on the oxidative phosphorylation. It emphasizes the huge production of metabolites such as lactate [9]. EMT leads to one of the major challenges in cancer treatment. i.e. - chemoresistance, which is mainly related to the alternation of the cancer metabolism, that arises due to transformation in the cell signalling. This chemoresistance such as in Breasts Cancers can be classified by the increased glycolysis, even under sufficient oxygen is available [10], whereas, in the case of Colon Cancer, cells exhibit defects



in ATP production inside the mitochondria. Therefore, it enhances or increases aerobic glycolysis which leads to abundant ATP production in the cancer cells. This property of chemoresistance mainly accounts for the increase in adaptation to protect the cancer cells from the cytotoxic drugs by undergoing self-mutation [11]. CSC (Cancer Stem Cells) has in-built chemo-resistance and, these cells of the tumor do not respond to the chemotherapeutic drugs and resist apoptosis. CSC can escape and spread along other body sites leading to new tumor formation in a new site.

Although in treating Cancer patients, the conventional method of using chemotherapeutic drugs like- Paclitaxel, Vancomycin, Doxorubicin, appears to be the first line of treatment, however, they are associated with several side effects, which mainly target the healthy cells of the body, especially the hematopoietic cells, hair follicles. On that note, new targeted therapies and alternatives came along to use compounds as ‘adjuvants’ that can minimize the side effects of Chemotherapy and maximize the life span of the patients. Phytochemicals like Curcumin, Emodin, Resveratrol, EGCG, Gingerol, and Nimbolide are few natural compounds produced by plants that can be used as an alternative to this conventional chemotherapy. In recent research, it is found that the natural method of chemotherapy based on phytochemicals has lesser overall side effects in comparison to the conventional method of chemotherapy. Looking forward to the future scenario, it holds a strong targeted approach, to reduce the mortality amongst the different types of cancer [12].

Phytochemicals in Cancer Chemoprevention

Cancer is a multi-mechanism cum multistage process that includes metastasis, angiogenesis, invasiveness, and epigenetic modulation. All these are different yet closely related in their initiation, promotion, and progression [13,14].

Initiation is the first step when a solitary use of a sub-carcinogenic dose of a cancerous mutagen takes place [15]. Exposure to these carcinogenic agents induces permanent damage and injuries to the genetic constitution which can be reversed. Promotion is the second step that results by continuously applying the irritating agent [16]. Reversible cellular explosion and selective clonal growth are included in it which further becomes irreversible.

Humans and other organism’s cells are exposed to numerous oxidizing agents which are crucial for life. These agents may be present in food, air, water or can be synthesized during the metabolic processes inside the cell [17]. The prominent factor which should be maintained is the equilibrium between oxidants and antioxidants to the optimal physiological conditions. Imbalance is created due to the production of high amounts of oxidants, which will lead to oxidative stress majorly in chronic parasitic infections and bacterial and viral infections [18].

This led to oxidative stress which causes damage to various

biomolecules like DNA, lipids, proteins which in turn, provokes the risk of cardiovascular and myelomas. The reduction of the initiation phase to a level of zero is nearly not possible. The major interference should be acquired at the promotion level to eradicate the premalignant cells before being malignant [19]. The tenure for the conversion of normal cells to become malignant takes time. Hence, the delaying of this conversion is a possible objective for the future [20].

Results and conclusions of various laboratory-based animal studies denote that, different cancers can be prohibited using certain chemicals. To avoid or slow down the oxidative stress created by free radicals; adequate amounts of antioxidants are necessary to be used. Cancer chemoprevention is the main cancer-preventive approach that exploits natural dietary phytochemicals or remedial drugs with fairly low toxicity. When phytochemicals are used as an adjuvant to these drugs, according to hypotheses and studies it is proved that these phytochemicals show anti-cancer, anti-chemotherapeutic, anti-oxidation, anti-tumorigenic activity and destroys CSCs, tumor-progression gets inhibit, blocks various metabolically driven pathways that produce tumor and metastasis, deduces EMT and so on. The anti-cancer properties of phytochemicals are presented in Table 1.

Different mechanisms involved in chemoprevention of different phytochemicals are [21].

