

# Beetroot as a Potential Functional Food for Cancer Chemoprevention, a Narrative Review

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Patients with cancer are prone to several debilitating side effects including fatigue, insomnia, depression and cognitive disturbances. Beetroot (*Beta vulgaris* L.) as a health promoting functional food may be potentially beneficial in cancer. As a source of polyphenols, flavonoids, dietary nitrates and other useful nutrients, beetroot supplementation may provide a holistic means to prevent cancer and manage undesired effects associated with chemotherapy. The main aim of this narrative review is to discuss beetroot's nutrient composition, current studies on its potential utility in chemoprevention and cancer-related fatigue or treatment-related side effects such as cardiotoxicity. This review aims to provide the current status of knowledge and to identify the related research gaps in this area. The flavonoids and polyphenolic components present in abundance in beetroot support its significant antioxidant and anti-inflammatory capacities. Most in vitro and in vivo studies have shown promising results; however, the molecular mechanisms underlying chemopreventive and chemoprotective effects of beetroot have not been completely elucidated. Although recent clinical trials have shown that beetroot supplementation improves human performance, translational studies on beetroot and its functional benefits in managing fatigue or other symptoms in patients with cancer are still lacking.

**Key Words** Beetroot, Betacyanin, Betaxanthin, Betanin, Cancer

## INTRODUCTION

Patients with cancer are prone to several debilitating effects due to chemotherapy or the disease itself. The behavioural disturbances experienced by patients with cancer include fatigue, insomnia, depression, and cognitive disturbances. These symptoms are very common and may persist for months or years even after completion of treatment and may affect patient's quality of life. Functional foods have long been linked to improve human performance and health, and hence are considered beneficial as part of the cancer patients' diet.

Beetroot (*Beta vulgaris* L.) is one of high-nutrient vegetables used for salads and juices, and a valuable source of natural pigments. It belongs to the botanical order *Amaranthaceae-Chenopodiaceae*, which is cultivated commercially. Beetroot, also known as table or garden beet, is usually grown for its roots. It has a characteristic earthy mushy aroma and flavour, mainly due to the presence of geosmin, a volatile bicyclic alcoholic compound [1]. Beetroot is known for its antioxidant activities and widely used as a remedy for a variety

of ailments including cardiovascular-related conditions, anaemia, sexual weakness and bladder stones [2]. Some recent clinical studies have also indicated the usefulness of beetroot in managing blood pressure and cardiovascular health [3-6]. Beetroot has also gained popularity as a supplement to boost energy and improve performance in athletes [7-10].

Interestingly, in the Traditional Persian Medicine practices, beetroot is one of the foods used in the prevention and managing of metastatic progression of cancer [11]. It is also widely used in other medicinal systems including the Arab, traditional Chinese and Ayurvedic medicine. Beetroot, juiced or blended, is a popular functional food among breast, prostate and colorectal cancer patients as reported in Trinidad. A study at two clinical sites on the island revealed that beetroot is being consumed by patients for the purpose of treatment, health improvement and amelioration of side effects associated with chemotherapy treatment [12]. Similarly, beetroot is also the most frequently used alternative dietetic measure among patients with cancer in Germany [13] and among a majority of gastrointestinal cancer patients in Serbia [14].

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Red beetroot is highly popular and widely used for cancer patients in some parts of the world. Although there is paucity of data indicating its direct role in cancer treatment and chemoprevention its antioxidant, anti-inflammatory and other supplementary effects are potentially beneficial for patients with cancer at certain stages of disease including during chemotherapy and post-chemotherapy. This narrative review aims highlight to provide the valuable phytochemical components present in red beetroot, the current knowledge on its health benefits as a possible chemopreventive functional food and to identify related research gaps in this area of research.

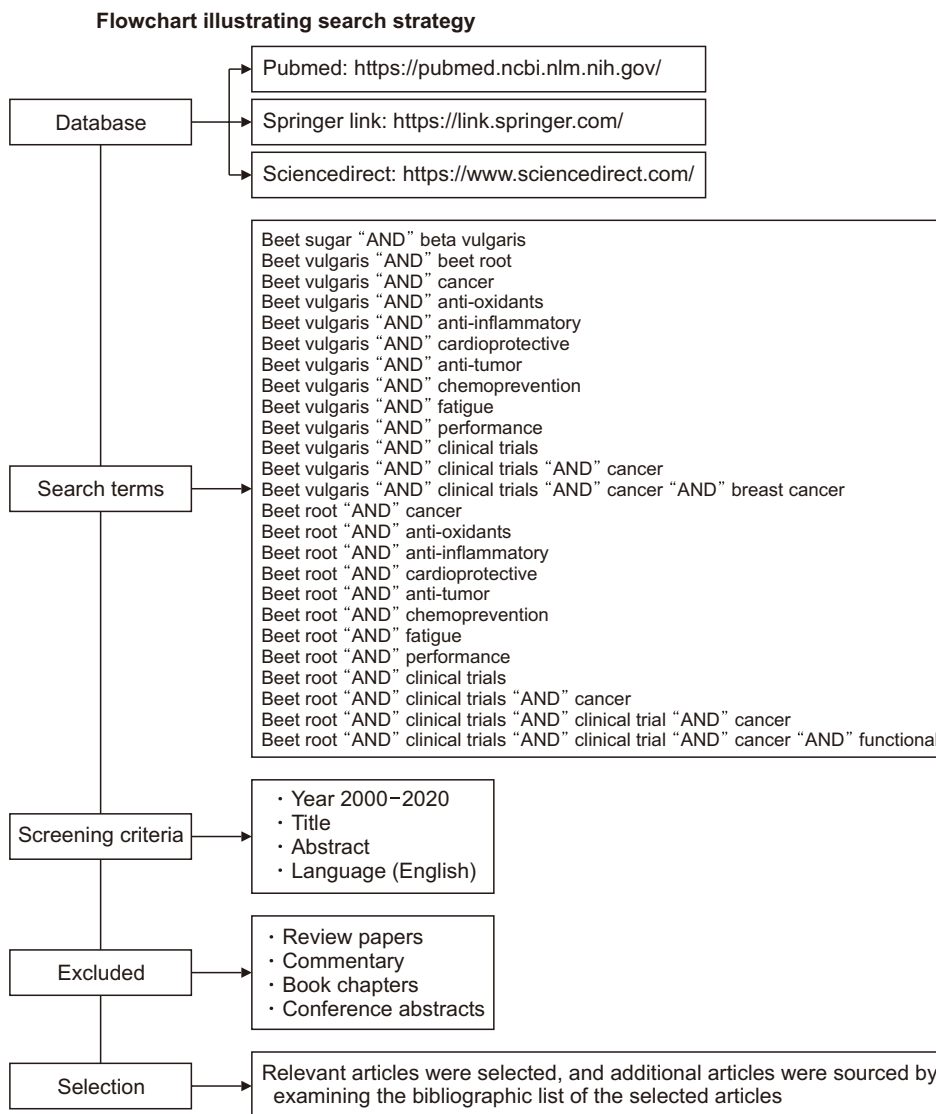
### DATA ANALYSIS

To summarize the current literature on beetroot and cancer, three databases such as Pubmed, Sciencedirect and Springerlink were screened. The search terms used included

beet, beetroot, sugar beet, beta vulgaris, cancer, antioxidant, anti-inflammatory, cardioprotective, anti-tumor, chemoprevention, fatigue, performance and clinical trials using Boolean operator "AND" in various combinations. Articles were first screened by year (2000 to 2021), followed by title, language and abstract. Only relevant articles were selected, and additional articles were sourced by examining the bibliographic list. Flowchart illustrating the brief search strategy is shown in Figure 1.

