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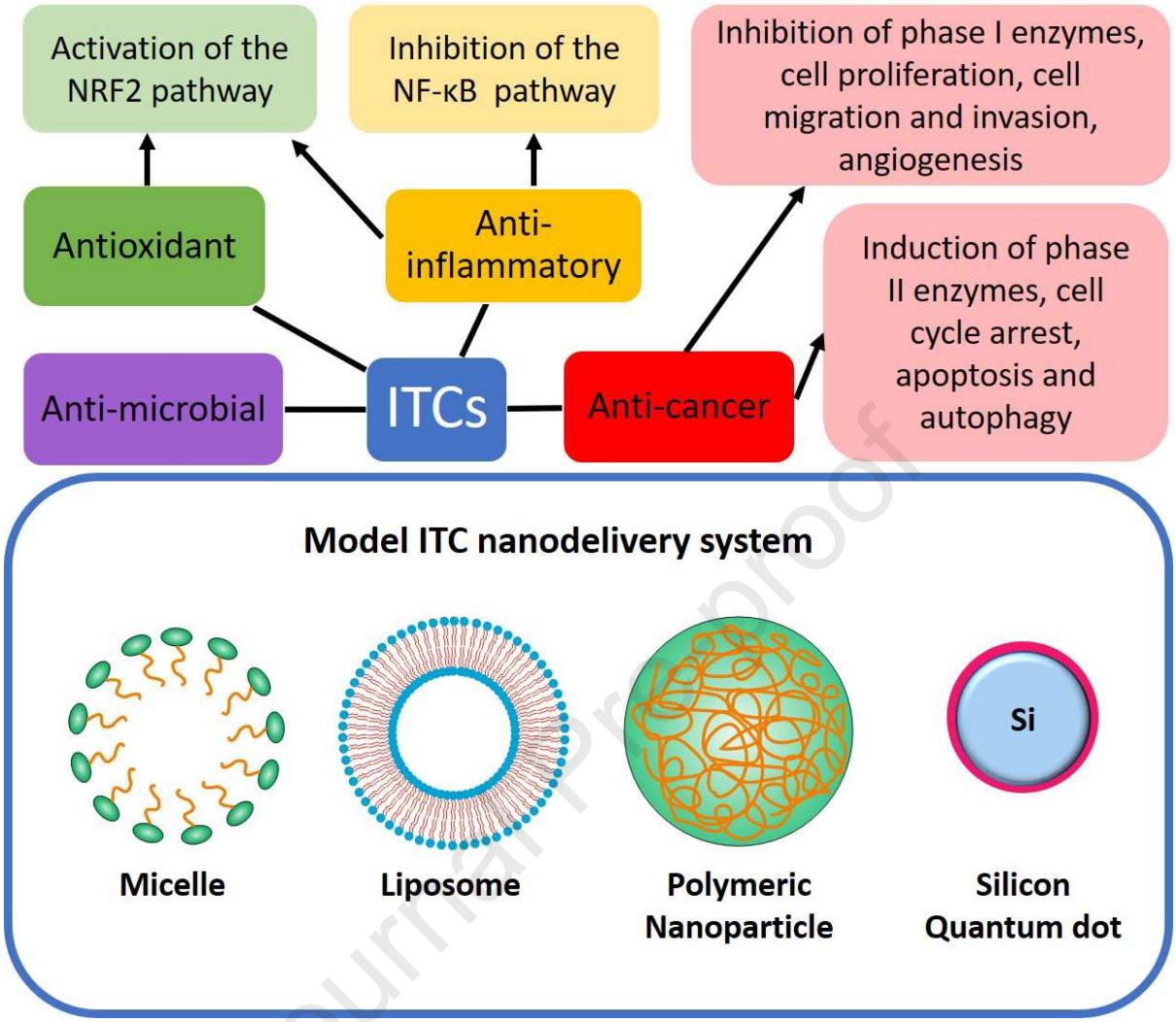
Graphical abstract



REVIEW ARTICLE

Nanodelivery of Natural Isothiocyanates as a Cancer Therapeutic

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Table of Contents

Abstract

Natural isothiocyanates (ITCs) are phytochemicals abundant in cruciferous vegetables with the general structure, R–N=C=S. They are bioactive organosulfur compounds derived from the hydrolysis of glucosinolates by myrosinase. A significant number of isothiocyanates have been isolated from different plant sources that include broccoli, Brussels sprouts, cabbage, cauliflower, kale, mustard, wasabi, and watercress. Several ITCs have been demonstrated to possess significant pharmacological properties including: antioxidant, anti-inflammatory, anti-cancer and antimicrobial activities. Due to their chemopreventive effects on many types of cancer, ITCs have been regarded as a promising anti-cancer therapeutic agent without major toxicity concerns. However, their clinical application has been hindered by several factors including their low aqueous solubility, low bioavailability, instability as well as their hormetic effect. Moreover, the typical dietary uptake of ITCs consumed for promotion of good health may be far from their bioactive (or cytotoxic) dose necessary for cancer prevention and/or treatment. Nanotechnology is one of best options to attain enhanced efficacy and minimize hormetic effect for ITCs. Nanoformulation of ITCs leads to enhance stability of ITCs in plasma and emphasize on their chemopreventive effects. This review provides a summary of the potential bioactivities of ITCs, their mechanisms of action for the prevention and treatment of cancer, as well as the recent research progress in their nanodelivery strategies to enhance solubility, bioavailability, and anti-cancer efficacy.

Keywords: Natural isothiocyanates, Allyl isothiocyanate, Benzyl isothiocyanate, Phenethyl isothiocyanate, Sulforaphane, Apoptosis, Cancer cells, Cancer therapeutic, Nanoparticle, Nanodelivery system.

1 Introduction

Naturally occurring isothiocyanates (ITCs) are biologically active hydrolysis (breakdown) products of glucosinolates from cruciferous vegetables (CVs). ITCs are abundant in a variety of vegetables such as broccoli, Brussels sprouts, cabbage, cauliflower, kale, mustard, wasabi, and watercress. They are bioactive organosulfur compounds, responsible for the sharp taste of vegetables and active ingredients in their defense systems [1]. In CVs, ITCs occur as glucosinolates and are hydrolyzed to ITCs by the action of myrosinase enzyme, which is expressed on the external surface of plant cell walls [2]. Additionally, they can be released by the action of intestinal microflora present in humans [3]. Each glucosinolate forms a different isothiocyanate when its hydrolyzed. For example, sulforaphane (SFN) is derived from the hydrolysis of glucoraphanin. SFN was first isolated from broccoli in 1992 [4], and is one of the most studied ITCs. Sinigrin, the glucosinolate precursor of allyl isothiocyanate (AITC), is abundant in mustard, horseradish and wasabi [5, 6]. The pungent taste of mustard and wasabi is a characteristic of AITC. It is also commonly called mustard oil. Garden cress is rich in glucotropaeolin, the precursor of benzyl isothiocyanate (BITC), while watercress is a good source of gluconasturtiin, the precursor of phenethyl isothiocyanate (PEITC) [7, 8]. The chemical structures of ITCs are summarized in Figure 1. Upon ingestion, ITCs are rapidly conjugated to glutathione (GSH) in the gut epithelium or liver [1]. They are then metabolized in the mercapturic acid pathway, and sequentially excreted in the urine mainly as N-acetylcysteine (NAC) conjugates. In cultured cell and animal models, isothiocyanates have demonstrated strong antioxidant and anti-inflammatory activities, as well as potent anti-cancer activities[1, 2, 9, 10]. This review summarizes the antioxidant, anti-inflammatory and anti-cancer activities of ITCs with the focus on recent progress of ITCs nanodelivery systems in cancer treatment.

