

# Cancer Chemoprevention by Flavonoids, Dietary Polyphenols and Terpenoids

Imran Sheikh <sup>1</sup>, VarRuchi Sharma <sup>2</sup>, Hardeep Singh Tuli <sup>3</sup>, Diwakar Aggarwal <sup>3</sup>, Atul Sankhyan <sup>4</sup>, Pritesh Vyas <sup>1</sup>, Anil K. Sharma <sup>3,\*</sup>, Anupam Bishayee <sup>5</sup>

<sup>1</sup> Department of Biotechnology, Eternal University, Baru Sahib, Sirmour, Himachal Pradesh, India

<sup>2</sup> Department of Biotechnology, Sri Guru Gobind Singh College Sector-26, Chandigarh (UT) India-160019

<sup>3</sup> Department of Biotechnology, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala (Haryana)

<sup>4</sup> Department of Dentistry, Swami Devi Dyal Hospital, and Dental College, Panchkula (Haryana) India

<sup>5</sup> Lake Erie College of Osteopathic Medicine, 5000 Lakewood Ranch Boulevard, Bradenton, FL 34211

\* Correspondence: [anibiotech18@gmail.com](mailto:anibiotech18@gmail.com);

Scopus Author ID 55693618000

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**Abstract:** The world population is aging, and cancer is always considered to be one of the major causes of death all over the globe. The advent of recent drug-targeted therapies undoubtedly is going to reduce the incidence of cancer over the coming years. However, the frequency of occurrence of such chronic diseases like cancer would continue to increase. Therefore, the search for a safer and cost-effective treatment is urgently needed. Phytochemicals found in plants, foods, vegetables, tea, etc. have emerged as proven therapeutic compounds modulating signaling pathways involved in cancer. We carried out a structured search of bibliographic databases for peer-reviewed research literature using the keywords: cancer chemoprevention, flavonoids, dietary polyphenols, terpenoids, bioactive, microbiota. Quality of the retrieved papers and characteristic outcomes of the articles included in the study was assessed by employing standard tools and deductive qualitative content analysis methodology. The development of personalized supplements comprising particular phytochemicals has been the key, especially dealing with chronic inflammatory disorders like cancer. Better understanding at the molecular level explains the influence of phytochemicals on human health, which has been extensively covered through this review. Moreover, the wide collection of dietary polyphenols that has significant properties in reference to human health has been highlighted. Furthermore, the etiology of end products of such phytochemicals, especially on the modulation of gut microbiota and the host-microbial interactions thereof, need to be properly understood. The present study summarizes the chemoprevention and treatment of cancer using the bioactive components, including flavonoids, dietary polyphenols, and terpenoids. Likewise, the effect of dietary polyphenols on the human gut microbiota has been realized more recently. However, more research is needed in this field, especially focused on the communications, interlinks between the gut microbiota and polyphenols with the precise mechanism of action.

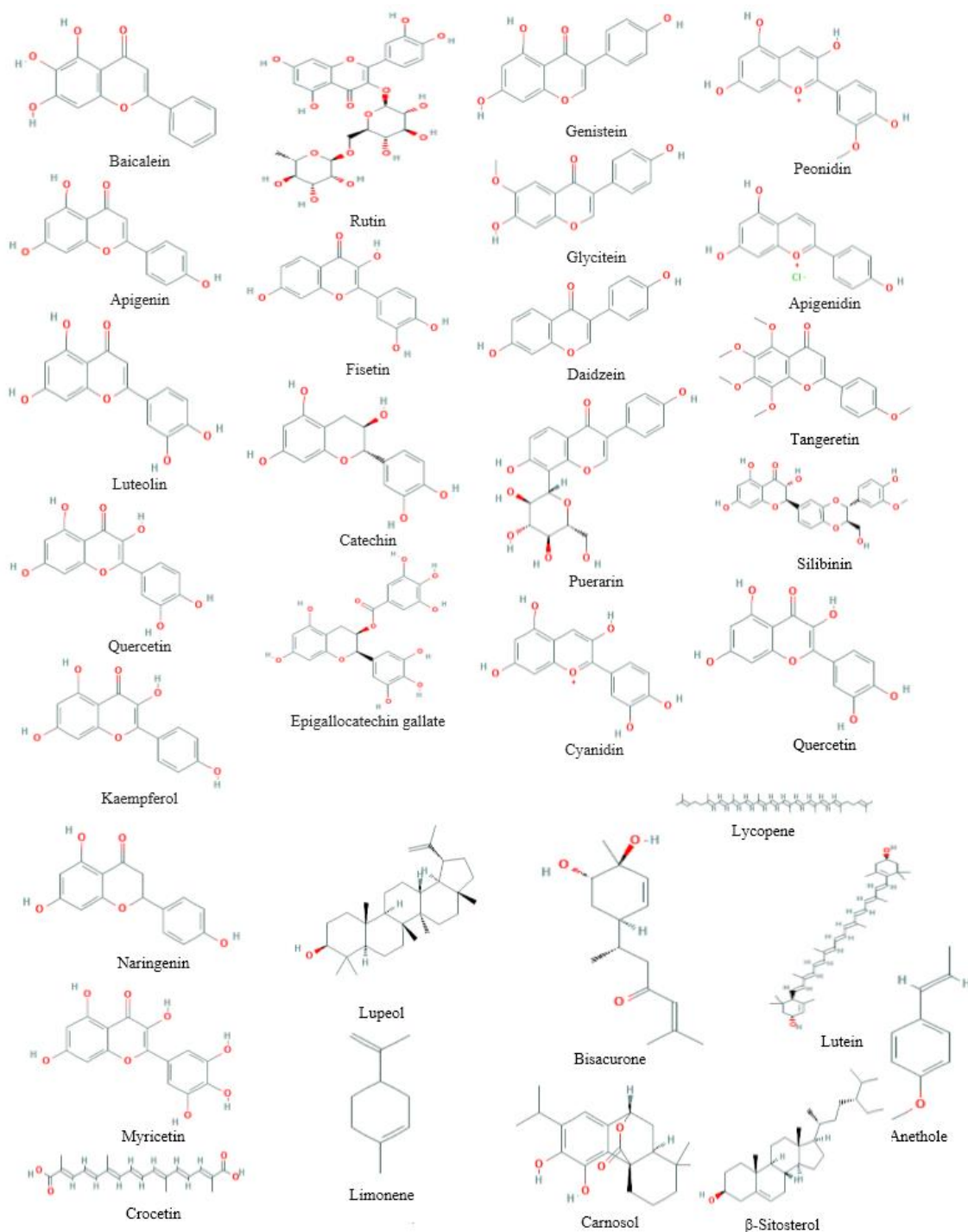
**Keywords:** Cancer chemoprevention; Flavonoids; Dietary Polyphenols; Terpenoids; Bioactive; Microbiota.

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## 1. Introduction

Cancer has been listed worldwide as a significant cause of mortality amid various developments in modern medicines. The development of more operational chemoprevention measures and methods of treatment are needed for the enhancement of recovery rates of cancer patients. As cancer is largely a preventable disease; thus, prevention is generally considered to

avert the disease. Dietary phytochemicals have a rich history of being used effectively for cancer treatment as these are considered to be most safe in terms of lower toxicity levels and the ease of availability.



**Figure 1.** Depiction of categories of major flavonoids and other dietary polyphenols and terpenoids along with their chemical structures.

It has been proposed in several studies that vegetables and fruit diets were often associated with a lower risk of cancer. There have been studies of successful phytochemicals disrupting signaling pathways leading to cancer. Hence, cancer chemoprevention and bioactivities of natural phytochemicals are of wide concern to the medical and scientific fraternity. A wide-array of putative chemo-preventive compounds are under investigation. Sporn *et al.* [1] first introduced the term chemoprevention by using either natural or synthetic