### Phytochemical and nutritional composition of beetroot

Phytochemicals present in beetroot are found to be beneficial for the human health. Betalains, pigments derived from betalamic acid, are an important group of bioactive phytochemicals in beetroot. Structurally, betalains are compounds with

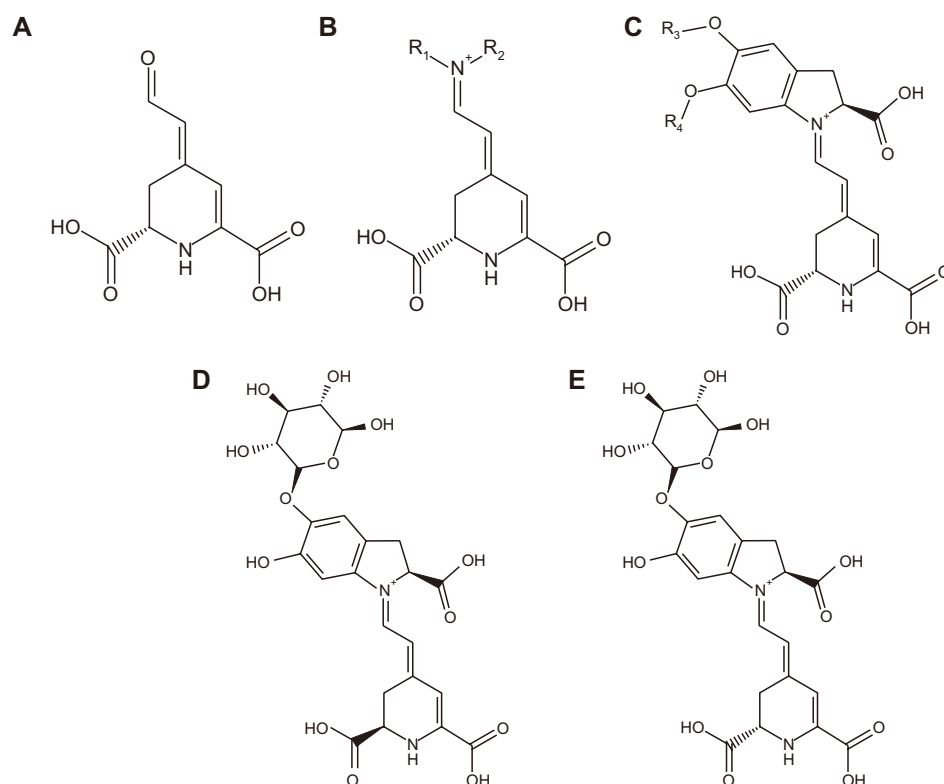


**Figure 1. Flowchart illustrating the search strategy for studies related to beetroot and cancer.**

positive nitrogen in a polyene system and this cyclic amine reactive group has been considered an important contributor to their reducing properties [15]. According to a recent study, red beetroot has the richest source of betalains among all tested plants such as prickly pear (*Opuntia ficus-indica*) and white beetroot varieties [16]. Betalains are synthesised from tyrosine into the yellow-orange betaxanthins and red-violet betacyanins [17]. Betalamic acid (Fig. 2A) is the common chromophore for all betalain compounds. The pigment classification as either betaxanthin (Fig. 2B) or betacyanin is dependent on the way in which betalamic acid is added as a residue (Fig. 2C). Betaxanthins (Fig. 2B), are betalamic acid conjugated with an amine or amino acid. Meanwhile, the betacyanins (Fig. 2C) are the end products of spontaneous Schiff base condensation between the conjugated betalamic acid moiety and the closed structure of cyclo-DOPA (cyclo-3,4-dihydroxy-phenylalanine) [17]. This reaction changes the absorption from 480 nm (betaxanthins, yellow) to 540 nm (betacyanins, violet). The colour is due to the presence of double bonds resonating in the structures. Red beetroot contains a large amount of betacyanins but lower levels of betanidin and betaxanthins [18]. More than 80% of total red beetroot pigments are made of betacyanins, mainly betanin (betanidin 5-O- $\beta$ -glucoside) (Fig. 2D) and its isomer, isobetanin (Fig. 2E). The concentration of betanin in red beet was reported to be 300 to 600 mg/kg [19]. Other betacyanins reported include prebetanin, neobetanin, amaranthin, lampranthin I and lampranthin II [20-23].

Other classes of phytochemicals found in beetroot include phenolics and flavonoids. Some betalains are also phenolic compounds, namely, isobetanin, prebetanin and neobetanin, vulgaxanthin I, vulgaxanthin II and indicaxanthin [24]. Other phenolic compounds isolated from beetroot include 5,5,6,6-tetrahydroxy-3,3-biindolyl, N-trans-feruloyltyramine, N-trans-feruloylhomovanillylamine, and phenolic acids such as 4-hydroxybenzoic acid, chlorogenic acid, caffeic acid, catechin hydrate and epicatechin [25-27]. On the other hand, flavonoids are, in general, secondary metabolites with a polyphenolic structure. They are typical biologically active compounds with health-promoting properties and are important components used for various applications. The flavonoids present in beetroot include betagarin, betavulgarin, cochliophilin A and dihydroisorhamnetin [28]. Other flavonoid compounds isolated are 3,5-dihydroxy-6,7-methylenedioxyflavone, 2,5-dihydroxy-6,7-methylenedioxyisoflavone, quercetin, rutin and kaempferol [20,24,28-31]. The major contributor to the earthy flavor in red beet is geosmin (*trans*-1,10-dimethyl-*trans*-9-decanol) [32,33]. Another unique feature of beetroot is its high concentration of volatile compounds such as pyridine and 4-methylpyridine. Additional components present include furfural, isopentanol, ethanol, dimethyl sulfide and isovaleraldehyde [32]. A summary of the phytochemical and nutritional components is shown in Table 1.