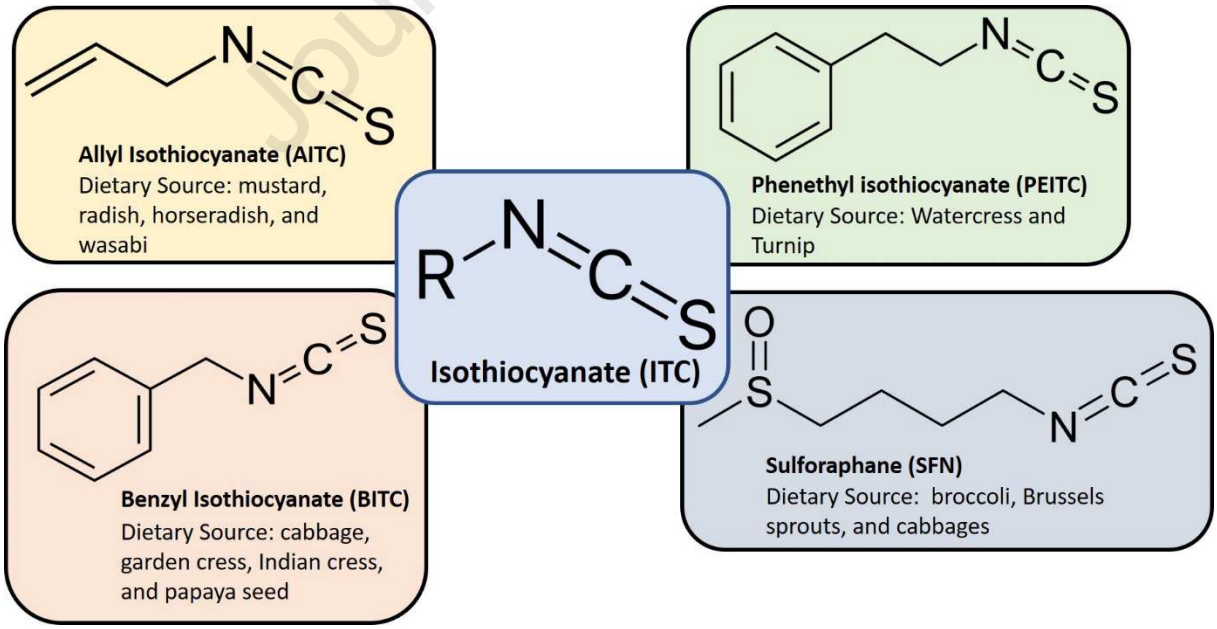

Figure 1. The basic structure and main types of natural isothiocyanates

2 Biological activities of natural isothiocyanates

As shown in Figure 1, the chemical structures of ITCs consist of a functional group -N=C=S, named as isothiocyanate group, with various side chains. The central carbon atom of the functional group makes ITCs as strong electrophiles. In general, ITCs can react readily with sulfur-, nitrogen- and oxygen-based biological nucleophiles, e.g. the thiol and amino groups of proteins [11]. Thus, the biological activities of ITCs may be due to the direct reaction with these functional groups in various proteins. The biological activities of ITCs and the underlining mechanisms are shown in Figure 2 which will be discussed in the following subsections.

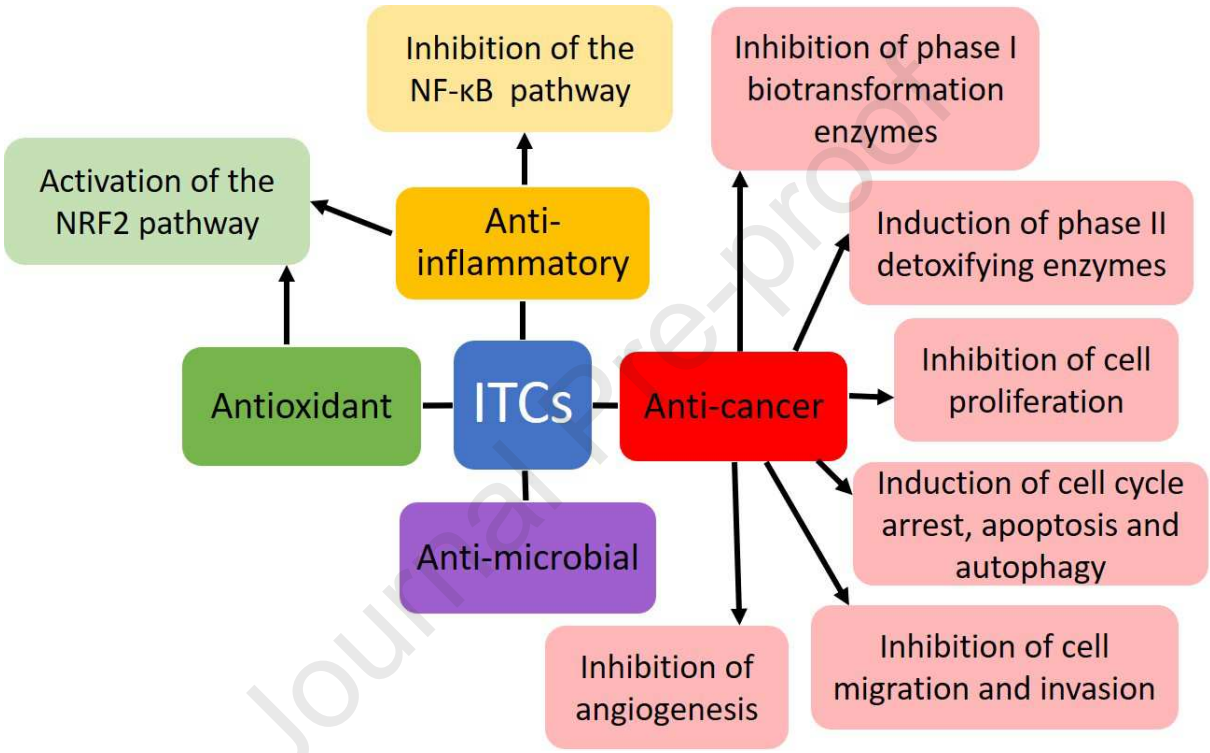

Figure 2. The main biological activities of isothiocyanates

2.1 Antioxidant activity

Many naturally occurring isothiocyanates, and in particular sulforaphane (SFN), have shown antioxidant effects via the activation of the nuclear factor E2-related factor 2 (Nrf2)-dependent pathway [12-14]. Binding of ITCs to sulfhydryl groups of Kelch-like ECH-associated protein 1 (KEAP1) blocks the cycle of KEAP1-dependent Nrf2 degradation, resulting in the release of Nrf2, and is followed by translocation of Nrf2 to the nucleus. Nrf2 could then bind to the antioxidant response element (ARE) located in the promoters of genes encoding antioxidant/detoxifying enzymes, which includes glutathione S-transferases (GSTs), thioredoxin (Trx), NADPH quinone oxidoreductase 1 (NQO-1), and heme oxygenase 1 (HO-1) [15]. In a number of animal studies, SFN was shown to have cytoprotective effects on many tissues and organs by activation of the Nrf2 pathway [16, 17]. For example, sulforaphane reduced oxidative damage-induced vascular endothelial cell injury in a type 2 diabetes mellitus mouse model by upregulation of the Nrf2 pathway [17]. Another example includes the attenuation of cellular damage caused by oxidative stress in lenses and lens cells by SFN though upregulation of the Nrf2 pathway [18]. Studies have

demonstrated that the upregulation of Nrf2/ARE dependent gene expression by ITCs was mediated by the mitogen-activated protein kinase (MAPK) pathway [19].

2.2 Anti-inflammatory activity

Isothiocyanates, especially sulforaphane exhibited strong anti-inflammatory activity though Nrf2 activation. The anti-inflammatory activities of Nrf2 include transcriptional upregulation of enzymes encoded by Nrf2-target genes, such as leukotriene B4 dehydrogenase [20], but also the blocking of pro-inflammatory cytokine transcription, such as IL-6 and IL-1β [21]. In addition, to direct anti-inflammatory effects mediated through Nrf2 signaling, SFN may impair the redox-sensitive DNA binding and transactivation of the pro-inflammatory nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [22], which altogether can lead to a decreased inflammatory response. BITC has greater affinity to inhibit the NF-κB than SFN due to the presence of additional benzyl structure [23]. The ITC modulation of Nrf2 and NF-κB pathways are especially important in chemoprevention because both oxidative stress and inflammation are significant contributors to the progression of cancer.