- Antioxidant activities
 - Scavenger free radicals
- Inhibition of
 - I. Cell Proliferation
 - II. Cell differentiation
 - III. Oncogene expression
 - IV. Signal Transduction Pathways
- Induction of
 - I. Tumor suppress gene expression
 - II. Cell cycle arrest
- Enzyme induction and enhancing detoxification.
 - I. Phase II enzyme
 - I. Glutathione peroxidase
 - II. Catalase
 - III. Superoxide dismutase
- Enzyme inhibition
 - I. Phase I enzyme (block activation of carcinogens)

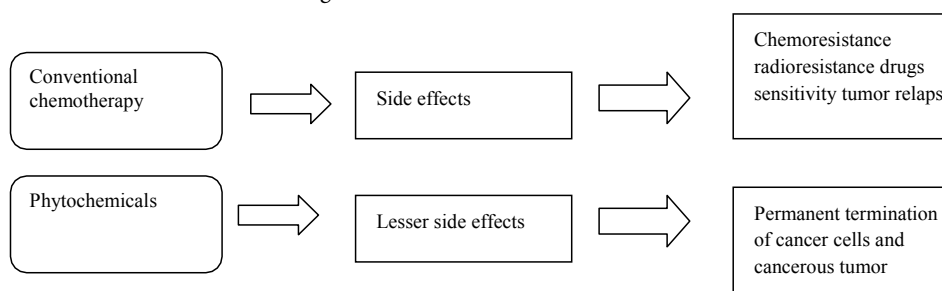


Figure 1: Graphical representation of advantage of phytochemicals over conventional chemotherapy.



Table 1: The anti-cancer properties of phytochemicals.

S. No	Phytochemicals	Anti-Cancer effects
1.	Alkaloids	Modifications of carcinogenic metabolism, tumor metabolism, inhibition of tumor cell growth
2.	Carotenoids	Inducers of differentiation
3.	Phenolic compound	Reduced incidents of neoplasia induced by chemical carcinogens, Preventing nitration of susceptible secondary amines and amides to form highly potent carcinogenic nitrosamines and nitroamides in our foods, potent chemical nucleophiles, inhibitors of promotion processes, inhibitors of kinases by reducing hyperproliferation of epithelial cells
4.	Nitrogen containing compounds	Inhibit the metabolic activation and carcinogenicity
5.	Organosulphur compounds	Induction of carcinogenic detoxification, inhibition of tumor cell proliferation, antimicrobial effect, free radical scavenger, inhibition of DNA adduct formation, induction to cell cycle arrest, induction to apoptosis

- II. Cyclooxygenase-2
- III. Inducible nitric oxide synthase
- IV. Xanthine oxide
 - Enhancement of immune functions and surveillance
 - Anti-angiogenesis
 - Inhibition of cell adhesion and invasion
 - Inhibition of nitrosation and nitration
 - Prevention of DNA binding
 - Regulation of Steroid hormone metabolism
 - Regulation of estrogen metabolism
 - Antibacterial and Antiviral effects

Role of Curcumin in Treatment of Cancer

Turmeric (*Curcuma longa*) is a short-stemmed perennial plant that grows throughout our Indian subcontinent as well as other tropical countries [22]. Curcumin is a polyphenolic compound that is generally used in the treatment of different types of cancer including Lung cancer and Breast cancer. Curcumin has been widely used in many countries due to its vital cum nutritive properties including anti-inflammatory [23], antioxidant, antimutagenic, antimicrobial properties [24,25]. Curcumin is also known as diferuloylmethane which belongs to a polyphenolic group, and its IUPAC name is (1E, 6E)-1, 7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, chemical formula of Curcumin is $C_{21}H_{20}O_6$ and the molecular weight is 368.38. It represents a promising candidate and an effective anticancer plant-based derivative to be used alone or in combination with other drugs. Cancer is a fatal disease defined as a hyper-proliferative disorder in which normal cells of the body cells losses their cellular homeostasis and begin to divide abnormally or without control and starts to invade nearby tissues. Thus, cancer cells spread to the other parts of the body by the blood and lymph system.