The basic nutritional composition of beetroot includes sugars, dietary fibre, fatty acids, minerals and vitamins (Table 1) [27,34]. Among sugars present, sucrose is the main com-



**Figure 2. Chemical structures of: (A) Betalamic acid; (B) Betaxanthin, where R1 is an amine or amino acid and R2 is normally hydrogen; (C) Betacyanins (when R3 and R4 are hydrogen, the structure corresponds to betanidin); (D) Betanin; (E) Isobetanin.**

**Table 1.** Phytochemical and nutritional composition of beetroot

No	Class		Compound (synonym)	References				
1	Betalains	Betaxanthin	Betanin (betanidin 5-O-beta-glucoside)	[15,16]				
			Betacyanin	Isobetanin (isobetanidin 5-O-beta-glucoside)	[17,27]			
		Betaxanthin	Prebetanin (betanidin 5-O-(6'-sulfate)-beta-glucoside)	[20-23]				
			Neobetananin (neobetananidin 5-O-beta-glucoside)					
			Amaranthin (betanidin 5-O-sophorobiuronic acid)					
			Lampranthin I					
			Lampranthin II					
2	Phenolics	Betalains	Vulgaxanthin I	[20,67]				
			Vulgaxanthin II					
			Indicaxanthin					
			Betanin (betanidin 5-O-beta-glucoside)					
			Isobetanin (isobetanidin 5-O-beta-glucoside)					
			Prebetanin (betanidin 5-O-(6'-sulfate)-beta-glucoside)					
			Neobetananin (neobetananidin 5-O-beta-glucoside)					
			Non-betalains		5,5,6,6-tetrahydroxy-3,3-biindolyl	[25-27,34]		
					5,6-dihydroxyindolecarboxylic acid			
					N-trans-feruloyltyramine			
		N-trans-feruloylhomovanillylamine						
		4-hydroxybenzoic acid						
		Chlorogenic acid						
		Caffeic acid						
		3	Flavonoids		Catechin hydrate	[20,24,26,28-31,34]		
					Epicatechin			
					Betagarin (5,2-dimethoxy-6,7-methylenedioxyflavanone)			
Betavulgarin (2'-hydroxy-5-methoxy-6,7-methylenedioxyisoflavone)								
Cochliophilin A (5-hydroxy-6,7-methylenedioxyflavanone)								
Dihydroisorhamnetin (3,4',5,7-tetrahydroxy-3'-methoxyflavanone)								
3,5-dihydroxy-6,7-methylenedioxyisoflavone								
2,5-dihydroxy-6,7-methylenedioxyisoflavone								
Quercetin (3,5,7,3',4'-pentahydroxyflavone)								
Rutin (3,3',4',5,7-pentahydroxyflavone-3-rutinoside)								
Kaempferol (3,4',5,7-tetrahydroxyflavone)								
4	Volatiles						4-methylpyridine	[32,33]
							Pyridine	
		Dimethylsulfide						
		Isovaleraldehyde						
		Ethanol						
		Isopentanol						
		Furfural (2-Furaldehyde)						
		Geosmin (trans 1, 10-dimethyl-trans-9-decalol)						
		5	Nutritional	Mineral		Calcium	[34,35,39,42]	
						Magnesium		
Potassium								
Sodium								
Vitamin								
Vitamin	Vitamin A							
	Vitamin C							
Carbohydrate	Sucrose							
Fat	Fatty acids							
Amino acid	Essential amino acids (EAA)							
	Non-essential amino acids (NEAA) – Glutamic acid							
	Gamma-aminobutyric acid (GABA)							
Others	Dietary nitrate (NO <sub>3</sub> <sup>-</sup> )							
	Dietary fiber							

ponent. Fatty acids are present in combination of saturated, monounsaturated and polyunsaturated acids which occur in minimal amounts. Minerals such as sodium, potassium, calcium and magnesium are present in relatively high concentrations while aluminium, barium, boron, copper, iron, manganese and zinc are found at lower levels. Beetroot are also rich in both vitamins A and C [27]. Moreover, beetroot contains a substantial amount of both non-essential and essential amino acids. Examples are methionine, threonine, lysine, leucine, isoleucine, tryptophan, phenylalanine, valine, tyrosine, cysteine, alanine, histidine, arginine, serine, proline, glycine and aspartic acid [27]. Interestingly, a large amount of glutamine is also present in beets [35]. Glutamine is a non-essential amino acid and is a precursor in nucleotide, glucose and protein synthesis [36]. Its metabolism produces large quantities of glutamate, a component required for glutathione synthesis. Glutathione is important for the maintenance of the cellular redox state [37,38]. In addition,  $\gamma$ -aminobutyric acid (GABA) and  $\beta$ -alanine were also isolated from the red beetroot [35,39]. Interestingly, GABA is known to be potentially useful as a component of functional food. As an important inhibitory neurotransmitter in the nervous systems, GABA has antioxidant, anti-anxiety, anti-hypertensive properties [40,41].

Dietary nitrate found in green leafy and root vegetables such as beetroot is an important source of nitric oxide (NO) formed via the nitrate-nitrite-NO pathway [42]. Ingested inorganic  $\text{NO}_3^-$  is metabolized in vivo to bioactive nitrite ( $\text{NO}_2^-$ ) and  $\text{NO}_2^-$  exerts its effects by conversion to functional nitrogen oxides, including NO [43]. NO is an important biologically active and signalling molecule involved in a multiple physiologic process, especially regulation of blood pressure and blood flow. It is a potent dilator, reduces systemic blood pressure and inhibits atherogenesis by reducing inflammatory cell recruitment and platelet aggregation [44]. NO-mediated signalling is crucial for protecting the heart against cellular injury or death. It also regulates mitochondrial respiration by inhibiting cytochrome *c* oxidase [45]. Dietary nitrate is an important component of the "Dietary Approaches to Stop Hypertension (DASH)" diet to lower blood pressure and the Mediterranean diet to lower cardiovascular and cancer risk [46]. Nitrate and nitrite are known to reduce blood pressure, protect tissues against ischemic injury, reduce oxidative stress, improves mitochondrial function and enhances exercise performance.

## Properties of beetroot that are potentially chemopreventive

### Antioxidant and anti-inflammatory activities

Red beetroot has been ranked among the ten most potent antioxidant vegetables [47]. Betacyanins are known to be a class of compounds with radical scavenging and antioxidant activities [18,48]. On the other hand, betanin, consisting of a phenolic and a cyclic amine group, is shown to be a very good electron donor, acting as antioxidants [18]. Hence, its

consumption may increase the protection against free radicals. Several earlier studies have also indicated that beetroot is an essential source of natural antioxidants [25,49-53]. Apparently, the antioxidant effects of beetroot is not limited to its tubers, but also evident in its leaves [54].

The antioxidant and anti-inflammatory capacity of beetroot has been evaluated in both in vitro and in vivo experiments. Beetroot ethanol extract (lyophilized) has shown substantial antioxidant, electron-donating ability and radical scavenging activities and was found to inhibit the nitric oxide production in lipopolysaccharide-treated mouse macrophage RAW 264.7 cells [55]. Antioxidant activity, evaluated using the cell-free system and three standard spectrophotometric tests, have shown that red beetroot extracts displayed the strongest antioxidant potential as compared with other vegetable extracts [16]. However, in the same study, there were no significant cytotoxic nor any protective effects against oxidative DNA damage in HT29 (human colon adenocarcinoma) cells challenged with reactive oxygen species (ROS) when 10% (v/v) water extracts of red beetroot was tested [16]. Similarly, the water extracts were not found to induce the activity of phase II detoxification enzymes significantly. This is in contrary to earlier published studies. Esatbeyoglu and co-workers reported that betanin significantly reduced  $\text{H}_2\text{O}_2$ -induced DNA damage in HT29 cells [56]. Betanin at a low concentration (15  $\mu\text{M}$ ) functioned as a free radical scavenger and as an inducer of endogenous cellular enzymatic antioxidant defence mechanisms [56]. However, the exact amount of betanin contained in the 10% (v/v) water extract used in the earlier study was unclear and hence, difficult to compare with results of studies that used betanin alone.