2.3 Anti-cancer activity

Cancer has been a major research focus over several decades [24]. The increasing understanding of cancer biology has led to a molecular approach to treat cancer and develop prevention strategies. AITC, BITC, PEITC, and SFN have been proven to exhibit anti-cancer effects against several different types of cancer [25-32]. Over the last decade, strong efforts have been made to understand the molecular mechanisms of ITC anti-cancer activities. SFN is the most studied ICT that acts on several hallmarks of cancer, possesses chemopreventive and chemotherapeutic potential [33-35]. The hallmarks acquired for tumor evolutions are genomic instability, sustained proliferative signaling, growth suppressor evasion, resistance to cell death, replicative immortality, deregulated metabolism, tumor-promoting inflammation, immune system evasion, angiogenesis and tissue invasion and metastasis [36]. Both *in vitro* and *in vivo* experiments demonstrated that SFN protects cells from DNA damage, which is mainly mediated by its activity on Phase II detoxifying enzymes. Phase II enzymes are regulated by the Nrf2-Keap system to maintain the homeostasis of cellular levels of GSH and Trx, which scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS) in cells [37]. The most prominent chemopreventive effect of ITC is associated to its ability to activate Nrf2 with the subsequent induction of Phase II enzymes. Molecular studies have shown that the induction on these phase II enzymes from ITCs depends on the ARE and that the regulation is associated with disruption of Nrf2-KEAP1 interactions and MAPK activation [38]. A lot of studies have proved that ITCs possess strong abilities to induce the activity of important Phase II enzymes including NQO1, GST, UDP-glucuronosyltransferase (UGT) and glutamate cysteine ligase (GCL) [4, 10, 27, 39, 40]. However, recent studies on tumor cell biology demonstrate that Nrf2 activation is not always leads to positive effect (anti-cancer) in cancer cells, for example aberrant activation of Nrf2 often results from is a common mutations in non-small cell lung cancer (NSCLC) and is associated with chemoresistance and radioresistance [41]. Constitutive activation of Nrf2 in cancer cells induces pro-survival genes, promotes cancer cell proliferation and avoidance of apoptosis, thus increasing cancer therapeutic resistance [37, 42, 43]. The controversial role of the Nrf2-Keap1 pathway in cancer prevention versus cancer progression has been explained by Kensler and Wakabayashi using a U-shaped dose-response curve [42]. They hypothesized that the chemopreventive effect only occurs when the expression level of Nrf2 falls within a

specific pharmacological range, while outside this range the risk of cancer is increased. In fact, genetic mutation of Nrf2/Keap1 induces permanent activation of Nrf2 signaling pathway causing cancer therapeutic resistance. In contrast, the transient activation of Nrf2 due to administration of ITCs has a less harmful effect [42].

There is now sufficient evidence from animal models to show that certain ITCs can also modulate the activity of phase I biotransformation enzymes, especially those of the cytochrome P450 (CYP) family [2]. In a primary rat hepatocyte-based model, AITC, BITC, PEITC, and SFN have been found to downregulate CYP3A2 mRNA expression [44]. Also, PEITC could inactivate CYP2E1 through heme destruction and protein modification [45]. It is suggested that inhibition of specific CYP enzymes involved in carcinogen activation could prevent the development of cancer.

ITCs have also been found to modulate the expression of the cell cycle regulators, cyclins and cyclin-dependent kinases (CDK), as well as induce apoptosis in a number of cancer cell lines by activating both extrinsic and intrinsic pathways [46]. AITC was found to induce mitochondrion-mediated apoptosis in human bladder cancer cells, which depended entirely on mitotic arrest and was mediated via Bcl-2 phosphorylation at Ser-70 [47]. In a mouse model of colorectal cancer, PEITC reduced both the number and size of polyps, which was associated with the activation of the CDK inhibitor, p21, inhibition of various cyclins and induction of apoptosis [48]. It has been widely demonstrated that SFN induces caspases activation, elevating expression of pro-apoptotic Bcl-2 proteins, which induces PARP cleavage and nuclear chromatin condensation in several cancer cell lines [49-52]. Apoptosis induction by sulforaphane could be also mediated by the MAPK signaling pathways, e.g. P38 in melanoma cells [51], or ERK and JNK in prostate cancer cells [53].

Several studies have also suggested that ITCs caninhibit cancer cell migration and invasion. For example, AITC reduced cell adhesion, migration and metalloproteinase (MMP) gene expression in SK-Hep1 cells [54]. In another study, AITC suppressed the epidermal growth factor (EGF) induced invasion and migration in HT29 cells [55]. In a breast cancer xenograft mouse model, BITC inhibited high fat diet-driven promotion of breast tumor growth, as well as lung and liver metastasis [56]. In a mouse model of breast tumor metastasis, PEITC inhibited the migration of tumor cells to the brain after injection into the hearts of mice [57]. The anti-migratory effect of SFN was associated with suppression of MMP [58] and down regulation of epidermal growth factor receptor (EGFR) [59]. SFN inhibited the migration and invasion of triple-negative SUM159 human breast cancer cells through suppressing the Hedgehog signaling pathway [60]. The epithelial to mesenchymal transition (EMT) describes a process of epithelial cell transformation in which the primary tumor cells lose their polarity and adhesion properties while gaining migratory and invasive properties. It is one of the common properties of tumor invasion and metastasis [61]. SFN inhibited EMT in thyroid cancer cells is associated with upregulation of E-cadherin and downregulation of SNAI2, vimentin, MMP-2 and MMP-9 [62]. Angiogenesis is a crucial process in tumor progression where new capillaries develop from pre-existing blood vessels to support tumor growth. ITCs have been shown to prevent the formation of such capillary-like structures from human umbilical endothelial cells, as well as inhibition of the expression and function of hypoxia inducible factors (HIFs) that control angiogenesis [63].

In conclusion, AITC, BITC, PEITC and SFN have efficient chemopreventive and chemotherapeutic effects. The chemopreventive effects of ITC are associated to its capability to activate the Nrf2-Keap-ARE

pathway with the final induction of Phase II enzymes. Nrf2 has a double-edged role in the context of cancer management. The transient activation of Nrf2 by nutraceutical intervention of ITCs could be beneficial to healthy people or an at-risk group who is exposed to potential carcinogens. Moreover, the chemotherapeutic effects of ITC are associated to its ability to modulate cell cycle arrest, induce apoptosis, and inhibit angiogenesis and tumor metastasis. However, clinical trials are needed to ascertain the possible beneficial effects of ITCs for adjuvant therapy against cancer, which will be discussed in the following section.

3 Natural isothiocyanates in human clinical trials

3.1 Clinical trials of natural isothiocyanates in cancer

A number of Phase I and II clinical trials on natural isothiocyanates are in progress or have been completed to assess their safety, tolerance, pharmacokinetics, and therapeutic benefit in the context of cancer (Table 1). To date, there are around twenty trials on SFN, four trails on PEITC, and one which is not specified. These clinical trials are mostly focused on breast cancer and prostate cancer, but also include some other cancer types including colon, lung, pancreatic, bladder, etc.

In a recent intervention study, the total sulforaphane metabolite concentration in urine was 0.08 μM/mM creatinine in women with abnormal mammograms who consumed ~81.7 g/d of cruciferous vegetables [64]. The study has also found that higher cruciferous vegetable intake is associated with decreased cell proliferation in breast ductal carcinoma in situ (DCIS) tissue, but not in benign or invasive ductal carcinoma (IDC) tissue. The same group has also examined bioavailability and chemopreventive activity of supplemental SFN in breast cancer patients [65]. Total sulforaphane metabolites in plasma and urine after consuming 224 mg glucoraphanin as the SFN source were 0.25 μM and 1.06 μM/mM creatinine, respectively. This study suggested that glucoraphanin supplementation is safe to use for a few weeks but may not be sufficient to produce changes in breast tissue tumor biomarkers (HDAC3/HDAC6, histone H3 lysine 18 acetylation (H3K18ac), Ki-67 and p21). Another Phase II study reports that in patients with recurrent prostate cancer, administration of 200 μmol/d of sulforaphane-rich extracts for 20 weeks is safe, but it does not lead to significant reduction in PSA levels in the majority of patients [66]. In a recent pilot study, Zhang *et. al.* evaluated the effect of SFN on blood HDAC activity, prostate tissue immunohistochemistry biomarkers and prostate RNA gene expression in prostate cancer patients using broccoli sprout extract (BSE) supplementation [67]. Despite urine and plasma SFN metabolites being statistically higher in the BSE supplementation group, like the breast cancer study there was no significant difference in HDAC activity or prostate tissue biomarkers. Interestingly, 40 differentially expressed genes have been identified that correlated with supplemental SFN, including downregulation of two genes previously implicated in prostate cancer development, *AMACR* and *ARLNC1*. Another pilot study to investigate the efficacy of a dietary supplement made by broccoli soup on prostate cancer patients demonstrated some promising results. It has been showed that consuming glucoraphanin-rich broccoli soup for a year affected gene expression in the prostate and is consistent with a reduction in the risk of cancer progression. The changes in gene expression and associated oncogenic pathways were attenuated in a dose-dependent manner.