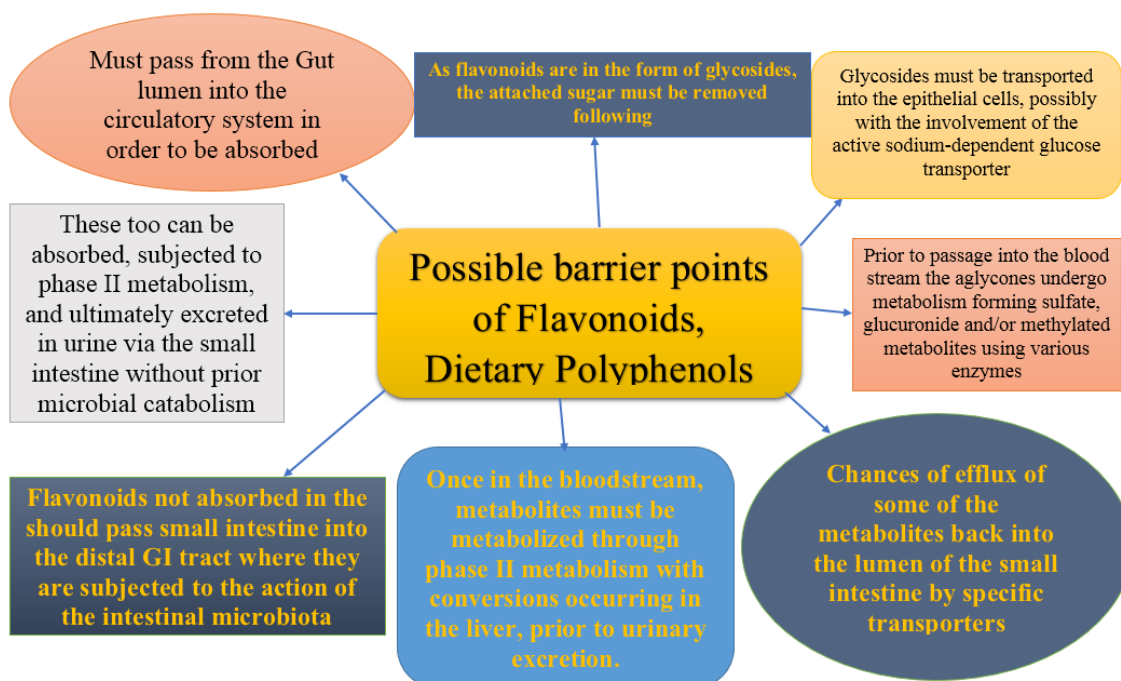
agents. A new definition of chemoprevention has emerged recently, describing them as the compounds with the potential of suppressing molecular pathways that are leading to cancer development and metastasis. Different food habits in various countries have become more accountable for lower or higher incidences of cancer progression in their ethnic groups, suggestive of a putative relationship between the food components and carcinogenesis [2]. For instance, in the Asian population, lower prevalence of cancers such as breast, prostate, and gastrointestinal tract cancers, have been reported. The compounds with chemo-preventive activities mainly consist of (i) polyphenols, such as green tea, quercetin extracted from onions, genistein, a soy flavonoid, resveratrol extracted from grapes or curcumin, etc. (ii) polyunsaturated fatty acids (n-3 PUFAs), (iii) carotenoids ( $\beta$ -carotene and lycopene or lutein), (iv) vitamins (Vitamin D, E, C/ folic acid, etc.), (v) minerals such as Se, Zinc, Calcium, (vi) essential ingredients, dietary fibers, etc. The diets in humans have an essential role in controlling or preventing various diseases [3]. The regular diet checkups and routine control over diet have a positive impact on any disease in humans, including cancer. Hippocrates has suggested, “Let food be thy medicine and medicine be thy food”. Diet in our body acts in both ways, either pro-healthy or can also act as harmful depending on the ingredients [2,4]. Some dietary substances were recorded as carcinogens that initiate or their gradual stimulation leads to tumor growth in the body [5,6]. Food, however, contains large-scale bioactive compounds that are useful to humans. Numerous studies in the literature have shown that there is a negative association between sufficient vegetable and fruit consumption or intake versus cancer. A well-balanced diet must be containing macronutrients such as omega-3 fatty acids and fibers, selenium, calcium, vitamin D and E, folates, etc., along with phytochemicals that are rich in cancer prevention properties *viz.* polyphenols, flavonoids, carotenoids (Figure 1 and Figure 2). Therefore, as evidenced through various researches, phytochemicals, or dietary agents have a profound role in cancer prevention and cure [7,8].

## 2. Flavonoids

A variety of edible items like fruits, vegetables, floral plants, chocolate, tea/leaves, wine products, and other plant sources are rich sources of dietary flavonoids [9,10]. Flavonoids can be further divisible into subfamilies, which may include flavones, flavonols, isoflavones, flavanones, and flavanonols, etc. [11]. Figure 1 clearly elucidates the categories of major flavonoids and other major polyphenols relevant to the present review, along with their chemical structures [7,12].

However, all the family members of this family share common basic chemical structural composition of having two benzene rings, which are connected by a three-carbon bridge, and forms a heterocyclic structure (C6-C3-C6) [13]. In terms of safety, flavonoid compounds have been reported not to exceed the toxicity limit of 140 g/day. Moreover, they do not exhibit any noteworthy adverse effects as well [14]. In reference to the pharmacological effects of flavonoid compounds, they have broad-spectrum properties, including strong antioxidant properties, anti-inflammatory effects, cardio-protective, hepatoprotective, antimicrobial, and anticancer activities [15,16]. Yet, isolation and purification of flavonoids is a difficult process. Epidemiological and clinical laboratory researches have shown that dietary flavonoid consumption decreases the risk of certain cancers [17]. Flavonoids have shown anti-proliferative effects in variety of cancers, including (a) silymarin, (b) genistein, (c) quercetin, (d) daidzein, (e) luteolin, (f) kaempferol, (g) apigenin, (h) epigallocatechin 3-gallate etc. [18].

These compounds have anti-tumorigenic effects against prostate, colorectal, breast, thyroid, lung, and ovarian cancers.



**Figure 2.** Possible challenges associated with pharmacokinetics and absorption of flavonoids, dietary polyphenols, and terpenoids.

There are some of the mediating factors that facilitate the chemopreventive efficacy of flavonoids, including inhibition of development of new cancer cells, prevention of carcinogens to reach to respective activation sites, reduction in the toxicity levels of particular compounds by the inhibition of their metabolism [19]. The molecular mechanisms by which flavonoids have shown anticancer include (1) stimulation of apoptosis [20] (2) cell cycle arrest at G1 or G2/ M phase, i.e., cycline-dependent kinases (CDKs) may inhibit cell cycle regulators (3) inhibition of enzyme metabolism (mainly cytochrome P450), which further inhibits the carcinogenic compound activation (4) reactive oxygen species (ROS) inhibition by activating phase II metabolizing enzymes and (5) vascular endothelial growth factor (VEGF) inhibition along with basic fibroblast growth factor (bFGF) guided angiogenesis [21]. Numerous flavonoids were recorded to inhibit multidrug resistance responsible for cancer relapse and chemotherapy failure [22]. Some of the flavonoids exhibit specific mechanisms of action that are not articulated as the characteristic of the family of flavonoids. Such flavonoids are genistein, isoflavones, and diadzein, which have been reported to suppress cancer growth as well as proliferation [23,24]. They have shown some structural similarity with estrogen, genistein, and diadzein, which are described to have strong efficacy against breast cancer [25,26]. Another flavonoid, silybin, has also been shown to have antioxidant and numerous pharmacological anti-cancer properties viz. inhibition of other factors including (1) Nuclear-factor kappa-B (NF- $\kappa$ B) mediated tumor-necrosis-factor (TNF) stimulation. Alpha ( $I\alpha$ ) to NF- $\kappa$ B (active form) was seen to inhibit phosphorylation and proteolytic decay of the kappa light polypeptide enhancer nuclear factor in B-cell receptor [27] (2) tyrosine kinases [28] (3) androgen receptors [29] and (4) the epithelial to mesenchymal transition through embryonic pathways [30,31]. Quercetin, another flavonoid that also exhibits antioxidant properties, has been found to exist in some dietary substances such as onions, berries, apples, red wine, etc.

[9,32]. Quercetin has been shown to display anticancer efficiency in colon cancer and neurogliomas as well. The efficacy of this flavonoid compound is attributed to the activation of signaling pathways for autophagy and mitogen-activated protein kinases (MAPK or extracellular kinases [33]) [34,35]. Several studies have been published on the prospective role of flavonoids in cancer treatment and prevention [10]. A variety of flavonoids and their essential formulations are available in dietary supplements such as milk thistle and red clover extracts [36]. However, none of the flavonoids mentioned here were authorized for clinical use. With numerous pre-clinical studies, it has been proposed that flavonoids have substantial anticancer effects [Table 1], however, there are many hindrances and challenges in flavonoids production as a clinically authorized product and about their role in significantly reducing the risk of cancer.