In another study, the antioxidant capacity of betanin was also found to be prominent as it significantly diminished the intracellular ROS level elevated by phorbol myristate acetate (PMA) stimulation (~3 fold) and significantly enhanced caspase-3 activity in stimulated neutrophils [57]. Betanin also decreased the content of DNA in the Comet tails in the PMA-stimulated neutrophils [57]. Similar observation was found in another work using Caco-2 intestinal cells. Betanin was found to reduce DNA damage caused by  $\text{H}_2\text{O}_2$  and significantly enhanced caspase-3 activity in both neutrophils and Caco-2 cells [58]. Based on these findings, betanin is likely to be responsible for the effect of beetroot products on oxidative DNA damage and apoptosis in neutrophils. Since cytokines and other inflammatory mediators produced by the white blood cells are direct contributors to cancer initiation, promotion and metastasis, functional food which mitigates chronic inflammation is thought to be an important cancer prevention strategy.

Beetroot juice containing 79.3 mg/100 mL of betaxanthines and 159.6 mg/100 mL of betacyanins was found to be protective against N-nitrosodiethylamine (NDEA)-induced oxidative stress and liver injury in male rats. NDEA is a food-born carcinogen and is present in smoked or salted meat [59].



The metabolic activation of NDEA by the hepatic microsomal cytochrome P450 system produces ethyl diazonium ion as a reactive intermediate which elicits DNA alkylation and subsequently promotes carcinogenesis. In this study, rats treated with beetroot juice prior to NDEA administration exhibited a significant reduction of DNA damage in blood leukocytes. Beetroot juice also restored the activity of some of the antioxidant enzymes in the liver and prevented xenobiotic-induced oxidative stress [59]. In addition, beetroot juice was found to reduce the levels of liver injury biomarkers including ALT, SDH, GGT and bilirubin and reduced DNA damage triggered by NDEA treatment [60]. The protective effect of beetroot juice against oxidative damages and the metabolic alterations induced by beetroot feeding may likely safeguard against liver damage [60]. Furthermore, the ethanol extract of beetroot was found to exert similar protective effects on hepatotoxicity by altering various indicators of liver damage induced by lipopolysaccharide or alcohol in experimental rats [55].

The anti-inflammatory effects of betalains and beetroot extract appear to be mediated by interfering with the NF- $\kappa$ B signalling cascade [2]. The transcription factor NF- $\kappa$ B promotes immunity directly by activating gene targets that up-regulates the inflammatory molecules such as chemokines and cytokines that stimulate the phagocytic cells [61]. In an animal model study to investigate the protective effect of beetroot extract on gentamicin-induced nephrotoxicity, up-regulation of nuclear expression of NF- $\kappa$ B (p65), production of TNF- $\alpha$  and interleukin-16 (IL-6), myeloperoxidase activity, and the nitric oxide level were significantly down regulated upon beetroot supplementation [2]. Beetroot extract treatment also significantly reduced the expression of cleaved caspase-3 and Bax protein and up-regulated the anti-apoptotic Bcl-2 protein in the kidney cells. It ameliorated the extent of histologic renal injury and reduced inflammatory infiltration in the tubules [2].

Betalains were also reported to suppress COX-2 expression, a pro-inflammatory enzyme responsible for prostaglandin biosynthesis [62-64]. The COX-2 inhibitory effects of betanin were found to be comparable to or greater than compounds such as lycopene, chlorophyll, bixin,  $\beta$ -carotene and cyanidin-3-*O*-glucoside. Its activities were also comparable to anti-inflammatory drugs such as celecoxib and ibuprofen [64]. Betanin-rich beetroot supplements, in sufficient doses, were capable of exhibiting anti-inflammatory effects in a way similar to synthetic drugs [65]. The anti-inflammatory effects of betanin were also demonstrated in the neutrophils from patients with bowel disease neutrophils. Betanin treatment for 24 hours in neutrophils isolated from blood of patients with Crohn's disease and ulcerative colitis showed an increased DNA damage in these cells, hence demonstrating a reduced neutrophil activity in inflammatory conditions [58].

### Anti-proliferative and other chemopreventive properties

The anti-proliferative and chemopreventive activities of beet-

root were demonstrated in both in vitro as well as in vivo (animal) studies. Betanin is also a major betacyanin component isolated from *Opuntia ficus-indica*. Several in vitro studies have indicated that betanin possesses cytotoxic and growth inhibitory activities against different cancer cell lines. For example, the proliferation of human chronic myeloid leukemia cell line (K562 cells) treated with betanin was reduced in a concentration- and time dependent manner with an IC<sub>50</sub> value of 40  $\mu$ M. Betanin-treated K562 cells appeared to undergo intrinsic apoptosis mediated by the mitochondrial release of cytochrome c into the cytosol [66]. Betanin exerted its pro-apoptotic activities through activation of procaspase-3 cleavage and caspase-3 activity followed by the loss of mitochondrial transmembrane potential [58]. This indicates that betanin elicits the release of ROS and triggers apoptotic cell death, further supporting its cancer preventive activity.

In addition, both betanin and betaine extracted from beetroots have demonstrated anti-proliferative effects against hepatocellular cells [67]. On the other hand, betacyanins tested in combination with vitexin-2-*O*-xyloside, produced a synergistic effect in inhibiting the proliferation of human urinary bladder cancer cells (T24) but not on normal human skin keratocytes. When used concurrently, both compounds increased the pro-apoptotic BAX protein levels and down regulated expression of BIRC5 (survivin) and CTNNB1 ( $\beta$ -catenin) which are prosurvival components [68]. In yet another study, doxorubicin and red beetroot extract exerted synergistic cytotoxicity against human pancreatic, prostate and breast cancer cell lines [69]. Since there is similarity in the configuration and chemical structure of both betanin and doxorubicin, a possible mechanism may include DNA intercalation [69].

Furthermore, Nowacki and co-workers [70] found that betanin-enriched beetroot extract induced apoptosis in breast cancer cells. Betanin/isobetanin-enriched concentrate produced from red beetroots inhibited proliferation of cancer cells and induced their death but has limited effects towards normal cells. The concentrate appeared to inhibit aggregated cancer cell proliferation (3D cell culture) through inhibition of the cell cycle progression, by decreasing the G1 cell number, promoting the increase of S phase and down regulating cyclin A2 and cyclin B1 levels in the breast cancer cells [70]. Further, expression of FAS, TRAILR4, Bad and p53 (apoptotic-related proteins) was significantly induced and the mitochondrial membrane potential was clearly MCF-7 cells treated with betanin-enriched red beetroot. Suggesting that both intrinsic and extrinsic pathways were involved [70]. Although lysosomal vacuole formation was observed in the extract-treated MCF-7 cells, there was insufficient evidence of autophagy. In a recent study, betavulgarin, isolated from beetroot was found to suppress the growth, migration, colony formation, and mammosphere formation in breast cancer cell lines. This compound also reduced the proportion of the CD44<sup>+</sup>/CD24<sup>-</sup> subpopulation and the expression of the self-renewal-related genes such as *c-Myc*, *Nanog* and *Oct4*.