There are only a handful of clinical trials on PEITC to evaluate its potential as an anti-cancer agent and these are mostly limited to lung cancer. A randomized, placebo-controlled double-blind Phase II clinical trial, involving volunteers who were cigarette smokers, examined metabolism and excretion of PEITC in human subjects, as well as the chemopreventive effect of PEITC on tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) driven carcinogensis. After daily administration of 40 mg PEITC, an average of 29% PEITC administered dose was excreted as N-acetyl-S-(N-2-phenethylthiocarbamoyl)-L-cysteine (PEITC-NAC) in the urine. Overall, the NNK metabolic activation ratio is reduced by 7.7% with PEITC treatment, which suggested a modest inhibitory effect of PEITC on NNK induced lung carcinogenicity. In addition, the effects of glutathione S-transferases M1 and T1 (GSTM1 and GSTT1) genotypes on metabolism and excretion of PEITC and its impact on NNK metabolism have also been investigated in this study. However, the results were complex and are poorly understood.

In addition, it is worthwhile to mention the studies on commercially available formulations of SFN, such as Sulforadex® (SFX-01) and BroccoMax®. These formulations, with enhanced SFN bioavailability and stability, have been evaluated on their own or in combination with other cancer therapeutics, such as endocrine therapies (ET), aromatase inhibitors (AIs), tamoxifen and fulvestrant. A recent completed Phase II trial concludes that administration of 300 mg SFX-01 twice a day in combination with ET was safe and well tolerated in patients with estrogen receptor (ER) positive and Her2 negative metastatic breast cancer [68]. The combinational therapy showed satisfactory anti-tumor activity and prolonged disease stabilization.

So far, we have seen growing numbers of clinical trials on SFN in forms of dietary supplement as well as commercial formulations. However equivalent trials on AITC and BITC are still missing. The results of these clinical trials on SFN only partially confirm its promising anti-cancer potential as demonstrated during *in vitro* studies, which could be a consequence of its instability, low bioavailability, and the different effects of SFN in the complex tumor microenvironment. More extensive studies with larger sample sizes are needed to understand the broad spectrum of applications of ITCs in cancer management. Therefore, it would be interesting to use nanoparticles to enhance its delivery, which will be discussed in the later section of this review.

3.2 Clinical trials of natural isothiocyanates in other diseases

A few clinical trials are in the pipeline to evaluate SFN in diseases other than cancer including diabetes (NCT02801448), kidney disease (NCT04608903), skin disorder (NCT03126539), blood/vascular disease (NCT01114399, NCT01715480), asthma (NCT01183923) and autism (NCT01474993, NCT02677051, NCT02879110). Most of these trials are still on going with no results published. Two clinical studies on type 2 diabetes (T2D) patients showed that intervention with broccoli sprout powder doses (112 or 225 μmol/d of SFN equivalents) for 4 weeks, could reduce serum insulin concentration [69] and achieve favorable lipid profiles [70]. In a recent Phase II trial, daily consumption of broccoli sprout extract (containing 150 μmol SFN per dose) effectively reduced fasting blood glucose and glycated hemoglobin (HbA1c) in obese patients with dysregulated type 2 diabetes [71]. In a Phase II trial on autism spectrum disorder (ASD), SFN treatment (50-150 μmol/d) for 18 weeks improved autism-related outcomes in young, male patients [72]. Findings from these studies would add valuable insight to incorporate SFN into T2D and ASD treatment methods.

266 Table 1: Summary of human clinical trials on ITCs in cancer therapeutics in progress or completed.

Isothiocyanate	Cancer type	Phase	Status	Information/Result	Reference
SFN	Colon Cancer	Not Applicable	Unknown	To assess cruciferous vegetable intake correlates with histone status and histone deacetylace (HDAC) expression. To measure SFN metabolites in blood as a biomarker.	NCT01344330; clinicaltrials.gov
SFN	Pancreatic Cancer	Not Applicable	Unknown	To determine the feasibility of the application of SFN and quercetin in patients receive palliative chemotherapy.	NCT01879878; clinicaltrials.gov
SFN	Smoking-Related Carcinoma	Early Phase I	Active, not recruiting	To determine 1) whether broccoli sprout/Avmacol® increases the urinary excretion of the mercapturic acid of the tobacco carcinogens. 2) Avmacol® upregulates the NRF2 target gene transcripts. 3) the effects of GSTM1 and GSTT1 genotypes in Avmacol® treatment of detoxification of tobacco carcinogens.	NCT03402230; clinicaltrials.gov
SFN	Head and Neck Cancer	Early Phase I	Active, not recruiting	To determine 1) the bioavailability of SFN in Avmacol®. 2) the level of pharmacodynamic upregulation of NRF2 target gene transcripts that occurs in the oral epithelium of patients.	NCT03182959; clinicaltrials.gov
SFN	Melanoma	Early Phase I	Completed	To determine 1) adverse effects with oral SFN. 2) visual and cellular changes of atypical nevi. 3) SFN levels in the blood (4) effect of SFN on STAT1 and STAT3 expression.	NCT01568996; clinicaltrials.gov
SFN	Lung Cancer	Phase II	Recruiting	To study 1) the effects of SFN to former smokers. 2) whether SFN might reverse some of the lung cell changes associated with future development of lung cancer.	NCT03232138; clinicaltrials.gov
SFN	Breast Cancer	Phase I and II	Recruiting	To determine 1) safety of SFN in doxorubicin (DOX) chemotherapy. 2) if SFN decreases DOX-induced inflammatory responses and enhances Nrf2- and SIRT1-target gene expression. 3) if SFN/DOX treatment mitigates DOX associated cardiotoxicity.	NCT03934905; clinicaltrials.gov
SFN	Breast Cancer	unknown	Completed	To investigate the protective effects of topical SFN on radiation-induced dermatitis.	NCT00894712; clinicaltrials.gov

SFN	Breast Cancer	Phase II	Completed	1) SFX-01(Sulforadex®) 300 mg twice a day was safe and well tolerated in patients with ER positive and Her2 negative metastatic breast cancer. 2) SFX-01 in combination with endocrine therapies (ET) demonstrated anti-tumour activity and prolonged disease stabilisation.	NCT02970682; clinicaltrials.gov [68]
SFN	Breast Cancer	Phase II	Completed	14-day intervention of broccoli sprout (SFN) significantly decreases ki67 positive cells, therefore decreases cellular proliferation.	NCT00982319; clinicaltrials.gov
SFN	Breast Cancer	Phase II	Completed	1) Higher SFN intake is associated with decreased cell proliferation in DCIS 2) No significant decrease in HDAC3, HDAC6, H3K18, Ki-67 and p21 activities between placebo- and SFN-treated interventional groups.	NCT00843167; clinicaltrials.gov [64, 65]
SFN	Prostate Cancer	Not Applicable	Recruiting	To study the oral intake of BroccoMax® (containing SFN) in changes in chemicals that feed prostate cancer.	NCT03665922; clinicaltrials.gov
SFN	Prostate Cancer	Not Applicable	Completed	Consuming glucoraphanin-rich broccoli soup affected gene expression in the prostate of men on active surveillance. Changes in gene expression and associated oncogenic pathways were attenuated in a dose-dependent manner.	NCT01950143; clinicaltrials.gov [73]
SFN	Prostate Cancer	Not Applicable	Completed	To investigate the relationship between ingestion of the bioactive compounds from broccoli and garlic, and prostate metabolism	NCT04046653; clinicaltrials.gov
SFN	Prostate Cancer	Not Applicable	Completed	1) No significant decrease in HDAC3, HDAC6, H3K18, Ki-67 and p21 activity between placebo- and BSE-treated interventional groups 2) 40 differentially expressed genes have been identified that correlated with BSE treatment, including downregulation of two genes previously implicated in prostate cancer development, AMACR and ARLNC1.	NCT01265953; clinicaltrials.gov [67]
SFN	Prostate Cancer	Phase I	Completed	To determine the safety and tolerability of single escalating doses of Sulforadex®	NCT01948362; clinicaltrials.gov
SFN	Prostate Cancer	Phase I	Completed	To determine the safety and tolerability of multiple doses of Sulforadex®	NCT02055716; clinicaltrials.gov
SFN	Prostate Cancer	Phase I and II	Completed	To study the effects of administration a high-sulforaphane broccoli sprout extract on 1) Phase II enzymes expression, 2) lipid and DNA oxidation, 3) serum	NCT00946309; clinicaltrials.gov