**Table 1.** Classification and sources of dietary phytochemicals possessing antitumor activities.

Sr. No.	Functional component	Dietary source	Functional Property Action Potential	Ref.
A	<b>Polyphenols</b> Flavonoids			
1	Apigenin	Parsley and celery	anti-inflammatory, antioxidant, antibacterial and antiviral activities	[37]
2	Butein	Indian cashew ( <i>Semecarpus anacardium</i> )	antioxidative, Inhibition of aldose reductase and advanced glycation end products inhibitory effects, inhibits TNF-dependent NF-kB degradation and phosphorylation	[26,38-40]
3	Catechingallate	Green tea	reverse methicillin resistance in bacteria such as <i>Staphylococcus aureus</i> anti-inflammatory activity in pancreatic tumor	[41]
4	Cyanidin	Wild blueberry ( <i>Vaccinium myrtillus</i> )	probable sirtuin 6 (sirt6) activator acts as a natural inhibitor of intestinal lipid digestion and absorption	[42]
5	Daidzein	Soybean	Inhibitory effects against prostate cancer, bladder cancer, breast cancer, diabetes	[43,44]
6	Delphinidin	Cranberry, strawberry, Pomegranate	antioxidant and anti-inflammatory properties	[45]
7	Epicatechin gallate	Green tea	antioxidant, tyrosinase inhibitory activity, beneficial in preventing metabolic syndrome	[46,47]
8	Fisetin	Strawberry, apple	antioxidant, anti-inflammatory activity, causes reduction in the age-related decline in brain function, activates key neurotrophic factor signaling pathways	[48,49]
9	Genistein	Soybean	antineoplastic agent, prostate cancer, bladder cancer, and breast cancer	[50,51]
10	Isoliquiritigenin	Licorice ( <i>Glycyrrhiza glabra</i> )	anti-inflammatory, antiviral, antidiabetic, antispasmodic, antitumor activities, anti-proliferative, a supplement to ease the menopause symptoms, an anti-tumor agent in the pituitary gland.	[52,53]
11	Kaempferol	Tea, broccoli, grapes	antioxidant, prevent arteriosclerosis, protects against various oxidative stresses, protects against inflammatory age-related chronic disorders.	[54]
12	Luteolin	Licorice ( <i>Glycyrrhizaglabra</i> )	neuroprotective, antioxidant, pro-oxidant activity, estrogenic, anti-estrogenic activity, anti-inflammatory, anti-cancerous.	[55,56]
13	Xanthohumol	Beer (from <i>Humulus lupulus</i> )	anti-inflammatory, antioxidant, hypoglycemic activities, anticancerous, fights with oxidative	[57-59]

			stress, regulate fat metabolism and storage, cholesterol modulation.	
14	Tangeretin	Citrus fruits	lowering of cholesterol levels, anti-tumor, and neuroprotective action.	[60,61]
15	Silibinin	Milk thistle ( <i>Silybum marianum</i> )	shows antioxidant, antineoplastic and hepatoprotective activities	[62-64]
16	Quercetin	Onion, apple, broccoli	reduces inflammation, blood pressure, and blood sugar levels	[65,66]
17	Naringenin	Grapes, citrus	anti-dyslipidemic, anti-obesity and anti-diabetic and antifibrotic properties.	[67,68]
18	Myricetin	Grapes, onion, tea	antioxidant, anticarcinogenic, anti-mutagenic, antiviral, antithrombotic, anti-inflammatory	[69]
<b>B</b>	<b>Terpenoids</b>			
	<i>Carotenoids</i>			
1	Crocetin	Saffron	antioxidant and anticancer properties	[70-72]
2	Lutein	Spinach	antioxidant properties	[73,74]
3	Lycopene	Tomato, Watermelon, red grapes	helps in improving heart health, lowering the risk of certain types of cancer	[75]
4	Lupeol	Mango, strawberry	anti-inflammatory, anti-cancer effects	[76]
5	Limonene	Citrus fruits, cherries, grapes	helpful against obesity, cancer, and bronchitis	[77]
6	Anethole	Sweet fennel ( <i>Foeniculum vulgare</i> )	used to flavor various foods and cosmetic products.	[78]
7	Bisacurone	Turmeric ( <i>Curcuma longa</i> )	anti-inflammatory, anti-oxidant, and anti-metastatic properties.	[79,80]
8	Carnosol	Rosemary	anti-cancer and anti-inflammatory in nature.	[81,82]
<b>C</b>	<b>Phytosterols</b>			
1	$\beta$ -Sitosterol	Nuts, grains, seeds	help to reduce cholesterol levels, effective against enlarged prostate, anticancer effects	[83,84]

### 2.1. Isolation and purification of flavonoids.

Low concentrations of the desired compound (from micro to milligrams per kg of plant masses) have been a major challenge in the extraction of flavonoids from the concerned plant sources [85]. The continuous removal of these anticancer compounds may lead to the elimination of the plant source, disrupting all plant communities and ecosystems. Secondary metabolites, minerals, vitamins, and fibers have all been derived from plants itself [36]. Thus, the complete plant ingredients could be responsible for the beneficial effects of anticancer products. However, the ability of flavonoids to form complexes with other compounds makes it more difficult to comprehend and identify the key molecule responsible for pharmacological effects. Combinatorial methods may be used to separate different compounds, including solvent extraction, column chromatography, medium-pressure liquid chromatography, vacuum column chromatography, and prepared high-performance liquid chromatography (HPLC) [86-88]. The implementation of such measures is a time-consuming process that may have an association with high costs [89]. Similarly, even with the involvement of these complex techniques, still, the yield of the isolated compound remains even less than 1g. Another reason attributed to low yield is the complex biosynthetic pathway of flavonoids resulting in varied flavonoids composition at different stages of plant development, even under changed environmental conditions [90, 91]. Different flavonoid compositions also affect the predictability of flavonoid yields at the time of extractions, though the data after each extraction has not been consistent [92]. Some disadvantages include labile flavonoid extraction in these compounds, which exposes them to exceptional rates of degradation or alterations in their chemical structures and subsequent loss of function during purification. Thus, flavonoids

harvested from plant products using existing techniques, have proven to be costs associated with low yields and cumbersome as well.

### 2.2. Challenges associated with Pharmacokinetics (PK).

Flavonoids usually have an inappropriate PK profile viz. ADMET profile [93] with lower solubility, poor oral absorption, and faster liver metabolism through phase I and II enzymes [94,95]. These flavonoids are usually consumed with supplementary food constituents. As a result, there is a precipitation of flavonoid compounds that limit their levels of absorption as well as bioavailability [96]. Flavonoids can also undergo metabolism via de-glycosylation before they get absorbed in the small intestine [97]. They may act as substrates for sulfation, O-methylation, and glucuronidation *in vivo* resulting in the rapid excretion in urine [98,99]. Besides, the unabsorbed part can reach the colon, which further can undergo degradation by the intestinal micro-flora either through ring fission [100], reduction [101], or hydrolysis. For example, in the case of quercetin taken orally, only a 20-30% quantity is bioavailable. In the case of silybin, its anti-cancerous properties are restricted by its low oral absorption and low bioavailability [102]. Complete degradation of flavan-3-ols has been reported to occur after its exposure to simulated intestinal secretions after 8 hours of time duration [103,104]. These above-mentioned PK liabilities display substantial barriers to the clinical developments of flavonoids [105] [Figure 2]. Moreover, the higher dosages of flavonoids ingested may result in proliferative and inflammatory responses [106]. Furthermore, due to their numerous *in vivo* interactions, flavonoids could affect bioavailability and efficacy of different drugs viz. certain flavonoids may affect cytochrome 450 (CYPs) [107], conjugation enzymes,  $\alpha$ -amylase,  $\alpha$ -glucosidases, bovine hemoglobin, multidrug resistance transporters (Morris and Zhang, 2006), colonic microflora and plasma proteins [108].

### 2.3. Interactions with ABC drug transporters.

The ATP-binding cassette (ABC) superfamily consists of some essential members serving as mediators between PK alterations (i.e., ADMET) and multidrug resistance (MDR) to various antineoplastic drugs, along with flavonoids, serving as substrates for these transporters [109-112]. The transporters, along with two transmembrane domains, are located on the cell membranes that recognize diverse compounds and form channels within the membrane in order to efflux these compounds [113,114]. ABC transporters are though omnipresent in our body but are present in higher densities in barrier-functioning tissues such as gastrointestinal tract, reproductive organs, kidney, liver, and blood-brain barriers [115]. ABC transporters have been widely known to have a role in controlling drug absorption, distribution, and excretion, which can reduce bioavailability and efficacy [116]. Several studies have been performed to explore possible interactions between flavonoids and ABC transporters. Flavonoids such as flavones (e.g., apigenin and chrysin), isoflavones (e.g., biochanin A and genistein), flavonols (kaempferol) and flavanones (naringenin) are known to inhibit the efflux function of ABC carriers such as ATP binding cassette subfamily B member 1 (ABCB1) and ABCG2 [117]. Flavonoids inhibiting ABC transporters could have potential advantages and disadvantages as well [118]. ABC inhibition of transporters may increase the bioavailability of certain poorly available drugs, potentially enhancing the absorption, distribution, bioavailability, and effectiveness of other drugs, including antineoplastics. This can be used to resolve multidrug resistance (MDR) and chemotherapy failure [117]. For

example, isoflavonoids may induce apoptosis in multidrug-resistant P388 leukemia cells and further overcome resistance mechanisms [119]. Epigallocatechin-3-gallate, when administered through intragastric gavage at a dosage of 10 mg/kg body weight as a suspension in 0.2% agar (once daily for 10 days), was reported to significantly decrease the expression of P-gp, resulting in increased atorvastatin and verapamil plasma levels in male Wistar rats which further potentiate their pharmacological effects [120-123]. However, inhibition of ABC transporters by the flavonoids may potentiate the toxicity of certain ABC substrates and cause unintended adverse or toxic effects of certain antimicrobials, immuno-suppressants, cardiovascular, and chemotherapeutic drugs [124].