Interestingly, betavulgarin inhibited the Stat3/Sox2 signaling and induced breast cancer stem cell death [71].

Oral consumption of red beetroot food color, in the form of commercial dye E162, inhibited N-nitrosomethylbenzylamine (NMBA)-induced tumor formation in the rat esophagus. The number of NMBA-induced esophageal papillomas were significantly reduced by almost half in animals receiving the food color as compared with controls [72]. In addition, the levels of inflammation and angiogenesis in the beetroot-treated animals were also reduced with a concurrent increase in the apoptotic rate. The mechanisms of chemoprevention with red beetroot appeared to involve reduction of cell proliferation, angiogenesis, inflammation and stimulation of apoptosis. Since red beetroot color contains betanins, these effects may be mediated through inhibition of oxygen radical-induced signal transduction [72].

In another study, oral administration of betanin in Institute of Cancer Research (ICR) mice inhibited PMA-induced promotion of mouse skin tumors and glycerol-induced promotion of lung tumors as compared with control [73]. Betanin, in the form of beetroot extract, also significantly decreased tumor multiplicity and burden in two mouse lung tumor models [74]. Subsequent immunohistochemical characterization revealed that betanin reduced angiogenesis and induced apoptosis in treated mice as well as in human cancer cells in vitro [74].

Apart from fresh beetroot juice, beetroot juice fermented with *Lactobacillus paracasei* 0920 and *Lactobacillus brevis* 0944 significantly reduced the number of carcinogen-induced aberrant crypt foci in N-nitroso-N-methylurea-treated rats. Hence, supplementation of diet with lacto-fermented beetroot juice was postulated to provide protection against precancerous aberrant crypt formation [75]. In a separate animal study, beetroot minimized radiation-induced DNA damage of splenocytes. Beetroot extract given orally three times to C57BL/6 mice and, at day 10 after  $\gamma$ -ray irradiation, boosted differentiation of hematopoietic stem cells (HSCs) into burst-forming units-erythroid [76]. Furthermore, beetroot-treated mice also displayed increased levels of red blood cells, hematocrit and hemoglobin. Beetroot supplementation stimulated differentiation of HSCs and preserved integrity of bone marrow [76].

Clinical experiences on beetroot extracts or juice in cancer are currently lacking to support the findings of both in vitro and animal studies. Only an isolated case report on an elderly patient diagnosed with chronic lymphocytic leukemia and her clinical experiences with beetroot juice was published. The patient who refused chlorambucil after a recurrence of disease, was started with beetroot-carrot juice [77]. In the clinical follow-up duration, administration of beetroot-carrot juice alone induced a reduction in lymphocyte and peripheral blood leukocytes count by 14.7% and 43.13%, respectively with a concurrent decrease in the uric acid level. Administration of beetroot-carrot juice for 15 days resulted in an improved appetite, a sense of general well-being and increased vigor. However, upon discontinuation of the beetroot-carrot

juice for 1 month, the patient experienced an increase in cell counts and up-regulation of the uric acid level. Interestingly, her condition was reversed when beetroot-carrot juice was reintroduced. This observation provides single but limited evidence for the effectiveness of the beetroot-carrot juice in eliminating malignant leukemic cells [77].

Polyphenol-rich foods are generally known to have anti-neoplastic effects. A clinical trial demonstrated significant short-term reduction of the prostate-specific antigen (PSA) level following supplementation with polyphenol-rich diet among elderly men [78]. Reduction in the serum PSA level is an endpoint biomarker for hormone-refractory human prostate cancer intervention. Since beetroot contains significant polyphenolic flavonoid antioxidants, its ability to inhibit manifestation of biomarkers of cancer is expected. However, there is certainly limited information on the direct effects of beetroot and its chemical composition on tumour markers i.e., cancer antigen (CA) 125, 15-3, 19-9 and carcinoembryonic antigen (CEA). Prospective clinical studies using beetroot may provide better insight into its underlying mechanisms when given along with standard therapies. A summary of cancer prevention effects of beetroot is shown in Table 2.

### Cardioprotective activities

Dietary supplementation of beetroot juice has been shown to mitigate anthracycline-induced cardiotoxicity [79]. Doxorubicin and epirubicin are anthracyclines and are usually part of breast cancer treatment protocol. Anthracyclines are important chemotherapeutic agents but unfortunately, chronic administration of anthracyclines induces cardiomyopathy and congestive heart failure [80]. For example, doxorubicin, a quinone-containing anthracycline antibiotic, is widely used to treat solid tumors such as breast and ovarian cancer. However, its clinical use is hampered by its adverse reaction such as cardiomyopathy and congestive heart failure. Although epirubicin or idarubicin, as second-generation analogs, may show improvements in their therapeutic index, there is still risk of cardiomyopathy [80]. One of the commonly known mechanisms of doxorubicin-induced cardiotoxicity is generation of ROS, which induces the apoptosis of the cardiomyocytes [80]. Thus, doxorubicin elicits the formation of hydrogen peroxide and superoxide anions ( $O_2^-$ ) through redox cycling of their aglycones which explains its anti-tumor activities [81].

Inflammation provoked due to ROS generation and oxidative stress is a major adverse effect, especially on the heart [82,83]. Hence, improving the antioxidant defences of cardiomyocytes is an important strategy to protect against doxorubicin-induced oxidative death [84]. In an animal study to determine the protective effect of beetroot juice against doxorubicin-induced cardiotoxicity, the combination of beetroot juice with doxorubicin significantly reduced doxorubicin toxicity in rat cardiomyocytes by reducing generation of ROS [84]. Therefore, beetroot juice supplement is postulated to be cardioprotective in patients treated with anthracycline chemo-