				dihydrotestosterone (DHT), testosterone (T) and 3-alpha-diol gluconate(3α-DG) levels.	
SFN	Prostate Cancer	Phase II	Completed	1) 5% of Patients who achieve a 50% decline in prostate-specific antigen (PSA) levels. 2) The percentage change in PSA from baseline to the final measured value at the end of study is 35%. 3) 90% of patients whose PSA has not doubled. 4) The half-life of SFN in blood is 1.8-5.5 hours.	NCT01228084; clinicaltrials.gov [66]
PEITC	Lung Cancer	Phase I	Completed	To determine 1) the maximum tolerated dose of oral PEITC in smokers. 2) pharmacokinetics of PEITC during exposure of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). 3) the perturbation of NNK metabolism by PEITC.	NCT00005883; clinicaltrials.gov
PEITC	Lung Cancer	Phase II	Completed	To determine 1) the effect of PEITC on urinary levels of NNK metabolism. 2) the effects of GSTM1 and/or GSTT1 Genotype on PEITC-NNK Association and on the metabolism and excretion of PEITC. 3) the effects of PEITC on molecular markers of cell proliferation (Ki-67) and apoptosis (caspase-3 and TUNEL) in bronchial tissue.	NCT00691132; clinicaltrials.gov [74]
PEITC	Oral Cancer	Phase I and II	Completed	To examine the effects of PEITC on oral cells with mutant p53	NCT01790204; clinicaltrials.gov
PEITC	Breast Cancer	Phase III	unknown	To explore the ability of PEITC to improve the restorative effects of radiotherapy in breast cancer patients	NCT02468882; clinicaltrials.gov
ITC	Bladder Cancer	Phase I	Recruiting	To study whether increase of cruciferous vegetable intake with the goal of attaining desirable urinary ITC levels improve bladder cancer survivorship.	NCT04548193 clinicaltrials.gov

4 Combinatorial strategies of natural isothiocyanates in cancer therapy

The combination of two or more therapeutic agents to specifically target cancer signaling pathways is a rapidly growing field of cancer therapy [75, 76]. When anti-cancer agents with different effects are combined, they could achieve greater efficacy with lower doses. This might be an additive or synergistic effect. A synergistic effect is the effect arising between two or more agents that produce an outcome greater than the sum of the individual components. Synergistic combination therapy allows each anti-cancer agent to be used at its optimal dose, with reduced side effects and minimized drug resistance [77]. There is a growing interest in natural compounds such as natural ITCs, which could be used together with conventional chemotherapeutic drugs in combination therapy. It has been reported by many studies that the combinational use of natural ITCs and other anti-cancer agents could achieve synergistic anti-cancer activity [78-82]. In a recent review, Kamal *at al.* have summarized studies on synergistic combination therapy of sulforaphane and various anti-cancer agents [83]. For example, SFN significantly enhances the anti-cancer activity of gemcitabine (GEM) [84], paclitaxel (PTX) and docetaxel (DTX) [85] in breast cancer, oxaliplatin (OX) in colorectal cancer [86] and cisplatin in prostate and pancreatic cancer [87].

4.1 Combinational use of ITCs and chemotherapeutic drugs

4.1.1 ITCs and cisplatin

Cisplatin (cis-diamminedichloroplatinum II, CDDP) is one of the most widely used chemotherapeutic drugs. However, its clinical application is often limited by low chemosensitivity, systemic side effects [88] and primary or secondary acquired drug resistance [78, 89]. A combination therapy with CDDP and other anti-cancer agents that enhance tumor sensitivity and decrease unwanted systemic toxicity would present a significant therapeutic benefit. Di Pasqua *et al.* have studied the combination of natural ITCs and CDDP on non-small cell lung cancer [90]. BITC and PEITC, but not SFN, are sensitize human non-small cell lung cancer NCI-H596 cells to various concentrations of cisplatin. The effect is synergistic rather than additive. They have found that neither cellular platinum accumulation nor DNA-platination account for the enhanced cytotoxicity, suggested the depletion of β-tubulin with pre-treatment of BITC or PEITC might be important for sensitization.

Wang *et al.* have examined the combination therapy of PEITC and cisplatin in cervical and breast cancer cells [91]. Treatment of 5 μM PEITC with 10 μM CDDP exhibits a synergistic effect on the induction of apoptosis in HeLa cells. The same effect has also been showed in MCF7 breast cancer cells, but not in normal MCF-10A cells, suggesting the normal MCF-10A cells are more resistant to the cytotoxic effects of PEITC plus CDDP than MCF-7 breast cancer cells. The selective toxicity of PEITC and CDDP combination therapy towards breast cancer cells could be a promising safer strategy for breast cancer treatment. Such synergistic effect was specifically blocked by a MEK1/2 inhibitor, but not by JNK or p38 inhibitors, signifying that ERK activation is involved in the mechanism of synergism. Interestingly, the researchers found that NF-κB signaling pathway is not involved in the synergistic effects of PEITC and CDDP.

Ling *et al.* reported that the combination of AITC with CDDP synergistically inhibits cancer cell growth and induces cell death *in vitro* and *in vivo* [79]. Their study revealed that AITC and CDDP combination

significantly inhibits cell growth and colony formation in comparison to single agent treatment in both OV-2008 ovarian cancer cells and HOP62 lung cancer cells. The combination therapy also enhances apoptosis in association with the downregulation of anti-apoptotic proteins Bcl-2 and surviving. The combination index (CI) was then calculated using Chou-Talalay equation to verify the type of interaction between AITC and CDDP in A549 and Hop62 lung cancer cells. A high synergistic effect (CI<0.5) has been found for the combinational treatment of AITC at 10-20 µM and CDDP at 8-16 µM. Further *in vivo* study on human lung cancer xenografts demonstrated that combination of AITC with CDDP could significantly suppress tumor growth without an observable increase in systemic toxicity in comparison with single agent treatment. Furthermore, their data revealed that addition of AITC to CDDP changes the profile of G2/M phase arrest and significantly extends the duration of G2/M phase arrest in comparison with single treatment. Like BITC and PEITC [88], the synergistic effects of AITC with CDDP have been found to be associated with rapid β-tubulin depletion and microtubule dysfunction.

In SFN and CDDP combination therapy against pancreatic and prostate cancer, MIA-PaCa2 and DU145 cells were exposed to treatment for 72 h and analyzed by MTT assay and morphological evaluation [87]. It was found that SFN increased the *in vitro* cytotoxicity from CDDP in both cell lines. SFN and CDDP combined treatment also showed significantly enhanced apoptosis compared to single agent alone. Another study done by Kerr *et. al.* reported the enhancement of anti-cancer activity of CDDP when combined with SFN against squamous cell carcinoma cells SCC-13 and HaCaT [92]. An increased suppression of cell proliferation, stem cell spheroid formation, and cell migration was observed in combination treatment compared to each agent alone. It is worth noting that several studies performed on combination therapy of SFN and CDDP suggested their synergistic effect might be caused by several mechanisms. Kaminski *et al*. reported combined treatment of SFN and CDDP in human ovarian carcinoma A2780 and SKOV3 cell lines results in synergy and antagonism, respectively. While SFN significantly potentiated CDDP-induced DNA damage in A2780 cells, it protected SKOV3 cells against CDDP-crosslinking. Such dual effects of SFN may be explained by different activation of the Nrf2 pathway [78]. A later study reveals that SFN and CDDP combination therapy induced a synergistic anti-cancer effect on malignant mesothelioma (MM) cells by enhancing ROS stress and mitochondrial membrane depolarization [93].