Phytochemicals such as Curcumin have anti-inflammatory and chemo-preventive properties which interact directly with intracellular and extracellular molecules that cause initiation and progression in cancer cells, thereby interacting with these molecules it reduces or inhibits the cancer cells' progression and invasiveness in cancer cells [26-29]. Curcumin is a yellow-colored phytochemical that has the potentiality to down-regulate invasion, cell proliferation, tumor cell migration, angiogenesis, aggressiveness, and induce apoptosis. It inhibits EMT and destroys CSC therefore, the properties of CSC to self-renew and differentiate drops down. It acts as an anti-metastatic and hence, research proved that it could reverse and retard the metastasis process by going through some signaling and apoptotic pathways. The mechanism of action of Curcumin generally up-

regulates the production of pro-inflammatory compounds such as cytokines, chemokines, Reactive oxygen species (ROS), overexpression of oncogenes, cyclooxygenase (COX-2), matrix metalloproteinase (MMPs), intracellular signaling pathway compounds, transcription factors such as nuclear factor κ B(NF- κ B), protein kinase B (AKH), signal transducer and activator of transcription 3 (STAT3) and activator protein 1 (AP1) which regulates and initiates deacceleration of the tumor cell proliferation transformation, invasion, metastasis, angiogenesis, chemoresistance and radio-resistance [27,28 and 30-38].

Role of Epigallocatechin-3-gallet in Cancer Treatment

Tea is a familiar beverage that people around the entire Earth consume as it has stimulating, refreshing, and energizing properties. There are multiple types of tea, like Green tea, Oolong tea, Black tea and so on that are preferred by humans for ages. Among these various kinds of tea, Black tea contains Theaflavins (TFs) and Catechins. Moreover, it also has high levels of green tea catechins, in other words, it contains EGCG immensely. According to herbal diagnoses and ancient medicines, Tea is referred to as one of the best remedies for many cardiovascular and inflammatory diseases. Black tea, as well as green tea, portrays anti-tumor, anti-inflammatory, anti-metastatic, antioxidant features. It also shows the metabolic regulatory effect as well as epigenetic modulator [39,40]. Hence, it holds the capability to lower down the tumor development and metastasis. DMBA (7,12-dimethylbenz[a]anthracene) acts as an immunosuppressor and laboratory-based carcinogen, especially used in research and mice models to induce tumors. As studied, DMBA/TPA induced skin carcinogen mice model showed a lower number of tumors and a current up-regulation of Mitogen-Activated Protein Kinases (MAPKs) along with the increased standard of immunosuppressor genes like p53. Soon, the cancer cells moved towards death and apoptosis, when treated with Black tea polyphenols and Resveratrol [41]. When DMH (1,2- dimethylhydrazine) induced mice, model was under observation, it created colorectal cancer, which was then treated by Black Tea polymeric phenols. As a result, it decreased the Wnt/ β catenin pathway. Thus, it controlled invasion and tumor growth [42]. EGCG is a major polyphenol that can be extracted from green tea. This very phytochemical has enormously dealt with a larger number of cancer types. EGCG can restrain the incidence of the tumor by incorporation of such factors that can push for apoptosis. Breast Cancer cell lines MDA-MB-23 showcase quick decline in the rate of proliferation and differentiation [43]. In the case of NSCLC cell lines A549, this kind of carcinoma progression even gets a drop off via p53 dependent suppressor gene functioning [44,45]. Furthermore, Human Pancreatic Cancer regrowth and aggressiveness also depreciate by pushing the cells towards death [46,47]. When it comes to diagnosing patients going through Chemotherapy for Colorectal Cancer, EGCG displays a good amount of anti-chemotherapeutic properties that can suppress the escalation [42]. Phytochemical EGCG portrays anti-cancer,



chemo-preventive, and anti-tumor characteristics. It retards the TGF- β signaling pathway, and EMT is triggered by modulating Smad 2 and ERK pathways while treating NSCLC or Lung Cancer [48].

In addition to such varied benefits of EGCG, it is also effective for Thyroid Cancer and has the potential to downregulate the spreading of Cancer, EMT, and metastasis [49]. If we focus on combinatorial effect and benefits, EGCG can be used with a chemotherapeutic drug called Gemcitabine, which in turn up regulates few apoptotic pathways and suppressing genes that works efficiently to halt further Cancer growth. As conclusion, EGCG is another such plant derivative that can curtail oncogenes to show their expression leading to the person's death.

Role of Emodin in Cancer Treatment

Emodin (1,3,8-trihydroxy-6-methyl-anthraquinone) is a member of natural compounds known as anthraquinones. It is known as an effective therapeutic agent in the treatment of many diseases including cancer. It is extracted from the roots and rhizomes of numerous plants like - Rhubarb, Buckthorn. Emodin showcases various biological functions, such as anti-inflammatory, antibacterial, and anticancer activity. A study revealed that Emodin has therapeutic effects on pancreatic cancer through various antitumor mechanisms [50]. It plays a vital role as a tyrosine kinase inhibitor, antineoplastic agent, laxative, and plant metabolite.