**Table 2.** A summary of cancer prevention effects of beetroot in *in vitro* or *in vivo* models

No	Test items and dose	Experimental model	Dose and treatment duration	Cancer preventive effects	References
<b>In vitro antioxidant and anti-inflammatory activities</b>					
1	Beetroot ethanol extract (lyophilized)	<ul style="list-style-type: none"> <li>Cell-free system using DPPH</li> <li>NO inhibitory efficacy in mouse macrophage RAW 264.7 cell line</li> </ul>	25-100 µg/mL	<ul style="list-style-type: none"> <li>Good antioxidant, electron-donating ability and radical scavenging activity</li> <li>Increases inhibition rate of NO production in LPS-treated cells</li> </ul>	[55]
2	Water extracts of beetroot	<ul style="list-style-type: none"> <li>Cell-free system using standard chemical tests</li> <li>Cellular antioxidant activity assay in HT29 (human colon adenocarcinoma) cells</li> <li>Activity of phase II detoxification enzymes: glutathione S-transferases (GST) and quinone oxidoreductase (NQO1)</li> </ul>	<ul style="list-style-type: none"> <li>10% (v/v) extracts (24 h)</li> <li>10% (v/v) (6-24 h)</li> </ul>	<ul style="list-style-type: none"> <li>Strongest antioxidant potential as compared with other plants</li> <li>No significant cytotoxic nor any protective effect against oxidative DNA damage in ROS challenged cells</li> <li>No significant ability to induce activity of phase II detoxification enzymes</li> </ul>	[16]
3	Betanin (red beet extract diluted with dextrin; CAS-Nr.: 7659-95-2)	<ul style="list-style-type: none"> <li>Comet assay in HT-29 cells</li> <li>Nrf2 dual luciferase reporter gene assay in Huh7 cells</li> <li>Antioxidant enzyme heme oxygenase-1 (HO-1) expression in Huh7 cells</li> <li>Glutathione (GSH) concentration in Huh7 cells</li> </ul>	<ul style="list-style-type: none"> <li>15 µM betanin (14 h)</li> <li>1-15 µM betanin (24 h)</li> <li>25 µM betanin (24 h)</li> <li>1-15 µM betanin (24 h)</li> </ul>	<ul style="list-style-type: none"> <li>Prevents DNA damage</li> <li>Induces Nrf2 at 15 µM betanin</li> <li>Increases in HO-1 protein concentration</li> <li>Increases cellular GSH</li> </ul>	[56]
4	Betanin (ABCR GmbH & Co. KG, Karlsruhe, Germany)	<ul style="list-style-type: none"> <li><i>In vitro</i> PMA-induced DNA damage in isolated human neutrophils (PMNs)</li> <li>DNA damage (Comet assay) in isolated human neutrophils</li> <li>Fluorometric analysis of caspase-3 activity</li> </ul>	<ul style="list-style-type: none"> <li>200 µM betanin (30 min)</li> <li>20-200 µM (24 h)</li> <li>20-300 µM (24 h)</li> </ul>	<ul style="list-style-type: none"> <li>Diminishes intracellular ROS level elevated by PMA stimulation (~3 fold)</li> <li>Decreases the percentage of DNA in the comet tails of the stimulated neutrophils</li> <li>Enhances caspase-3 activity in stimulated neutrophils</li> </ul>	[57]
5	Betanin (ABCR GmbH & Co. KG)	<ul style="list-style-type: none"> <li><i>In vitro</i> H<sub>2</sub>O<sub>2</sub>-induced DNA damage in isolated human neutrophils and Caco-2 intestinal cells</li> <li>Caspase-3 activity</li> </ul>	<ul style="list-style-type: none"> <li>200 µM (24 h)</li> <li>200 µM (24 h; neutrophils)</li> <li>20-200 µM (24 h; Caco-2 cells)</li> </ul>	<ul style="list-style-type: none"> <li>Betanin reduces DNA damage (~14%) caused by H<sub>2</sub>O<sub>2</sub></li> <li>Enhances caspase-3 activity in neutrophils and Caco-2 cells</li> <li>Triggers apoptotic cell death</li> </ul>	[58]
<b>In vivo antioxidant and anti-inflammatory activities</b>					
6	Beetroot juice (79.3 mg/100 mL betaxanthins and 159.6 mg/100 mL betacyanins)	<ul style="list-style-type: none"> <li>NDEA and CCl<sub>4</sub>-induced oxidative stress rat model</li> </ul>	8 mL/kg/day for 28 days	<ul style="list-style-type: none"> <li>Reduces DNA damage in blood leukocytes</li> <li>Restores the activity of some of the antioxidant enzymes in the liver</li> <li>Prevents xenobiotic-induced oxidative stress</li> </ul>	[59]
7	Beetroot juice (79.3 mg/100 mL betaxanthins and 159.6 mg/100 mL betacyanins)	<ul style="list-style-type: none"> <li>Phase I and phase II enzymes, DNA damage and NDEA-induced liver injury model in rats</li> </ul>	8 mL/kg/day for 28 days	<ul style="list-style-type: none"> <li>Reduces biomarker levels of liver injury such as ALT, SDH, GGT and bilirubin</li> <li>Reduces DNA damage triggered by NDEA treatment</li> </ul>	[60]



Table 2. Continued

No	Test items and dose	Experimental model	Dose and treatment duration	Cancer preventive effects	References
8	Beetroot ethanol extract (lyophilized)	Alcohol induced liver damage model in rats	• 200 or 400 mg/kg for 4 weeks	<ul style="list-style-type: none"> <li>Decreases serum AST, ALT and <math>\gamma</math>-GTP concentrations</li> <li>Decreases fat accumulation and inflammatory cell infiltration</li> <li>Improves morphological characteristics of damaged liver lesion</li> <li>Exert protective effects in hepatotoxicity</li> </ul>	[55]
9	Beetroot ethanol extract (evaporated dry)	<ul style="list-style-type: none"> <li>Gentamicin-induced nephrotoxicity in rats</li> <li>Oxidative/nitrosative stress, inflammatory and apoptotic markers</li> </ul>	• 250 and 500 mg/kg weight for 20 days before gentamicin treatment and there after concurrently with gentamicin for 8 days	<ul style="list-style-type: none"> <li>Inhibits gentamicin-induced up-regulation of inflammatory markers and nitric oxide level</li> <li>Reduces the expression of apoptotic markers in the kidney cells.</li> <li>Reduces inflammatory infiltration in the kidney tubules</li> </ul>	[2]
In vitro antiproliferative and other chemopreventive activities					
10	Betain and betaine isolated from beetroot extracts	• MTT assay in HepG2 cells	• 0-200 $\mu$ g/mL	<ul style="list-style-type: none"> <li>Inhibits cell proliferation in a dose dependent manner</li> <li>Inhibits HepG2 cells by 25%</li> </ul>	[67]
11	Betacyanins purified from beetroot	• Sulforhodamine B (SRB), apoptosis marker assay in urinary bladder cancer cells (T24) and normal human skin keratinocytes (NCTC 2544)	• 800 $\mu$ g/mL • 50 $\mu$ g/mL at 24, 48 and 72 h	<ul style="list-style-type: none"> <li>Betacyanins and vitexin-2-O-xyloside synergistically inhibit proliferation of tumor cells and not normal cells</li> <li>Induces apoptosis markers in tumor cells</li> </ul>	[68]
12	Beetroot extract (diluted with dextrin)	• Trypan blue cell viability assay in human pancreatic (PaCa), breast (MCF-7) and prostate cancer (PC-3) cell lines	• 0.29-290 $\mu$ g/mL at 72 h	<ul style="list-style-type: none"> <li>Synergistic antiproliferative effects when used in combination with doxorubicin</li> <li>IC<sub>50</sub> values reduced to almost 40%</li> </ul>	[69]
13	Betanin/isobetanin enriched powder from beetroot	• Cell proliferation, apoptosis and autophagy assay in mouse melanoma cell line (B16F10), human breast cancer lines (MCF-7, MDA-MB-231), human colorectal cells (HT-29) and normal human fibroblasts (MRC-5)	• 48 h • IC <sub>50</sub> about 25 $\mu$ M for B16F10 and MCF-7 cells and 35 $\mu$ M for MDA-MB-231 cells	<ul style="list-style-type: none"> <li>Decreases cancer cell proliferation and viability.</li> <li>Increases the expression of apoptosis-related proteins and autophagosome vesicles</li> </ul>	[70]
14	Betavulgarin isolated from beetroot	• Breast cancer cells (MDA-MB-231 and MCF-7)	• MDA-MB-231 ( $\geq$ 100 $\mu$ M) and MCF-7 cells at $\geq$ 50 $\mu$ M for 24 h	<ul style="list-style-type: none"> <li>Suppresses proliferation, migration, colony formation, and mammosphere formation</li> <li>Reduces the size of the CD44<sup>+</sup>/CD24<sup>-</sup> subpopulation</li> <li>Reduces the expression of the self-renewal-related genes, <i>c-Myc</i>, <i>Nanog</i> and <i>Oct4</i></li> <li>Inhibits the Stat3/Sox2 signaling pathway and induces breast cancer stem cells death</li> </ul>	[71]