4.1.2 ITCs and taxanes

Nunez-Iglesias *et al*. investigated the cytotoxic effects of glucosinolate-degradation products (AITC, PEITC, SFN, 4-pentenyl-isothiocyanate (4PI), iberin (IB), or indole-3-carbinol (I3C)) in absence or presence of DTX in androgen-independent human prostate cancer PC3 and DU145 cells. It was observed that the combination therapy of ITCs and DTX was more effective in reducing viability of prostate cancer cells compared with each agent alone. The index of survival rate has been used to calculate the interaction of ITCs and DTX. It was found that the combination of DTX with AITC or PEITC significantly caused a synergistic sensitization of PC3 and DU145 for DTX induced apoptosis and DTX induced cell growth inhibition [94]. They have also suggested potential mechanism for the synergistic effect, such as degradation and polymerization of α and β tubulin, modulation of the intracrine metabolism of androgens mediated by CYP3A4, and the expression of efflux transporters and/or GSH activity. Burnett *et al*. studied the combination effect of sulforaphane with paclitaxel or docetaxel on SUM149 and SUM159 breast cancer cells *in vitro* and *in vivo* [85]. *In vitro* results suggested that combination of a minimally cytotoxic SFN treatment (5 µM) with either PTX or DTX lowered their IC50s to less than 50% of the original value. *In*

vivo study with SUM149 implanted NOD/SCID mice also showed similar effects when treated with SFN and DTX combination.

Overall, natural ITCs are proven to potentiate the activity of several classes of chemotherapeutics including cisplatin, paclitaxel, and docetaxel through additive and synergistic effects. Such combinational therapy has efficacy against a variety of cancer types in several model systems. Further clinical studies are needed to evaluate safety and efficacy of the combinational use of ITCs with chemotherapies.

4.2 Combinational use of ITCs and other anti-cancer agents

Gupta *et al*. reported synergistic anti-cancer activity of laccaic acid (LA) and PEITC combination in colorectal cancer via dual inhibition of DNA methyltransferase-1 and Histone deacetylase-1. In the HT29 cell line, treatment with the combination showed reduced cell viability with increased apoptotic cell death compared to LA and PEITC alone. In the *in vivo* study using a 1,2-dimethyl hydrazine induced colon cancer rat model, combination therapy significantly improved mortality, fecal consistency score, IL-6, TNF-α, DNMT1 and HDAC1 levels, and attenuated the number of aberrant crypt foci which depicted a better prognosis [80].

A recent study combined a classical antihistaminic drug, Loratadine (LOR) and SFN using a self-microemulsifying drug delivery system. Combination of a minimally cytotoxic SFN treatment with LOR achieved a 95% reduction of the LOR IC50 value in MIA PaCa-2 cells and a 90% reduction in Panc-1 cells [95], which suggested SFN largely enhanced the anti-cancer activity of LOR in pancreatic cancer. Another study found that combinational use of salinomycin (SAL) and SFN synergistically inhibited cell viability, proliferation, migration and invasion and enhanced apoptosis in Caco-2 and CX-1 cells. Similar results were also seen in the xenograft model. In the combination therapy, decreased expression of PI3K, p-Akt and Bcl-2 and increased expression of Bax, p53 and cleaved PARP suggests PI3K/Akt pathway is involved in synergistic effect of SAL and SFN induced apoptosis [96]. Synergistic effects of SFN were also observed in triple combination therapy. A combination of curcumin (CUR), SFN, and dihydrocaffeic acid (DHA) was evaluated against human colon cancer cells [97]. At cytotoxic concentrations designed to kill 50% and 75% of cells, the effects of CUR-DHA, SFN-DHA, and CUR-SFN-DHA combination were additive, while SFN-CUR combination showed a relatively high antagonistic effect. Interestingly, at 90% cytotoxicity, SFN-DHA combination exerted a significant synergistic effect. This combination is significantly more cytotoxic for cancer cells than healthy cells. These studies on combination strategies of ITCs provided ample evidence that combining ITCs with other anti-cancer agents pose a potential way forward for improved outcome. Further nanoformulation based on these combination therapies could result in additional enhancement of anti-cancer efficacy through targeted delivery.

5 Nanodelivery of natural isothiocyanates in cancer therapy.

The bioactivity of ITCs is largely dependent on the absorption, metabolism, distribution, and excretion in human body. Despite various cellular and animal models confirming the benefit derived from many ITCs against cancer, the clinical utilization of ITCs is still limited [98-100] due to its low solubility, stability, and bioavailability, as well as the “biphasic dose response”. To overcome these drawbacks, scientists have employed recently developed nanodelivery technology. In these applications, nanomaterial has been employed as transport modules to carry ITC and/or other chemotherapy agents to achieve therapeutic

synergism in cancer treatment. Different types of nanodelivery systems have been developed for this purpose. These nanodelivery systems can be easily fabricated to selectively target tumor cells as opposed to normal cells [101]. Some of the main nanodelivery systems used in cancer therapeutics are micelles, liposomes, dendrimers, polymeric nanoparticles, carbon nanotubes, quantum dots (QDs), magnetic iron oxide nanoparticles and gold nanoparticles. Figure 3 shows a schematic representation of major nanodelivery systems used in cancer therapy. A micelle is a self-assembly vesicle with an outer hydrophilic tail region and hydrophobic core center [102]. A nanosized liposome represents a self-assembled phospholipid bilayers vesicles entrapping one or more aquatic compartments [103, 104]. A dendrimer is a highly branched, symmetric, star-shaped macromolecule with nanometer-scale dimensions [105]. A polymeric nanoparticle can be synthesized using biodegradable and biocompatible polymers or copolymers [106]. A solid lipid nanoparticle (SLP) contains a surfactant outer layer and lipids in solid phase with the advantage of entrapping lipophilic molecules without applying organic solvents [107]. Both gold and iron oxide nanoparticles are metallic nanoparticles which have imaging functionalities used for either passive or active drug delivery in cancer diagnosis and treatment. QDs are semiconductor crystals in the range of 2–10 nm, which possess strong photoluminescence [108-111]. Most importantly, these inorganic nanoparticles can be synthesized and modified with various chemical functional groups which facilitate their application as drug carriers for cancer therapeutic agents [111, 112]. Anti-cancer therapeutic agents e.g., ITCs can be encapsulated within the NP carriers or be physically adsorbed on or chemically linked to the NP surfaces. Many nanodelivery systems loaded with ITCs have been proven to be efficacious in inhibiting cancer cell proliferation, migration, and invasion. Results from studies reporting anti-cancer effects of the ITC nanodelivery systems are discussed in subsections below.