It is demonstrated that Emodin inhibited the growth and proliferation of various tumorigenic cells derived from different tumors, such as Cervical, Breast, Lung, Colorectal, and Prostate cancers [51]. Through studies, we can conclude that Emodin raises the therapeutic effect of Gemcitabine in Pancreatic Cancer cell lines without additional toxic effects [52]. It is suggested that Emodin has anti-inflammatory effects in both in vitro and in vivo systems. Apoptosis could be an anti-proliferative and antineoplastic effect of Emodin [51]. Few studies demonstrated that Emodin plays a role in inducing apoptotic cell death in various cancer cells [53]. Emodin also increases the power of anticancer effects when dosed with Cisplatin while diagnosing Gallbladder and Ovarian cancer cells through ROS-

dependent pathways [54,55].

Emodin may protect cultured human kidney (HEK 293) cells and murine splenocytes against the cisplatin-induced procedure, gamma radiation-induced oxidative stress [56,57]. It is supposed to be reviewed that Emodin has differential effects on normal cells and cancerous cells [51].

It is suggested from in vivo and in vitro laboratory experimental models that Emodin is a potent anti-tumorigenic agent for cancer treatment particularly in digestive system cancers such as pancreatic cancer by regulating multi-molecular targets. This is involved in tumor growth, invasion, angiogenesis, and metastasis. Multiple research work is speeding up on this project. In near future, this review paper possibly provides information regarding the promising anticancer actions of Emodin in cancer treatment.

Role of Gingerol in Cancer Treatment

From the term named 'Gingerol', it can be easily understood that this plant derivative is withdrawn or extracted from Ginger. Ginger is a very popular ingredient that falls under spice and herbs. It comes from a family called Zingiberaceae. Generally, the Gingerol compound is found in the rhizomes of Ginger (*Z. Officinale Roscoe*). It can be also a phenol compound which is a member relative of Capsaicin and Piperine. Chemical constituents of Gingerol are - few phenols, terpenes, lipids, organic acids, and some raw fibers [58,59]. According to ancient medicinal recipes and rituals, Ginger was always used in winters or throughout the year. It showcases innumerable as well as valuable features that can restore a person's well-being. Moreover, it also involves antioxidant, anti-cancerous, anti-fungal, anti-bacterial, neuroprotective characteristics that it is mostly taken to reduce various abnormal function and irritation involved with any disorder and diseases [60]. If we talk about, Gingerol being an adjuvant, it reveals wide advanced features which can control Carcinoma and its growth. Mammary tumor or orthotopic tumor gets inhibited and decline in the levels of metastasis, proliferation, and development [61]. 5mg dose-dependent treatment in such Cancers shows caspase-3 activation

Table 2: The anti-cancer functions of phytochemicals.

Compound	Source	Structure	Function	Reference
Curcumin	Turmeric Rhizomes (<i>Curcuma longa</i>)		It induces the initiation of p53-dependent and p53- independent, G2/M phase cell cyclearrest, thereby restricting cell proliferation and tumor progression.	Choudhuri, et al. (2005), Moos, et al. (2004), Jee, et al. (1998), Kuttan, et al. (1987)
EGCG	Green Tea leaves (<i>Camellia sinensis</i>)		It suppresses escalation of cancer cells, EMT, aggressiveness, metastasis.	Chenga, et al. (2020)
			It up-regulates MAPK and activates immunosuppressor genes like p53.	Srivastava, et al. (2011)
			It deaccelerates Wnt/ β catenin pathway, invasion, and tumor growth.	Maru, et al. (2008)
			It modulates Smad 2 and ERK pathway and down- regulates TGF- β cascade.	Li T, et al. (2019)
			Acts as chemo-preventive, anti-cancer, and anti- inflammatory agent.	Rady Siddique, et al. (2018)
Emodin	Traditional herb Rhubarb or (<i>Rheum officinale</i>) and (<i>Polygonum cuspidatum</i>)		Emodin acts as a tyrosine kinase inhibitor, an antineoplastic agent, a laxative, and a plant metabolite.	Wei, et al. (2013)
			It raises the therapeutic effect of Gemcitabine in Pancreatic Cancer cell lines without additional toxic effects.	Niraj, et al. (2016), Alok, et al. (2019)
			It plays a role in combination with paclitaxel against breast cancer and ovarian cancer.	Tiku, et al. (2014), Yi, et al. (2004)
			It may protect cultured human kidney (HEK 293) cells and murine splenocytes against cisplatin-induced procedure, gamma radiation- induced oxidative stress.	Tseng SW (2002)
Gingerol	Ginger (<i>Z. Officinale roscoe</i>)		It portrays anti-cancer, anti- fungal, anti-bacterial, neuroprotective properties.	Beta M, et al. (2019), Arya, et al. (2017)
			It triggers NF- κ B, STAT3, MAPK, PI3K, ERK1/2,Akt, TNF- α anti-cancerascades.	Tyagi P, et al. (2015)
			It suppresses invasion, metastasis, and tumor growth.	Santos L, et al. (2018), Gundala et al. (2013)
			Activates caspase-3 and other cancer inhibiting genes.	Martin, et al. (2017)