**Table 2. Continued**

No	Test items and dose	Experimental model	Dose and treatment duration	Cancer preventive effects	References
<b>In vivo antiproliferative and other chemopreventive activities</b>					
15	E 162-water (78 µg/mL E 162 dye powder in water)	• N-nitrosomethylbenzylamine (NIMBA)-induced tumors in the rat esophagus (F344 rats)	• 35 weeks	<ul style="list-style-type: none"> <li>Reduces NIMBA-induced esophageal papillomas by 45%</li> <li>Reduces rates of cell proliferation in cancerous lesions</li> <li>Reduces level of angiogenesis and inflammation</li> <li>Increases rate of apoptosis</li> </ul>	[72]
16	Beetroot extract (betanin) (TCI/America, Portland, OR, USA)	• Mouse skin and lung carcinogenesis model	• 0.0025% (w/v) betanin in drinking water for 20 weeks	<ul style="list-style-type: none"> <li>Inhibits TPA-induced promotion of mice skin tumors</li> </ul>	[73]
17	Betanin extract (betanin) (TCI/America)	• VC and B(a)P-induced lung tumors in mice	• 25 and 100 µg/mL betanin in drinking water for 20 weeks	<ul style="list-style-type: none"> <li>Decreases tumor multiplicity and tumor load</li> </ul>	[74]
18	Beetroot extract (extracted with 70% ethanol)	• γ-ray irradiation in C57BL/6 mice	• 400 mg/mouse orally three times	<ul style="list-style-type: none"> <li>Induces caspase-3 expression</li> <li>Inhibits angiogenesis</li> <li>Stimulates cell proliferation</li> <li>Minimizes DNA damage of splenocytes</li> <li>Repopulates S-phase cells</li> <li>Boosts differentiation of HSCs into burst-forming units</li> <li>Enhances level of hematocrit and hemoglobin and RBC</li> </ul>	[76]
<b>Chemoprevention clinical studies</b>					
19	Beetroot-carrot juice	• Case report of a patient diagnosed with B-cell chronic lymphocytic leukemia (B-CLL)	<ul style="list-style-type: none"> <li>330 mL of fresh raw beetroot-carrot juice orally (beetroot 200 g + carrots 250 g) 2 h before breakfast 6 times/week for 1.5 month</li> <li>330 mL of fresh beetroot-carrot juice 6 times per week, in combination with the chlorambucil protocol 8 mg/day for 37 days</li> </ul>	<ul style="list-style-type: none"> <li>Decreases leukocyte and lymphocyte count from</li> <li>Reduces level of uric acid in blood</li> <li>Increases appetite,</li> <li>Improves fatigue</li> <li>Decreases leukocyte, lymphocyte and reticulocyte counts</li> <li>Improves renal function</li> <li>Improved blood urea, serum creatinine and uric acid levels</li> <li>Decreases LDH level</li> </ul>	[77]
20	Beetroot (concentrated organic beetroot crystals)	• Untreated squamous cell cancer of the head and neck (Randomized phase II Trial)	• 10 g Beetroot powder mixed with 4-8 oz	<ul style="list-style-type: none"> <li>Duration of study from December 2014-May 2018</li> </ul>	ClinicalTrials.gov Identifier: NCT02058849
21	Dietary supplement: beetroot juice	• Malignant breast tissue neoplasm	<ul style="list-style-type: none"> <li>5-day dietary nitrate intervention programme, taking 3 doses of 7 cl (centiliter) (0.4 g nitrate per dose) concentrated beetroot juice</li> </ul>	<ul style="list-style-type: none"> <li>Duration of study from May 2019-June 2020</li> <li>Unpublished</li> </ul>	ClinicalTrials.gov Identifier: NCT03944226

NO, nitric oxide; LPS, lipopolysaccharide; ROS, reactive oxygen species; NDEA, N-nitrosodiethylamine; ALT, alanine aminotransferase; SDH, sorbitol dehydrogenase; GGT, gamma glutamyl transferase; AST, aspartate aminotransferase; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; VC, vinyl carbamate; B(a)P, benzo(a)pyrene; RBC, red blood cell.

therapeutic drugs. The clinical application of beetroot juice as an adjunct therapy to combat against cardiotoxicity caused by anthracycline drugs is promising and would have a beneficial public health impact [79].

### Ameliorating cancer-related fatigue

Fatigue is a common adverse condition which affects the quality of life of patients with cancer [85]. It is one of the most frequently reported complaints among cancer patients [86,87]. As high as 60% to 93% of patients undergoing radiotherapy and 80% to 96% of patients on chemotherapy experienced fatigue [87,88]. Fatigue is reported as one of the most distressing symptoms associated with cancer and its treatment [89]. It is an independent predictor of poor quality of life and patient satisfaction [90]. In addition, the degree of anemia was also found to be predictive of the degree of fatigue among patients with cancer [91].

Off-treatment fatigue, weakness, and less vitality were more prevalent among women who had breast cancer as compared with women who had benign breast problems [92]. In an epidemiology study, breast cancer survivors were found to be complaining of lethargy more frequently than the reference group. A significant number of the breast cancer survivors experienced sleep disturbances, pain and depression which were associated with severe fatigue [93]. In one meta-analysis, one in four breast cancer survivors suffered from severe fatigue. Some of the risk factors included chemotherapy, higher disease stages and combination cancer therapy [94]. In one longitudinal study, persistent fatigue continued to be a challenge for breast carcinoma survivors [95].

The pathogenesis of cancer-related fatigue is currently not well understood. However, its development may be caused by a variety of mechanisms [96]. Cancer-related fatigue could be related to the effects of cancer or its treatment on sleep or circadian rhythms, muscle energy metabolism and central nervous system [97]. Findings from animal and human research suggest that several cancer-related symptoms, notably fatigue and stress, may involved the actions of proinflammatory cytokines [98]. In addition, there were studies which showed links between fatigue and inflammatory markers. Fatigued cancer survivors are characterized by an increased level of TNF- $\alpha$ , monocyte production of IL-6, elevated plasma IL-1 receptor antagonist and soluble IL-6 receptor (sIL-6R/CD126) levels, etc., indicative of immune activation [99,100]. Furthermore, the pathogenesis of fatigue is also thought to be related to hormonal changes such as deprivation of androgen or premature menopause in women [101-103]. The usual approaches to treatment of cancer-related fatigue include either pharmacologic management or non-pharmacologic intervention such as patient education. Interestingly, in a systematic review of 77 randomized controlled trials involving non-pharmacologic treatments of cancer-related fatigue, results were promising for non-pharmacologic intervention [104]. These include psychoeducation, hypnosis, exercise, relaxation and

cognitive-behavioral interventions.