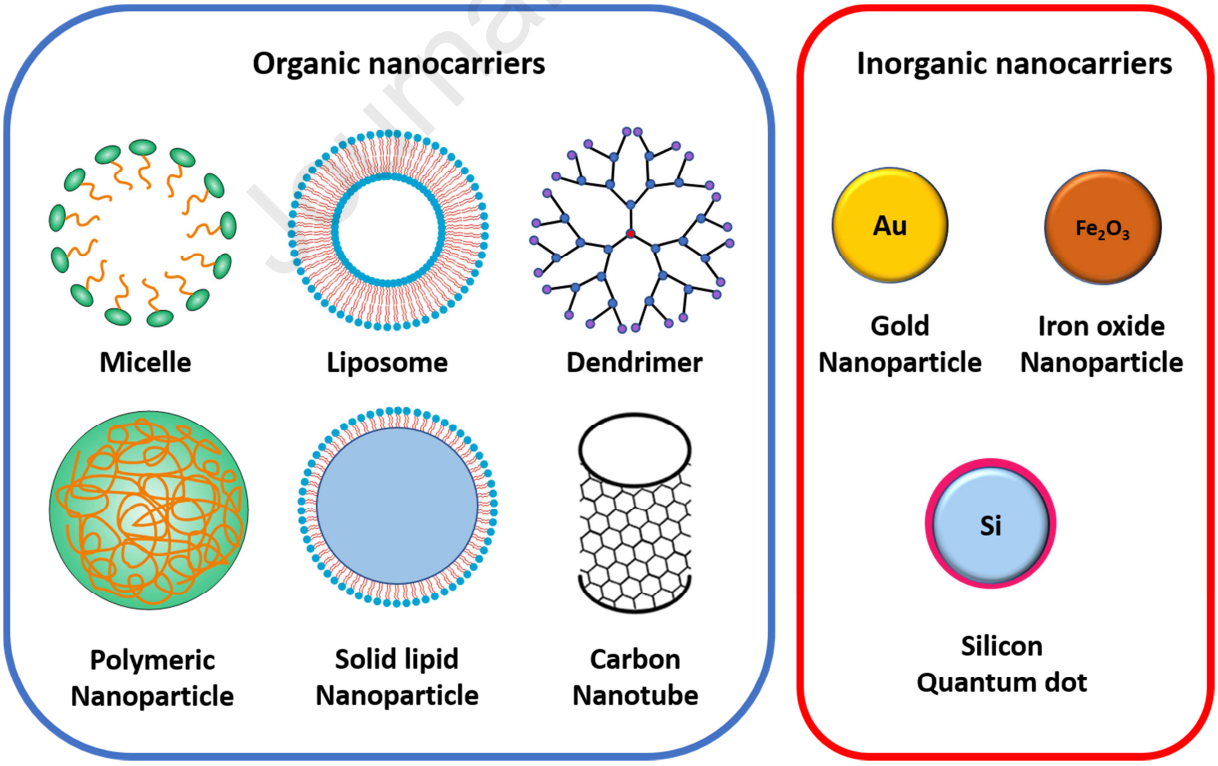

Figure 3. Schematic representation of major nanodelivery systems for cancer treatment

5.1 Nanodelivery of AITC

The obstacles to the direct clinical application of AITC include poor aqueous solubility, instability at high temperature, and susceptibility to degradation by nucleophilic molecules such as H_2O or those containing -OH, -SH and -NH_2 groups [113, 114]. ATIC is easily hydrolyzed to allylamine in aqueous solution and was reported to decompose by up to 75% when incubated in water at 37^{o}C for 10 days [115]. Several encapsulation methods using nanodelivery systems have been employed to protect AITC against degradation and enhance targeted delivery to cancer cells.

Li *et al.* prepared an oil-in-water AITC nanoemulsion by the emulsion inversion point (EIP) method [116]. They studied the optimal hydrophilic–lipophilic balance (HLBop) value of surfactants containing Tween 80 and Span 80 and synthesized nanodroplets with diameters of 137–215 nm. Over a 6.5 month period, the nanodroplet sizes and the counts (polydispersity indication) decreased only slightly by 4–13% indicating the nanoemulsion was very stable in aqueous storage conditions. Moreover, the nanoemulsion demonstrated superior protection against AITC degradation (78% remaining after 60 days at 30°C), as compared with zein protein nanoparticles (undetectable after 60 days storage) as well as non-encapsulated aqueous dispersion (4% remaining after 60 days at 30°C). Their work suggests that nanoemulsion is a promising approach to enhance the aqueous stability of AITC and may also be applicable to the stabilization of other chemicals that are susceptible to nucleophilic degradation in aqueous systems.

In the studies of Encinas-Basurto *et al.*, AITC has been encapsulated into poly (lactic-glycolic acid) nanoparticles (PLGA NPs) to extend its shelf life and enhance its antiproliferative properties [117]. The AITC-loaded PLGA NPs were synthesized using a simple emulsion-solvent evaporation method. The obtained AITC PLGA NPs had a particle size of 200 ± 3 nm with a polydispersity > 2%, and zeta-potentials of -8.0 ± 0.9 mV. These nanoparticles demonstrated reduced degradation, volatility and an extended shelf life when compared with free AITC. *In vitro* cell viability and uptake of AITC PLGA NPs in cancerous HeLa and MDAMB-231 cells showed that the sustained release of AITC from polymeric NPs resulted in a significant toxicity towards tumor cells. Thus, PLGA NPs could be used as protective nanodelivery systems to enhance the biological activity of AITCs. The same group subsequently modified the surface of AITC PLGA NPs further using a specific antibody to target the Epidermal Growth Factor (EGF) receptor overexpressed on the epithelial squamous carcinoma cells [118]. AITC-loaded PLGA NPs showed more effective anti-cancer properties when compared with free AITC. The attachment of the anti-EGFR antibody on the NP's surface further enhanced their cytotoxicity towards the tumor cells. This targeting ability was additionally tested by co-culturing cervical HeLa cells (EGFR low) and A431 cells (EFGR overexpressed). The antibody bonded NPs were solely localized in A431 cells, whereas non-functionalized (no antibody bonding) NPs were distributed randomly between both cell types and at much lesser extents. These findings demonstrated a successful nanodelivery strategy that not only enhances the delivery of natural anti-cancer compounds to the tumor tissue, but also specifically targets the tumor cell receptors followed by tumor sensitization.

Liu *et al.* took a different approach to make AITC-conjugated silicon quantum dots (AITC-SiQDs) for the treatment of liver cancer [119]. To prepare the AITC-SiQDs, hydrogen terminated SiQDs were synthesized by galvanostatic anodization of a porous silicon layer [120], followed by a reaction with allyl bromide. The bromine-functionalized QDs were further reacted with potassium thiocyanate to form isothiocyanate-functionalized SiQDs, i.e., AITC-SiQDs. The obtained AITC-SiQDs were sphere shaped

and around 4 nm in diameter. The AITC-SiQD size is much smaller than other AITC polymeric NPs but was in agreement with the SiQD size in previous study [120]. The resultant QDs showed similar anti-cancer properties compared to free AITC at high doses while avoiding the low doses stimulation effect. After one hour of incubation with AITC-SiQDs, the intrinsic fluorescence of SiQDs was detectible inside HepG2 cells. The fluorescent signal optimum at around 12 hours indicating the internalization of a large number of AITC-SiQDs. In addition, AITC-SiQDs exhibited a lower but long-lasting activation of Nrf2 which correlated with their levels of cellular uptake. These findings suggested the SiQD nanodelivery system could be a promising platform to avoid the biphasic effect of free AITC, and that AITC-SiQDs have the potential to be used in anti-cancer treatment.

One of the notable works performed by Chang *et al.* was synthesized the water-soluble AITC NPs using oil-in-water (O/W) microemulsion [121]. The obtained AITC NPs were about 9.4 nm and stable during heating up to 110 °C or under three freeze-thawing cycles in DMEM. AITC NPs effectively inhibited proliferation and migration of HT1376 cells, which showed improved anti-cancer and antioxidant activities when compared to free AITC. Moreover, compared to AITC alone and empty NPs, these AITC NPs possessed a better inhibitory effect on lipopolysaccharide (LPS)-induced TNF-α, IL-6, nitric oxide (NO) and inducible nitric oxide synthase (iNOS) production in RAW 264.7 macrophage cells. These results demonstrated the potential of AITC nanoemulsion as a therapeutic agent for the treatment of bladder cancer.

Both nano and micro emulsions have been used to improve solubility and stability of AITC in biological systems. The obtained AITC nanoparticles demonstrated improved anti-cancer and antioxidant activities when compared to free AITC. The attachment of targeting motifs to the nanoparticle surface could further enhance their efficacy towards tumor cells.

5.2 Nanodelivery of BITC

In recent years, BITC has been of special interest due to its distinct *in vitro* and *in vivo* anti-cancer abilities, and antiproliferative and antimicrobial properties [122-124]. Like AITC, due to its strong electrophilic nature, BITC can easily reacts with nucleophiles under physiological conditions. It also has a characteristic pungent smell, poor solubility, limited bioavailability and is strongly volatile. Such properties impede its potential as an effective anti-cancer agent while the research community is still struggling to find an appropriate delivery system to overcome all its shortcomings. Nanoencapsulation methodology could potentially increase BITC absorption, stability, activity, and decrease its excretion from the circulatory system. Furthermore, such nanodelivery systems may have the ability to enhance BITC therapeutic performance and reduce toxicity, ease of handling and improve its shelf live.