#### *2.4. Interactions of intestinal microflora.*

Depending on the compound, a substantial proportion can hit the colon after oral administration of flavonoids and undergo microflora degradation and enterohepatic circulation [125]. Colonic microflora is considered to be the most abundant human microbiome [126,127]. These microorganisms were shown to bio-transform other drugs into metabolites, altering their effectiveness and toxicity [128]. They not only also act as pathogen barriers but also protect against harmful xenobiotics. Colonic microflora may also decrease cholesterol absorption and improves intestinal mucus production [129,130]. The role of colonic microflora in the absorption, metabolism, and bioavailability of flavonoids is yet to be established [131]. Unabsorbed flavonoids can be bio-transformed into small phenolic compounds having similar effects but with improved bioavailability in comparison to parent compounds [132]. By comparison, through the enzymes glucuronidase and sulphatase, colonic microflora can extensively metabolize flavonoids, producing metabolites that are predominantly inert and are rapidly excreted polar compounds [133]. Some flavonoids (e.g., apigenin, genistein, naringenin, and kaempferol) are more vulnerable than others to microfloral degradation, resulting in a lower bioavailability [134]. Recent research has shown that certain flavonoids can inhibit intestinal microflora and the associated processes of fermentation [135]. Ellagitannins and flavan-3-ols from raspberry extracts were shown to inhibit ellagitannins and  $\beta$ -galactosidase [136]. In addition, antibiotic usage should be controlled when used along with flavonoids because they can alter gut microflora composition that ultimately affects flavonoid bioavailability [137]. The wide range of flavonoid structures and the microbial composition of the gastrointestinal tract, thus reduce the predictability of the types of interactions that occur, as well as the effects and permeability of the resulting compounds.

#### *2.5. Approaches to overcome pharmacokinetic/pharmacodynamics (PK/PD) and other barriers.*

There are several approaches to strengthen and resolve the therapeutic applications of dietary flavonoids.

##### *2.5.1 Improving purification and isolation yields.*

Current conventional isolation and purification methods usually result in lower flavonoid extraction yield, while having higher extraction costs. Nonetheless, optimizing conditions in these conventional extraction methods will certainly increase the flavonoid yield. Response Surface Methodology (RSM) was used to optimize flavonoid extraction from herbal medicines like *Citrus aurantium* L., with ethanol [138]. RSM is an experimental designed



quantitative and statistical method [139] that had significantly increased the yield of Chinese Huangqi flavonoids when the extraction parameters were optimized having an ethanol concentration of 52.98%, extraction time of 2.12 hrs, extraction temperature of 62.46°C while the liquid-solid ratio of 35.23 [138]. However, these optimization parameters are required for each flavonoid plant source, which is again a laborious and time-consuming process. Therefore original concrete methods need to be used to minimize the cost and degradation of extracted flavonoids from their natural sources [140]. The use of high-speed, counter-current chromatography with lower costs and higher yields, have been tried in the past success as an innovative approach [141]. Nano-harvesting, using nanoparticles in order to remove flavonoids from their source, is another innovative approach adopted previously [142]. This technique avoids the use of organic solvents, allowing continuous processing of flavonoids and opening up a new age of natural product extraction methods [143]. The ultrasonic extraction method employed previously was aimed at enhancing extraction performance and minimizing the extraction time [144,145]. However, the extraction of other compounds from the same plant source will seriously harm plant ecological communities. Therefore, industrial-scale microbial production of plant-natural products like flavonoids is actually an attractive option [146]. This strategy will preserve environmental resources and use low-energy and waste emission-related economic stocks.

#### 2.5.2. Resolution of pharmacokinetics issues of flavonoids.

A variety of methods or solutions persist in order to address factors that lower flavonoids bioavailability. For example, flavonoid formulation can lead to increased bioavailability compared to flavonoid alone or other types of glycosides [147]. Such derivatives are substrates for other intestinal carriers that improve absorption [148]. Quercetin-4'-O-glucoside administration resulted in plasma levels five times greater than quercetin-3-Orutinoside. Therefore, transforming quercetin glycosides into glucosides can be considered as an approach to improve flavonoid bioavailability [147]. The use of bio-enhancers can be employed to incorporate piperine, an amide alkaloid extracted from Piperaceae plants [149]. Piperine greatly inhibits the conjugation of various phase II UDP-glucuronosyltransferase enzymes, such as quercetin [150] and epigallocatechin-3-gallate [151], reducing metabolism while increasing bioavailability [150]. Also, the ability of intestinal microflora modulators can be considered to enhance flavonoid bioavailability [152]. One of the most effective techniques for optimizing PK/PD parameters is to optimize the flavonoid structure in order to generate original derivatives. To retain their desired effects, these compounds must contain the essential parent pharmacophore. Methyl and hydro-silybin derivatives are reported to be ten-fold stronger than silybin [153]. Introducing hydrophobic functional groups (e.g., ethyl substitution) to the quercetin hydroxyl (OH) groups significantly enhance their stability by preventing hydroxyl group oxidative degradation [154]. It has also been shown that blocking other quercetin groups (e.g., C3 hydroxyl and C7 hydroxyl groups) by adding lipophilic moiety pivaloxymethyl (POM), increases the solubility, stability (half-life increased from 10 h for quercetin to over 72 h for its quercetin-POM conjugates at pH 7.4) and efficacy by preventing chemical and metabolic hydrolysis [155]. Emulsified flavonoids are released gradually over time, allowing for a higher absorption surface region, eventually increasing absorption and bioavailability after oral administration [156]. Another method is the advanced delivery system of nano-crystal, self-stabilized Pickering emulsion, which was effectively used for the distribution of certain flavonoids like silybin [157]. Formulating flavonoids as povidone-mixed microparticles

were shown to substantially improve their release and PK profile [158]. Quercetin encapsulation in Zein nanoparticles has been shown to increase protective efficacy in a mouse endotoxemia model [159]. Protein-complexed flavonoid was shown to improve *in vitro* stability [160]. Several studies show that flavonoids can be used to improve chemical stability as well [161].

### 2.6. Dietary polyphenols.

Polyphenols are a significant class of phytochemicals. These plant-derived polyphenols are instrumental in shielding plants from photosynthetic stress, reactive oxygen species (ROS), and herbivore consumption. Also, polyphenols are the most abundant compounds present in human food, including flavonoids and phenolic acids. There is a growing understanding that lower cancer incidence may be due to the use of various nutrients, particularly polyphenol-rich diets. In recent years, a systematic study of polyphenolic compounds chemo-preventive ability has clearly established their health benefits, including anti-cancer properties [Table 1]. A large number of studies in cultivated cells, animal models, and human clinical trials demonstrated a protective effect of dietary polyphenols against different cancers [162,163]. Over 8,000 different polyphenols exist and can be classified into ten general categories based on their chemical structure [164]. Phenolic acids, flavonoids, stilbenes, and lignans are the most common polyphenols in food worldwide. EGCG (green tea), curcumin (curry), and resveratrol (grapes and berries) are among the most widely studied and feasible cancer chemo-preventive polyphenols. Chemo-preventive effectiveness involves their ability to suppress or reverse cancer by acting on intracellular signaling network molecules involved in cancer initiation and/or promotion, or their ability to promote cancer arrest or reversal [165]. Polyphenolic compounds can also induce apoptosis in cancer cells by modulating several main elements in apoptosis-linked cell transduction pathways (caspases, *bcl-2* genes) [166].

**Table 2.** Association between flavonoids or foods rich in phenolic compounds and cancer prevention.

	Effects	Sample size	Ref.
Flavonoids	Decrease cancer risk at all sites	9959 Men	[167]
	Decrease cancer risk in the oral cavity, pharynx, larynx, and esophagus	540 People	[168]
Quercetin, Onions, white grapes	Decrease recurrence of lung cancer	582 People	[169]
Quercetin	Decrease the incidence of lung cancer	10054 Men	[170]
Quercetin, kaempferol	Decrease the risk of gastric cancer	354 People	[171]
Catechins	Decrease the incidence of rectal cancer	34651 Women	[172]
Tea	Decrease the risk of colon cancer	12170 People	[173]
Green tea	Reduced risk of cancer in different organs	8552 People	[174]
	Reduced risk of breast cancer recurrence and metastasis	472 People	[175]
Black tea	No association with gastric cancer	11902 Men and 14409 Women	[176]
	No association with risk of colorectal, stomach, lung and breast cancer	58279 Men and 62573 Women	[177]
Soya	Decreased risk of lung cancer	999 Men	[178]
	Decreased risk of breast cancer	34759 Women	[179]