and other tumor-inhibiting pathways which later on triggers genes that express further to Cancer cell decline [62]. Treating other types of Cancer patients suffering from Lung Cancer, Breast Cancer, Colon Cancer, and a few more, also improves the recovery rate and alteration of its side effects. MDA-MB-23 cell lines, A549 cell lines walk towards cell death and come under controlled differentiation [61,63]. This phytochemical showcases astonishing outcomes when prostate cancer cell lines were treated under adjuvant therapy. The progression and proliferation of cancerous cells started to decline [64]. In the case of GI carcinoma, it has also portrayed enormous beneficial results by diminishing the cancer cell progression. It triggers NF- κ B, STAT3, MAPK, PI3K, ERK1/2, Akt, TNF- α , and few more cascades to inhibit Cancer [65]. Some common and important signaling pathways get under standard, up as well as downregulation.

Advantages of Phytochemicals Over Conventional Chemotherapy

Phytochemicals are naturally occurring compounds that are produced by plants ("Phyto" means "plant"). It serves as a major resource for novel drugs and an integral source for cancer therapy. Phytochemicals protect cells from getting damaged which could lead to cancer. The mass usage of synthetic, natural, or biological agents to reduce the incidence of cancer in healthy individuals is known as cancer chemoprevention [66]. These chemo preventive agents inhibit the development of cancer.

In this world, cancer cases increase at an alarming rate. To control cancer, conventional chemotherapies have to some extent failed. Excessive toxicity of chemotherapies clearly demands an alternative approach. One of the principal modes to treat cancer patients is chemotherapy, which has been already in process for the last 70 years by targeting the proliferative nature and metastasizing ability of tumor cells [67]. It is studied that the treatment of chemotherapy should interfere with the biochemical program that is involved or committed to cellular replication which causes selective cell death and the host's cell adapts and recover from toxicity [68]. Mainly, cancer treatment is targeted at its proliferation potential. It also focuses on the point of its ability to metastasize and secondary cancer growth. Hence, it is concluded that the majority of chemotherapeutic drugs take advantage of the fact that cancer cells divide rapidly [69].

In the future, each patient should have a unique chemotherapy protocol. That approach may result to improve the therapeutic quality by selecting and prescribing well-matched drugs. It is supposed to eliminate ineffective ones [70]. It is demonstrated that natural compounds target different signaling cascades involved in cancer progression and differentiation of cancerous cells [66].

Concerning all these studies, it is suggested that the novel chemotherapeutic agents will be much effective against the tumor cells. Using various phytochemical compounds in combination with such chemotherapeutic drugs provides a new aspect to the standard cancer therapy for improving the hazardous condition of a Cancer patient, yet its outcome in a complex and complementary way.

Conclusion

It is well known that cancer is a disease with various etiologies. Conventional cancer therapies cause multiple side effects which represents a serious economic challenge. There are more than 5000 phytochemicals present in grains, fruits, beans, vegetables, and other plants, though a large amount of such plant-derived chemicals is

undiscovered. Phytochemicals prevent DNA damage and help in DNA repair. It helps to slow down cancer growth by regulating hormones. To prove it as a healthy procedure in chemoprevention reduces side-effects and for further treatment, these natural phytochemicals play a vital role. Usage of Phytochemicals is an attractive approach, further efforts are fully on their way to justify thoroughly and to understand their potentiality, pharmacokinetic performances, pharmacodynamics responses, metabolisms, toxicities, drug-to-drug interactions, polymorphisms, and its formulations, stabilities, degradations, and dosage regimens. We hold a motive to work more on this project and to find out undiscovered phytochemicals and identify their related carcinogenesis biomarkers. In the near future, we will continue to be committed and active in this research field.

Conflict of Interest

The authors declare no conflict of interest regarding this paper.

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