Functional foods have been increasingly accepted as part of a healthy lifestyle and foods. A nitrate-dietary supplementation with beetroot juice is postulated as a nutritional strategy in patients undergoing chemotherapy and post-chemotherapy due its antioxidant and chemopreventive activities. Symptoms of fatigue may be ameliorated with beetroot supplementation due its high content of dietary nitrates and subsequent production of NO. NO is a ubiquitous signalling molecule with important physiological functions in human tissues [105].

NO plays a crucial role in skeletal muscle metabolic and vascular control. Beetroot juice contains high levels of inorganic nitrate ( $\text{NO}_3^-$ ), which serves as a precursor of NO. Beetroot supplementation provides dietary inorganic nitrate ( $\text{NO}_3^-$ ) which positively affect muscle metabolic and haemodynamic function [106,107]. Oral  $\text{NO}_3^-$  intake, either as beetroot juice or pure sodium  $\text{NO}_3^-$ , are found to enhance endurance exercise performance and capacity in young healthy volunteers [107-112]. In humans, acute (2 to 3 hours) and chronic (3 to 6 days) dietary nitrate consumption has been shown to improve exercise tolerance and reduce blood pressure [112,113]. In addition, beetroot supplementation ameliorates the muscle metabolic perturbations that occur during exercise, improves muscle oxygenation and elevates human mitochondrial efficiency [113-115]. In healthy elderly subjects, serum nitrate concentrations were found to be inversely associated with general fatigue scores based on a self-rating scale (Multidimensional Fatigue Inventory) [116,117]. Similarly, in another study, the level of the job strain appeared to be directly proportional to the fatigue among women but inversely associated with NO levels. NO has the capability to buffer the association between fatigue and job strain [118]. Hence, based on these observations, beetroot juice supplementation and its ability to increase exercise performance and tolerance in healthy subjects may ameliorate cancer-related fatigue. Currently, there are yet any studies to provide direct evidence supporting beetroot's effects on combating fatigue among patients with cancer.

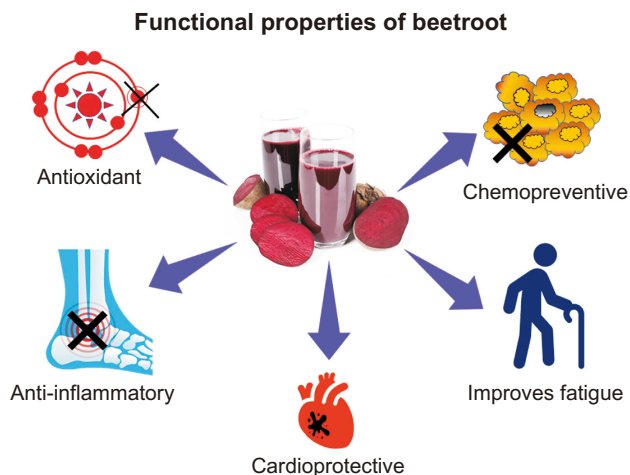
## CONCLUSION AND FUTURE PERSPECTIVES

Beetroot is a vegetable rich in micro-nutrients and bioactive constituents with health beneficial properties and has been gaining attention as a health promoting functional food. The multiple bioactive constituents include the water-soluble betalains consisting of betacyanins and betaxanthins, polyphenols, flavonoids and saponins. Beetroot extracts and betacyanins have been extensively studied both in vitro and in vivo. A variety of studies have demonstrated that beetroot extracts and betanin pigments were effective in preventing experimentally induced carcinogenesis. On the other hand, the flavonoids and polyphenolic components present in abundance in beetroot support its significant anti-inflammatory

and antioxidant capacities. Although most in vitro and in vivo studies have shown promising results, the molecular mechanisms of betanin chemoprevention have not been completely elucidated and clinical studies on beetroot and cancer are still lacking. In addition, the different extract preparation methods and the lack of pharmacokinetic studies with betanin alone make it difficult to determine if the therapeutic concentration or dosage used in these studies are indeed achievable in human plasma concentration.

In fact, despite containing the richest amount of anti-oxidant compounds, the red beet extract showed neither stronger cytotoxic effect towards HT29 human colon cancer cells, nor the ability to up-regulate the enzymes involved in detoxification as compared with other vegetable or herbal extracts [16]. Although beetroot supplementation has been studied in humans, most clinical studies were performed on a limited sample size and focussed on exercise performance and endurance in healthy cohorts. Two relevant clinical trials involving beetroot and cancer are listed in the ClinicalTrials.gov (US National Library of Medicine) database, which have yet to be published. So far, there has been no clinical study which specifically examines the association between beetroot supplementation and chemo-prevention or cancer-related symptoms such as fatigue, quality of life and well-being or prognosis of disease. Evidence supporting the use of beetroot in managing fatigue and/or managing the harsh side effects of chemotherapy is inevitable for its clinical application. Both epidemiological and randomized clinical studies on beetroot supplementation and patient with cancer are certainly warranted.

Although beetroot, especially nitrates and the betalains, are well absorbed and has good bioavailability in humans, there are still insufficient data on its efficacy and long term safety of beetroot supplementation to propose the food as a long-term strategy in managing diseases like cancer. In pregnancy, nitrate-rich dietary supplementation may be problematic as it may cause a wide range of unexpected maternal and fatal adverse reactions such as thyroid problems, alteration in embryonic cells, methemoglobinemia and other disorders [119]. Hence, intake of excessive beetroot during pregnancy may pose a health hazard. Although beetroot intake provokes no immediate negative health consequences, long term supplementation of beetroot juice should be cautioned in patients with metabolic syndromes or diabetes due to its high sucrose content. In addition, due to beetroot's rich oxalate content, this vegetable can be harmful if taken in large quantities, particularly for individuals at risk of calcium oxalate stone formation in the kidneys [42]. The excretion of red or pink urine after intake of beetroot occurs in 10% to 14% of the population. This symptom appeared to be more common in malabsorption and iron deficiency cases [120]. Furthermore, the composition of volatile compounds such as pyridines and 4-methyl-pyridines in beetroot would also warrant further studies with regards to their toxicological properties



**Figure 3. Functional properties of beetroot.**

[32]. In addition, their possible interactions with anticancer drugs should also be considered, since a recent case report described a woman who developed methotrexate intoxication after drinking beetroot juice as a herbal remedy [121].

In summary, beetroot is a valuable vegetable to be consumed for health maintenance and has great potential to be used for chemoprevention and in patients with cancer to manage fatigue and other side effects of chemotherapy (Fig. 3). However, long term safety assessment of dietary beetroot supplementation and relevant translational studies are necessary for the clinical setting.

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## CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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