### 3. Tea

Tea (*Camellia sinensis*) has been the most popular drink consumed by over two-thirds of the water-side population worldwide. The Chinese used tea as a drink as early as 3000 BC to as late as the sixth century. This tea simply comprised of two or three leaves, ending apical buds of *C. Sinensis*, *C. asamica*, and other southern varieties. Several million tons of dried tea

is produced annually of which about 20% is the green tea, mostly consumed in Asian countries where tea is a common drink, while about 78% is the black tea, mostly consumed in Western nations and some Asian countries. Around 2% of dried tea is oolong tea, mainly produced and consumed in Southeast China. Black tea is produced by crushing leaves, resulting in oxidase-dependent polyphenol polymerization leading to the production of theaflavins, arubigins, and other oligomers in a fermentation method. Theaflavins, like theaflavin, theaflavin-3-O-gallate, theaflavin-3-O-gallate, and theaflavin-3-3'-O-digallate, have dihydroxy or trihydroxy substitution benzotropolone rings, giving the characteristic color and taste of black tea. This tea is partially fermented with monomeric catechins, theaflavins, and arubigins. Green tea is produced at high temperatures by steaming or drying fresh tea leaves. Green tea primarily consists of polyphenols, flavandiol, flavonoids, and phenolic acids, adding up to 30% of dry weight. Most polyphenols, also called catechins, caffeine, theobromine, and theophylline, are common alkaloids that account for around 4% of dry weight [180]. Polyphenols are present at 30-35% in dry tea leaves, which ultimately determine the consistency of the drink. Tea polyphenols are known to exhibit anti-carcinogenesis effects through a variety of mechanisms that vary for different types of cancers and for the same cancer in different populations. Several labs have reported inhibitory effects of tea polyphenols on tumor production and growth, primarily due to antioxidant and possible anti-proliferative effects of polyphenolic compounds present in green and black tea. These polyphenolics can inhibit carcinogenesis by preventing the endogenous formation of N-nitroso compounds, suppressing carcinogen activation, and trapping genotoxic agents. Yang *et al.* [180] demonstrated a high affinity to metals, alkaloids, and biological macromolecules, including lipids, carbohydrates, proteins, and nucleic acids. They capture and detoxify free radicals produced during various metabolic processes, including radiation and light exposure. Tea polyphenols conduct their inhibitory actions in different stages of mutagenesis, carcinogenesis, invasion, and tumor cell metastasis. They act as desmutagens and bioantimutagens intracellularly. Tea polyphenols also possess the ability to modulate, block, inhibit, or hinder DNA replication and repair.

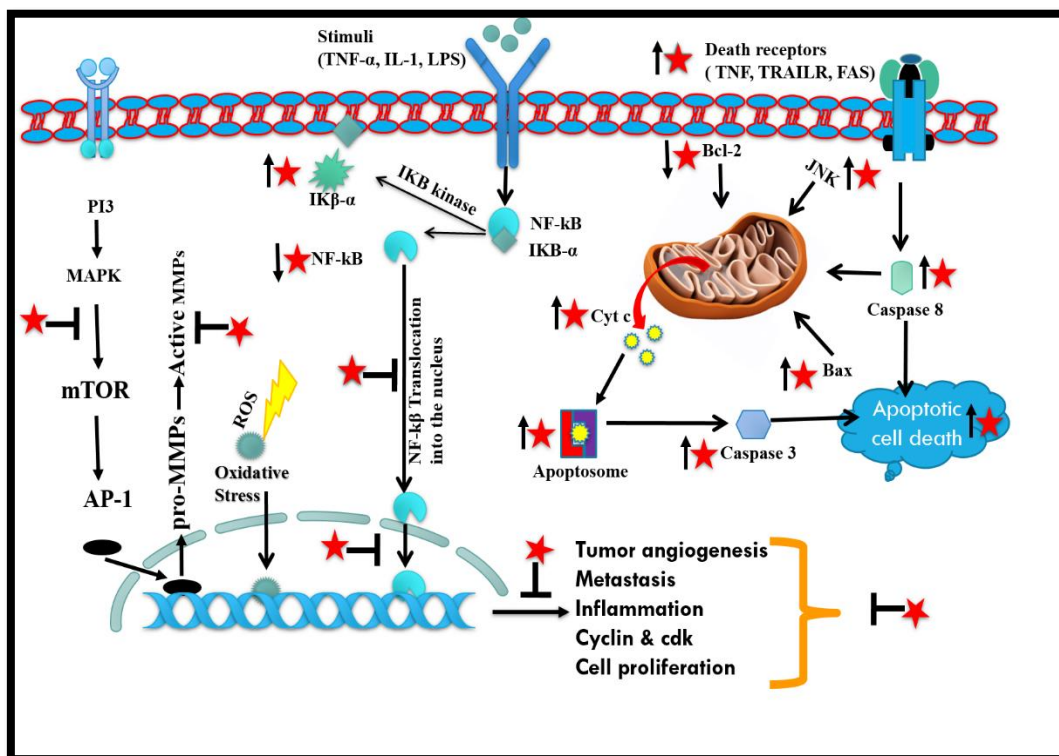
### *3.1. Green tea from a health perspective.*

Effects of green tea on humans, livestock, and laboratory experiments have been thoroughly studied, supporting the notion that green tea can support many health conditions. Green tea intake could be significantly correlated with a lower risk of stroke mortality and pneumonia. Moreover, the intake imparts a lower risk of cognitive impairment, depression, and psychological distress, which was further confirmed by other studies. Green tea consumption can also lower-down the risk of osteoporosis. Randomized placebo-controlled studies have shown that green tea decreases cardiovascular risk factors and disability prevention effectively [181-184].

#### *3.1.1. Anticancer Effects.*

Specialized studies have seen conflicting evidence between green tea and reducing the risk of cancer, while other studies did not find any sort of connection. Limited and heterogeneous clinical trials reported conflicting findings due to variations in diet, climate, and population [185]. Several population-based clinical trials have shown that green and black teas can have beneficial therapeutic effects against cancer. For example, Japanese people who frequently consume green tea are at lower risk of cancer incidence; however, the same test

could not be used to determine whether green tea prevents cancer in people from other countries [186]. However, there exists a strong association between foods rich in phenolic compounds or flavonoids and their anticancer potential. Several clinical trials and published research suggest that polyphenols for tea or green tea may be responsible for cancer prevention [187]. Figure 3 elucidates the plausible anticancer mechanism of action of flavonoids, polyphenols, and terpenoids. These phytoconstituents are known to inhibit cell survival signaling pathways resulting in the downregulation of cyclin and CDK proteins. Major signaling cascades, such as mitogen-activated protein kinase (MAPK), mammalian target of rapamycin (mTOR), AKT serine/threonine-protein kinase B (AKT), matrix metalloproteinases and caspase-3/-8,-9 have been reported to be playing a significant role against metastasis [188].



**Figure 3.** Schematic representation of the anticancer mechanism of action of flavonoids, polyphenols & terpenoids. These phytoconstituents inhibit cellular survival pathways and downregulation of cyclin and CDK proteins. Major signaling cascades, such as mitogen-activated protein kinase (MAPK), mammalian target of rapamycin (mTOR), AKT serine/threonine-protein kinase B (AKT), matrix metalloproteinases and caspase-3/-8,-9 have been reported as key players for their anti-malignancy potential.

### 3.1.2. Bladder cancer.

Some clinical trials explored the correlation between tea and bladder cancer. Women drinking black tea or powdered green tea were reported to be less likely to develop bladder cancer in one of the studies. Interestingly, the same group of researchers found patients with bladder cancer who had green tea or black tea, were having a higher survival rate than others [189].

### 3.1.3. Esophageal cancer.

One of the research groups from India showed that black tea consumption could lead to the development of oesophageal cancer, which can be well correlated with that of the

Chinese cohort group who used to consume hot black tea. Throughout India, black tea is usually taken with milk that further neutralizes the beneficial effects of tea [190,191]. Furthermore, Catechin content in green tea is reported to be higher than black tea, which could further explain the contrary relationship between tea and esophageal cancer risk.

#### 3.1.4. Prostate cancer.

Prostate cancer is a model candidate disease for chemoprevention as higher latency is diagnosed in men over 50 years of age [192]. Therefore, even a minor delay in cancer progression using chemopreventive therapy will improve the patient's quality of life [193]. Cultural, epidemiological, and migration studies further suggest that Asians are at a lower risk of cancer due to the regular consumption of green tea in comparison to Western societies [194]. Preclinical animal studies and lab reports also suggest the protective efficacy of green tea against prostate cancer [142,195].

#### 3.1.5. Skin cancer.

Naturally occurring plant products, i.e., polyphenols, were extensively used to prevent UV-induced skin photo-damage and skin cancer risk. Dietary polyphenols can be used as an ideal chemopreventive agent for various skin disorders because they have anti-inflammatory, immune-modulatory, and anti-oxidant properties. In addition, keeping in view of many carcinogenic environmental factors that are not so easy to regulate, people can change to a healthy lifestyle and good dietary behaviors along with the use of skin care products to avoid skin photo-damaging.

#### 3.1.6. Cervical cancer.

It is the third most common malignancy in women worldwide, as this malignancy is considered to be the most common gynecological cancer in the developing world. By extensive and systematic use of cervical cytology screening, it was established that this malignancy affects women's lives during the time of their highest productivity in both developing and developed countries. It is recognized that regular fruits and vegetable intake can significantly reduce the epidemiological risk of cancer [196]. Further, the regular intake of green tea has also been reported to decrease the incidences of other types of cancer, including cervical cancer [197].

#### 3.1.7. Pancreatic cancer.

Limited studies have suggested a link between green tea and pancreatic cancer. The hospital-based case-control analysis found no pancreatic cancer risk associated with the consumption of green tea in Japan [198]. A systematic study comprising of 100,000 Japanese adults up to 11 years and 233 incidences of cancer, found no association between green tea intake and pancreatic cancer risk [199]. Nonetheless, a higher percentage of mortality from pancreatic cancer was found in another retrospective study in Japan spanning up to 13 years with 292 incidences of pancreatic cancer (patients consuming <1 cup/day of green tea) [200]. The epidemiological data available so far, are insufficient to conclude that green tea or black tea can protect against pancreatic cancer.

### 3.2. Antioxidative role of tea polyphenols.

The antioxidant tea polyphenols and flavonoids were thought to be closely linked to their anti-carcinogenic activity. Reactive oxygen species (ROS), including superoxide and hydroxyl radicals, play key roles in carcinogenesis by mutagenizing DNA, altering gene expression, and affecting cell growth and distinction. Reports indicate that the green tea preparations inhibited the development of NNK-induced 12-o-tetradecanoylphorbol-1, 3-acetate-induced hydrogen peroxide in mouse epidermis, and NNK-induced 8-hydroxydeoxyguanosine in the mouse lung. In another study, tea preparations were shown to inhibit decarboxylase, protein kinase C, lipoxygenase, and cyclo-oxygenase as well. The polyphenolic fractions present in tea and green tea were reported to inhibit the activation of carcinogens and growth-related signal transduction pathways, as demonstrated through *in vitro* and few *in vivo* studies [201,202]. Another study revealed the activities of glutathione peroxidase, catalase, glutathione S-transferase, NADPH-quinone oxidoreductase, uridine diphosphate-glucuronosyltransferase, and methoxyresorufin Odealkylase were increased in animals having oral tea intake. Tea preparation was reported to inhibit nitrosation *in vitro* studies as well as in humans [203], which could be a vital factor in combating other types of cancer, such as gastric cancer as well.

### 3.3. Coffee polyphenols.

Coffee polyphenols viz. Caffeic and chlorogenic acids were tested *in vitro* for their modulatory effects in two human breast cancer cell lines in order to check their effects on methylation of synthetic DNA substrates and the methylation status of the RAR $\beta$  promoter region [204]. DNA methylation was found to be inhibited by these coffee polyphenols in a concentration-dependent manner catalyzed by DNMT1, primarily by a non-competitive mechanism. Such polyphenolic compounds partly inhibit the methylation of RAR $\beta$  promoter region in MCF-7 and MAD-MB-231 human breast cancer cells. Caffeic acid phenethyl ester (CAPE), a catechol destroys different cancer cell types but is harmless to normal cells. Numerous studies have shown that CAPE's inhibitory effects occur both *in vitro* and *in vivo* in many cancer models such as colon cancer [205], lung cancer [206], melanoma [207], glioma [208], pancreatic cancer [209], gastric cancer [210], cholangiocarcinoma [211], and hepatocellular carcinoma [212].

### 3.4. Sulforaphane.

Broccoli is a good source of this phytochemical, which is having a dietary anti-carcinogenic activity, including enhanced xenobiotic metabolism, cell cycle arrest, and apoptosis. Sulforaphane was also reported to control DNMT1 in colon cancer cells [213].

### 3.5. Isothiocyanates.

Isothiocyanates are also the dietary phytochemicals found in a wide variety of cruciferous vegetables having anti-cancer activity. Treatment with phenethylisothiocyanate, a gluconasturtiin metabolite derived from watercress, has been shown to lead to demethylation and GSTP1 re-expression [214], while treatment with various isothiocyanates has been shown to prevent oesophageal tumorigenesis [215].

### 3.6. Curcumin.

Curcumin is a polyphenolic compound with a variety of pharmacological effects, including antioxidant, anti-inflammatory, anti-proliferative, and anti-angiogenic activity. Curcumin was used in traditional remedies and Asian cooking for decades, giving the food the perfect yellow hue. It is well-established now that curcumin exhibits inhibitory effects on cyclo-oxygenases 1, 2 (COX-1, COX-2), lipoxygenase (LOX), TNF- $\alpha$ , inducible nitric oxide synthase (iNOS) and NF- $\kappa$ B [216], suggestive of its potent anti-inflammatory role. Curcumin has also been shown to inhibit cancer growth, having a combination of anti-oxidant, anti-proliferative, pro-apoptotic, and anti-angiogenic properties through the regulation of several pathway genes and molecules. Curcumin, however, displays limited bioavailability due to its poor absorption and rapid metabolism [217]. In order to improve the bioavailability and absorption, liposomal curcumin, curcumin nanoparticles, and other structural analogs of curcumin were synthesized and investigated to establish the absorption and anti-cancer activity of curcumin [218].

### 3.7. Rosmarinic acid.

Many Lamiaceae herbs commonly use it as culinary herbs. Oregano, basil, thyme, and peppermint contain a natural carboxylic acid antioxidant. Rosmarinic acid demonstrated a significant inhibitory effect on DNMT1 activity in MCF7 breast cancer cells in nuclear extracts. However, hypermethylated genes cannot be demethylated using this compound, such as RASSF1A, GSTP1, and HIN-1 [219].

### 3.8. Resveratrol.

It is a phytoalexin produced by many plants but can also be chemically synthesized due to its excellent medicinal properties, i.e., potential anti-cancer, anti-inflammatory, blood-sugar-lowering, and other beneficial effects. Resveratrol is a poor DNMT activity inhibitor in MCF-7 cell nuclear extracts as rosmarinic acid was unable to reverse methylation of multi-tumor suppressor genes [219]. Resveratrol increased the activity of adenosine analogs in MCF-7 cells to inhibit methylation and increase in RAR $\beta$ 2 expression [220].

## 4. Terpenoids

Terpenoids are used in fragrance, flavor, pharmaceutical, and chemical industries and are the largest class of natural products with 25,000 chemical structures [221]. Terpenoids comprise of various subclasses based on their chemical properties, including monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, and tetraterpenoids. Naturally, derived terpenoids have anti-cancer activities and used as a major bioactive component in conventional Chinese medicine, and the therapeutic efficacy of such compounds has been confirmed by centuries of clinical use.

### 4.1. Monoterpenoids.

#### 4.1.1. Limonene.

It can be extracted mainly from essential citrus fruit oils and plant organisms. It is used as cleaning agents and fragrance additives in industries. Limonene occurs in two active forms,

L-limonene and D-limonene, which are mirror images of each other. D-limonene is mainly used in cancer research as it contains various citrus oils (e.g., lemon, peach, mandarin, lime, grapefruit). Moreover, it is known to prevent liver cancer by increasing liver enzyme levels that can detoxify carcinogens [222].

The therapeutic effects of D-limonene have been well documented for the last two decades. It was previously shown to significantly inhibit a variety of malignancies, including pancreatic, stomach, colon, skin, and liver cancer. D-limonene was reported to prevent tumor growth and metastasis in an orthotopic mouse model for human gastric cancer, probably through its anti-angiogenic, pro-apoptotic, and antioxidant activities. The combination of D-limonene and cytotoxic agents such as fluorouracil (5-FU) and docetaxel, seemed more successful than any single treatment against cancer [223]. D-limonene has been shown to inhibit 3-hydroxy-3-methylglutanyl coenzyme A (HMGCo-A) reductase [224], which inhibits the isoprenylation of small G-proteins such as p21 [225]. This influence is thought to contribute to the effectiveness of D-limonene in chemoprevention and cancer care. However, this hypothesis does not seem relevant to all types of cancers [226]. Other apoptotic studies stated that D-limonene up-regulates Bax protein expression, cytochrome c release from mitochondria, and caspase-3 and 9 cleavages. Such evidence indicates that mitochondrial mortality is mainly linked with D-limonene-induced apoptosis [227].

#### 4.1.2. Cantharidin.

One of the few non-plant-derived terpenoids that have been reported as an anti-cancer agent [228]. This is a natural defensive toxin produced by as many as 1,500 species of blister beetle with perhaps the best-known example being the Spanish fly, *Cantharis vesicatoria* [229]. This bears intrinsic similarities with extremely toxic synthetic herbicides such as endothelial, endothelial anhydride, and endothelial thioanhydride. Indeed, all these herbicides are considered respiratory carcinogens, and thus a structural similarity exists that involves cantharidin's carcinogenic action. Anti-cancer cantharidine properties have been associated with strong *in vitro* anti-cancer activity against a wide variety of cancer cells, including leukemia, colorectal carcinoma, hepatoma, bladder carcinoma, and breast cancer [230]. Despite its well-known anti-cancer properties, cantharidine's therapeutic use is limited due to its serious side effects and extreme toxicity. The chemical modifications of cantharidin have been recommended for therapeutic use in order to produce analogs with similar anti-cancer properties while having a less detrimental effect on non-cancer or normal cells. Serine/threonine-protein phosphatase 1 (PP1) and 2A (PP2A) have been the best-known cantharidin targets so far. Potent and selective inhibitors of these two phosphatases have long been recognized, which play an important role in cell cycle regulation, apoptosis, and cell-lipids determination. Cantharidin has been reported to inhibit the function of PP1 and PP2A distilled catalytic subunits at submicromolar levels [231].

#### 4.2. Sesquiterpenoids.

##### 4.2.1. Artemisinin and its derivatives.

This is an active terpenoid derived from Chinese herb *Artemisia annua* L., commonly used in East Asia and Africa for malaria treatment. This drug, along with its variants (artesunate, artemether, and arteether), has been seen to have higher intrinsic antimalarial activity and have substituted quinine in many nations as a therapy for falciparum malaria,



typically paired with other antimalarial medicines. Moreover, Artemisinin and its derivatives (ARTs) were used to regulate schistosomiasis, immunosuppression, and cancer treatment, as well [232,233]. Chemically, artemisinin is a trioxane lactone sesquiterpene forming a peroxide bridge for its function. The anti-cancer properties of Dihydroartemisinin (DHA) and artesunate have also been documented previously. ARTs are known to prevent the spread of cancer in a variety of malignancies, including leukemia, breast cancer, cervical cancer, prostate cancer, colon cancer, hepatoma, gastric, melanoma, and lung cancer [234,235]. These appear to bypass multidrug-resistant (MDR) cancer cells displaying significant anti-cancer potential [236,237]. Many xenograft animal models have demonstrated the anti-cancer potential of ART's *in vivo* as well [238]. ARTs have been successfully used in carboplatin or gemcitabine-sensitized combinatorial chemotherapy in xenograft tumor models [239,240]. In another study, deferoxaminemesilate powder, which is an iron chelator, was shown to retain DHA-induced apoptosis or proliferative inhibition [241]. Tumor suppressor p16 and the antioxidant protein catalase were found to make ART cells immune, while the oncoprotein c-MYC was reported to sensitize ART cells [33]. Nonetheless, the evidence clearly supports the anticancer properties exhibited by ARTs. ARTs mediate G1 cell cycle inhibition by affecting cyclin D, cyclin E, CDK2, CDK4, p21, p27, NF-kB, etc. [242,243] and by stimulating p38 MAPK enhancing Fas expression and caspase stimulation [244]. ARTs also regulate urokinase plasminogen activator (u-PA), MMP2, MMP7, and MMP9, avb3 integrins, and vascular endothelial growth factor (VEGF), thus inhibiting angiogenesis, metastasis, and invasion [245].

#### 4.3. Diterpenoids.

##### 4.3.1. Tanshinone IIA.

These are key diterpenoid agents commonly used in cardiovascular disease control [246]. *Salvia miltiorrhiza* Bunge derived diterpenoid analog, tanshinone IIA is the most common and well studied for its *in vitro* and *in vivo* anti-cancer activities as seen in most human carcinomas including leukemia, breast cancer, colon cancer, and hepatocellular carcinoma [247]. Tanshinone also demonstrated synergistic effects when paired with other anti-cancer medicines, including doxorubicin and cisplatin [248]. Tanshinone IIA is a minor DNA groove binder that damages the DNA structure and effectively prevents RNAPII attachment to DNA and initiates RNAPII phosphorylation. Such a process is the molecular basis of tanshinone IIA's anti-cancer property. Tanshinone IIA also induces differentiation of several types of cancer cells [249,250] and prevents cancer cell invasion and metastasis by reducing levels of u-PA, MMP2, MMP9 and NF-kB and increasing concentrations of TIMP1 and TIMP2 metalloproteinase inhibitors [251].

##### 4.3.2. Triptolide.

*Tripterygium wilfordii* Hook F. derived ripoxidetriptolide or 'thunder god vine' was explored for analyzing its potential as an anti-cancer drug. This medicinal plant's derivatives have been used in traditional Chinese medicine for a wide range of diseases, from asthma to inflammatory disorders. Besides its well-known immune-suppressive and anti-inflammatory functions, triptolide also has significant anti-proliferative effects [252]. *In vivo* anti-cancer efficacy of triptolide has been verified in several pre-clinical trials in xenograft animal models. Triptolide and its derivatives were also used in clinical cancer therapy trials. Evidence suggests that triptolide has a major effect on cancer cell transcriptional machinery, which may be

partially responsible for anticancer activities of triptolide. This influences a variety of factors in transcription, including NF- $\kappa$ B, p53, NF-AT and HSF-1 [253,254]. More recent research by Wang *et al.* [255] found that by inducing proteasome-dependent degradation of the largest RNA polymerase II (*Rpb1*) subunit in cancer cells, triptolide inhibits global gene transcription. Despite all these advances, the exact triptolide targets in cancer cells remain elusive.

Different attempts have been made to classify the molecular targets of triptolide that have contributed to the discovery of a variety of possible molecular targets, including polycystin-2 calcium channel [256] comprising of a 90-kDa nuclear protein [257] and a newly identified human XPB, a TFIIH transcription factor subunit [258]. Triptolide's covalent binding to XPB and the consequent inhibition of ATPase activity of XPB is evident in triptolide's known cellular and physiological behaviors. Furthermore, triptolide has been shown to cause DNA damage in cancer cells, possibly due to faulty excision nucleotide repair because of XPB inhibition.

#### 4.3.3. Andrographolide.

Andrographolide is the primary bioactive ingredient of *Andrographis paniculata*, a common Chinese plant used in many Asian countries to treat colds, cough, laryngitis, and diarrhea. Bioactive *Andrographis paniculata* molecules, including andrographolide, displayed varying degrees of anti-inflammatory and anti-cancer efficacies both *in vitro* and *in vivo* models [259,260]. Andrographolide was reported to have beneficial effects on diabetes as it can minimize blood glucose levels by increasing glucose usage [261]. To date, NF- $\kappa$ B transmission blockage has been suggested to counteract many of andrographolide's beneficial effects. NF- $\kappa$ B inhibitory activity is partly due to its covalent regulation of reduced cysteine in the p50 oligonucleotide-binding pocket, the NF- $\kappa$ B transcription factor [262]. Cytokine, chemokine, adhesion molecules, nitric oxide, and lipid mediators have been shown to decrease andrographolide levels by inhibiting the NF- $\kappa$ B signaling pathway [259]. NF- $\kappa$ B inhibition induces attenuated neointimal hyperplasia in arterial restenosis by controlling NF- $\kappa$ B targets gene expressions, such as E-selectin and vascular adhesion molecule-1 [249]. Andrographolide also exhibits protective effects on beta cells through its NF- $\kappa$ B inhibitory and antioxidant activity. Andrographolide was also found to decrease p65 phosphorylation in Ser536 and I $\kappa$ B $\alpha$  in Ser32/36, resulting in inhibition of aberrant NF- $\kappa$ B activation, attenuation of neoplastic cell proliferation, and promotion of human-lung squamous cell carcinoma apoptosis, with concomitant reduction of NF- $\kappa$ B targeting *in vitro* [263]. In addition to interference in NF- $\kappa$ B signaling, andrographolide therapy was also found to affect a wide variety of signaling pathways and factors, including JAK-STAT and PI3 K inhibition, suppression of HSP90, cyclins and cyclin-dependent kinases, metalloproteinases, growth factors, and activation of tumor suppressor proteins p53 and p21.

#### 4.3.4. Oridonin.

Oridonin is a biologically active ingredient isolated from *Rabdosiarubescens*, a Chinese herb for mouth and throat washing. Recently, many solid tumors, including hepatic cancer, skin carcinoma, osteoma, and colorectal cancer, have beneficial effects on oridonin. Oridonin prevents T-cell leukemia in adolescents, acute lymphoblastic leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, and multiple myeloma cells [264]. Anti-cancer activity *in vivo* was shown in a colorectal colostomy model [265]. Inhibiting binding NF- $\kappa$ B DNA

activity, apoptosis is considered primarily responsible for oridonin-mediated cancer cell death associated with blocking of NF- $\kappa$ B signaling pathway [264]. More experiments in a colorectal tumor model showed that after oridonin therapy, the levels of the activator protein-1 (AP-1) decreases, followed by NF- $\kappa$ B and p38 down-regulation. These results indicate that AP-1 downregulation is the initial response to oridonin therapy. NF- $\kappa$ B expression and mitogenic protein kinase pathways impede tumor development [265]. These effects also lead to oridonin-induced cancer cell apoptosis [266]. Studies have shown that, besides apoptosis, oridonin-treated cancer cells also undergo autophagy. However, the associations of these events with oridonin therapy are still unclear. Autophagy inhibition was shown to reduce oridonin-induced apoptosis in p53-dependent human sarcoma cells HT1080, suggesting a combination of oridonin-induced apoptosis and autophagy to mediate cell death [267]. Nonetheless, 3-MA autophagy or siRNA inhibition against LC3 and beclin 1 in murine fibrosarcoma L929 cells facilitated oridonin-induced apoptosis [268], consistent with another finding that autophagy increases p38 MAPK-NF- $\kappa$ B signaling cell survival and prevents ROS-mediated oridonin-induced apoptosis [269]. A more recent study showed that N-acetylcysteine, a ROS scavenger, significantly decreases apoptosis and autophagia in human cervical carcinoma cells [270]. The reasons for these variations remain uncertain and may be due to cancer cell existence or heterogeneity differences.

#### 4.4. Triterpenoids.

##### 4.4.1. Celastrol.

The bioactive terpenoid from *Tripterygium wilfordii* Hook, also known as tripterine. Has been known to possess a variety of biological activities viz. anti-oxidant, anti-cancer, and anti-inflammatory [271]. Celastrol is the one that has attracted much interest, particularly against inflammation. Estostrol has been used in animal models of collagen-induced arthritis, Alzheimer's disease, asthma, and lupus [272]. Several studies have successfully shown the celastrol inhibition of the synthesis and secretion of pro-inflammatory cytokines and adhesion molecules [273]. Celastrol also decreases inflammation and oxidative stress in vascular smooth muscle cells that are caused by hypertension. Heme oxygenase-1 has increasingly been recognized as a crucial factor for mediating estostrol's anti-inflammatory effects [274]. Estostrol therapy may inhibit different signaling pathways and can contribute to their anti-cancer effects as well.

##### 4.4.2. Cucurbitacins.

Cucurbitacin and its derivatives form a class of cucurbitane, which are effective insect attractants that are commonly used as bait in insecticides [275]. Studies show that cucurbitacins have important human pharmacological activities, including anti-cancer, anti-inflammatory, and hepatoprotective effects [248]. Accumulated studies have shown that most cucurbitacins prevent the spread of multiple tumor cells at nanomolar levels *in vitro*. Cucurbitacins cause cell cycle arrest, mainly G2/M [248] and S phase arrest [276]. Additionally, some studies show that cucurbitacins induce differentiation in multiple tumor cell lines [277]. More recent research indicated that cucurbitacin B causes autophagy but has been viewed as a survival aid [278]. While several pieces of evidence suggested their widespread role, the effects of cucurbitacins on anti-angiogenesis were not well known. Cucurbitacins actively affect tumor cell invasion and *in vitro* migration, further inhibiting metastasis *in vivo* [279,280]. Future research must

emphasize on combining cucurbitacin therapy with another widely prescribed chemotherapeutic agent. Once paired with gemcitabine [281], cisplatin, doxorubicin, 5-fluorouracil, paclitaxel [277], and docetaxel [282] Cucurbitacins showed synergistic effects both *in vitro* and *in vivo* models. The mechanisms behind cucurbitacin's anti-tumor activity need to be further researched.

#### 4.4.3. Alisol.

Alisol derivatives are special triterpenoid-type protostane compounds isolated from *Alismaorientalis* (Sam.) Juzep rhizome, a well-known herbal medication for the treatment of hypertension, hyperlipidemia, and urological diseases in East Asia [283-285]. Such compounds have now gained growing attention because of their possible activities against cancer [286]. Alisol B induces endoplasmic reticulum stress, autophagy, and apoptosis in many cancer cell lines, with Ca<sup>2+</sup> ATPase as its key molecular target [287]. Alisol B 23-acetate mediates G2/M cell cycle arrest and induces apoptosis in cancer cells and inhibits the PI3K/Akt signaling pathway, Bax/Bcl-2 ratio up-regulation and caspase activation that contributes to its anti-cancer effects [288]. Furthermore, alisol B 23-acetate is suggested as a potential MDR-reversing agent that restores the sensitivity of MDR cells [289].

#### 4.4.4. Pachymic acid.

This is a lanostane-type triterpenoid derived from *Poria cocos* and is known to have anti-inflammatory [290] and anticancer activities [291,292]. Data on anti-cancer activities and the pachymic acid action mechanism are minimal. It shows cytotoxicity and induces apoptosis in A549, DU145, and HT29 cells (human lung cancer cells, human prostate cancer cells, colon cancer cells, respectively [291,293]. Pachymic acid treatment also activates PARP, caspases-9, and caspases-3 [294]. Inhibitory effects on both DNA topoisomerase I and II have also been seen [295]. Pachymic acid suppresses invasion of non-lethal MDA-MB-231 and MCF-7 breast carcinoma cells, associated with decreased MMP9 secretion [296]. Pachymic acid was also found to decrease PMA-caused NF-κB transcriptional activity [291,297].

#### 4.5. Tetraterpenoids.

Carotenoids are the most common tetraterpenoids, with over 600 recognized natural structural variants. They are natural fat-soluble pigments that vividly paint plants and animals [298]. Carotenoids are structurally differentiated by three aspects such as (i) either being simple unsaturated hydrocarbons with a particular lycopene structure or their corresponding oxygenated analogs, typically referred to as xanthophylls; (ii) eight isoprene units are found to be linked head-to-tail in lycopene to give it a conjugated network that is basically responsible for the chromophoric character (iii) at both the molecule terminals, lycopene cyclisation results in a bicyclic hydrocarbon commonly known as β-carotene that occurs most abundantly in higher plants [299,300]. The dietary intake of carotenoids was reported to decrease the risk of several cancers, suggesting preventive carotenoid functions in cancer. Pre-clinical research has found that carotenoid therapeutic functions such as β-carotene, α-carotene, lycopene, lutein, zeaxanthin, β-cryptoxanthin, fucoxanthin, canthaxanthin, and astaxanthin were all anti-carcinogenic [300,301].

#### 4.5.1. Lycopene.

Lycopene is an open-chain hydrocarbon containing 11 conjugated and 2 non-conjugated double bonds arranged in a linear series, primarily from tomatoes [302]. Clinical studies have examined the ability of tomato-derived carotenoid lycopene for the anti-cancer function of natural compounds extracted from the human diet [302,303]. A Phase II clinical trial investigated the effectiveness of lycopene alone or with soy isoflavones on serum prostate-specific antigen (PSA) levels in men with prostate cancer. Lycopene and soy isoflavones delayed the growth of hormone-refractory and hormone-sensitive prostate cancer [304]. In addition, a small, randomized clinical trial found that lycopene supplementation can increase lycopene levels in prostate tissue, modulate biomarkers of growth and differentiation, and decrease aggressive clinical parameters of clinically located prostate cancer [304]. ROS scavenging has shown that lycopene exhibits antioxidant effects, which helps lycopene to prevent lipid peroxidation and DNA damage. At the same time, lycopene induces enzymes from the cellular antioxidant protection systems by activating the transcription mechanism for the anti-oxidant response factor [305]. The molecular mechanism which accounts for lycopene's anti-cancer activity remains unclear despite the increasingly accumulating data. Recent work using proteomic analysis found that lycopene modulates the expression of a wide variety of proteins, including proteins from the cell cycle and heat shock proteins [306]. This strategy can represent a powerful approach for gaining mechanistic insights into lycopene's mode of action.

## 5. Conclusions

Natural dietary phytochemicals were commonly used in *in-vitro*, *in-vivo*, and preclinical cancer research, which has shown varying efficacy in the trials. However, a wide range of mechanistic experiments has shown significant chemopreventive effects of phytochemicals. Cancer chemoprevention has remained an appealing approach as far as the treatment with natural phytochemicals is concerned. More attempts are urgently needed in order to better understand their potencies, pharmacokinetic effectiveness, pharmacodynamic responses, metabolism, toxicity, drug-drug interactions, polymorphism, and formulations. Natural dietary phytochemicals remained a promising, active area of potential research. Nevertheless, more research is required in this field to determine the most suitable targets for these phytochemicals to carry out tailor-made clinical studies that produce reliable results. Therefore, using phytochemical supplements in focus groups and patients is a very effective tool for cancer prevention and care. Bioavailability of polyphenols in the human intestine is the main concern mainly influenced by their degree of polymerization. The growth, bioavailability and biological activity of phenolic metabolites depend primarily on gut microbiota, particularly after ingestion of high-molecular-weight polyphenols in food. While extensive research has been conducted on the broad range of health-promoting properties of dietary polyphenols, their impact on intestinal ecology control and the two-way relationship "polyphenols ↔ microbiota" is still poorly understood. Some studies have documented the impact of dietary polyphenols on human gut microbiota, mostly focusing on single polyphenol molecules and selected populations of bacteria. Further research is required in this field, focusing on reciprocal interactions between gut microbiota and polyphenols with mechanisms of action and the effects of these interactions on human health.

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## Conflicts of Interest

The authors declare no conflict of interest.

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