Qhattal *et al.* reported an oil-in-water nanoemulsion system to entrap BITC [125]. The nanoemulsion was prepared by either spontaneous self-nanoemulsification or homogenization–sonication. Both the nanoemulsion achieved high encapsulation efficiency (EE) of BITC with low polydispersity and good colloidal stability. In addition, the BITC nanoemulsion showed enhanced aqueous solubility as compared to pure BITC. They were also easily taken up by human cancer cells A549 and SKOV-3 and inhibited cancer cell growth. Later, Kumar *et al.* encapsulated BITC in a nanoemulsion through ultrasonication using Tween 80 or decyl-β-d-glucopyranoside as stabilizer [126]. The average size of nanoemulsion particles were found to be 31.68 ± 1.78 nm and a near complete EE value of 99%. The nanodelivery system showed good

stability at pH 5, 7 and 9. Under highly acidic or basic conditions, i.e., at pH 2 and 12, the size of NP increased abruptly as the storage time increased. The occurrence of aggregation might be due to ineffective electrostatic repulsion and hydrolysis [127, 128]. The BITC nanoemulsion showed improved anti-cancer activity against breast cancer cell lines as compared to its bare administration.

In a recent research, Uppal *et al.* developed cerium oxide nanoparticles (Ceria) based drug delivery system using ultrasonic nanoemulsification [129]. The synthesized NPs (size ≤5 nm) were then loaded with BITC. The average particle size of BITC Ceria NPs were 5.1 ± 0.8 nm with zeta-potential value of −14.92 ± 1.1 mV. The formulation achieved high encapsulation efficiency and a good drug loading. Compared to Ceria alone, these NPs inhibited cell viability more effectively in MDA-MB 231 cells. The same group has also produced a new rhamnolipid based nanoemulsion system employing the heating stirring-sonication method [130]. The optimized nanoemulsion exhibited good long-term stability, very high encapsulation efficiency, sustained release and increased cytotoxicity against MDA-MB 231 cells as compared to BITC alone.

Overall, nanoemulsification is the main synthesis method used for entrapping BITC toin nanodelivery systems. These BITC nanoemulsionsnanoemulsion show enhanced absorption and bioavailability as well prolonged shelf-life. High encapsulation efficiency along with a sustained release can be achieved by nanoemusionsnanoemusion. Finally, compared to its free form, BITC nanoemulsion showed improved anti-cancer activity against several cancer cell lines.

5.3 Nanodelivery of PEITC

PEITC, a naturally occurring isothiocyanate, has been reported to have good anti-cancer activity in both *in vitro* and *in vivo* models [74, 131, 132]. Several studies have reported that PEITC could inhibit proliferation and induce apoptotic cell death in several cancer cell lines, including breast cancer [31], prostate cancer [133], cervical cancer [134], lung cancer [74] and liver cancer [30, 135, 136]. Several studies have also suggested that PEITC can sensitize cancer cells to chemotherapy drugs such as cisplatin and doxorubicin (DOX), demonstrating a synergistic effect. Nanontechnology has allowed the development of new nanodelivery systems that can be used to explore such potential in cancer treatment.

Pasqua *et al*. showed that PEITC could enhance the efficacy of CDDP in non-small cell lung cancer [90]. Based on this concept, liposomal nanoparticles containing both PEITC and CDDP have been developed [137]. The resultant NPs were approximately 130 nm, with a high negative zeta-potential of -65 mV. The drug loading of CDDP and PEITC were approximately 1% w/w each. In NCI-H596 NSCLC cells, liposomes containing a combination of CDDP and PEITC showed the greatest toxicities among all treatments. These liposome NPs are also highly stable in circulation. The protective formulation allows synergistic treatment of CDDP and PEITC to reduce the NSCLC tumor more effectively with fewer side effects than free CDDP and PEITC treatments. Thus, they could be a promising system for clinical development. Sun *et al.* has further expanded their work to use a lesser amount of CDDP than the previous formulation (1:3 ratio of CDDP to PEITC compared to 1:2 ratio of CDDP to PEITC) [138]. The optimized nanoliposome formulation was much more toxic towards both A549 and H596 human NSCLC cell lines than the WI-38 and BEAS-2B human normal lung cell lines. These findings suggest that combined PEITC and CDDP nanoliposomes have good specificity and selectivity toward tumor tissues and could provide a promising cancer treatment.

Pulliero *et al.* evaluated the ability of nanoliposomes to modify the pharmacodynamics of PEITC [139]. The nanoliposomes with a mean size of 70 nm were synthesized using (1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA), cholesterol and D-alpha-tocopheryl polyethylene glycol succinate (TPGS) by a simple ethanol injection method. Their data suggested that PEITC NPs significantly increased the ability of PEITC to protect against cigarette smoke condensate induced DNA damage and enhanced its ability to activate protective apoptosis in bronchial epithelial cells both *in vitro* and *ex vivo*.

Seema *et al.* designed a PEITC nanocomposite using graphene oxide (GO) as nanocarrier [140]. GO has a unique graphene basal plane that could be modified with functional groups such as carboxylic (COOH), hydroxyl (OH) and epoxides groups etc. These functional groups enable further functionalization of GO with drug loading and biomolecules (e.g., RNA/DNA). The nanocomposite was around 6 nm and exhibited sustained release of PEITC under both physiological and intracellular lysosomal conditions. Cell viability assays suggested that the nanocomposite has much better anti-cancer activity against HepG2 liver cancer cells when compared to the crude PEITC and was also found to be nontoxic to normal 3T3 cells. This study demonstrated that PEITC conjugated GO could be an efficient nanodelivery system for pharmaceutical applications in cancer therapies.

In a recent study, Wu *et al.* established a complex black phosphorus nanosheets (BPN) based nanodelivery system for simultaneously delivery of DOX and PEITC. The BPNs/DOX was first coated with a polydopamine (PDA) layer through dopamine polymerization, followed by binding of polyethylene glycol–amine (PEG-NH2) via the Schiff base reaction [141]. The BPNs-PDA-PEG/DOX was then conjugated with PEITC and this system was shown to effectively decrease mutant p53 levels in resistant cancer cells and enhance DOX sensitivity. Furthermore, the phenolic hydroxyl groups of BPNs-PDAPEG-PEITC/DOX can chelate manganese ions (Mn^{2+}) which exhibit a strong T1 contrast in magnetic resonance imaging (MRI). Thus, BPNs-PDA-PEG-PEITC-Mn/DOX could be used as theragnostic agent for MRI-guided photothermal therapy/photodynamic therapy (PTT/PDT) as well as synergistic chemotherapy to overcome drug-resistance. Both *in vitro* and *in vivo* experiments have demonstrated the BPNs-based drug delivery system has effectively inhibited drug resistance tumor with minimal side effects. This triple synergistic nanodelivery system has a great application potential in the treatment of MDR breast cancer.

Several distinct nanodelivery systems have been developed for PEITC including nanoliposomes, nanocomposite using graphene oxide and black phosphorus nanosheets. Nanodelivery of the combinational therapies of PEITC with cisplatin or doxorubicin exhibit enhanced anti-cancer efficacy with reduced side effects. These synergistic nanodelivery systems have good specificity and selectivity towardstoward tumor tissues and could provide a promising application potential in the treatment of non-small cell lung cancer and breast cancer.

5.4 Nanodelivery of SFN

Sulforaphane is one of the most studied natural ITCs and has significant antioxidant, anti-inflammatory and anti-cancer activities. *In vitro* and *in vivo* studies have confirmed the chemoprotective effects of SFN in various tumors, including those of the breast, prostate, lung, and colon through variety of molecular mechanisms [33, 142-144]. Moreover, a number of studies have suggested that SFN may target cancer stem

cells (CSCs) in different types of cancer through activation of microRNA-124 (miR-124), modulation of NF-κB, sonic hedgehog (SHH), epithelial-mesenchymal transition and Wnt/β-catenin pathways [145-147]. However, due to high lipophilicity, poor aqueous solubility, and low stability due to sensitivity to oxygen, heat and alkaline conditions, the therapeutic potential of SFN is greatly hindered. To enhance its aqueous solubility and bioavailability, several different nano formulations of SFN have been developed, including polymeric nanoparticles, micelles, liposome, carbon dots, metallic and magnetic nanoparticles. In addition, using an advanced nanodelivery system, SFN can be combined with other phytochemicals and chemotherapies to achieve synergistic effects towards tumor cells, e.g., CUR, DTX and CDDP.

Huang *et al* designed a combined docetaxel and sulforaphane loaded poly (D, L-lactide-coglycolide)/hyaluronic acid (PLGA-b-HA) based nanoparticle [148] to simultaneously target differentiated breast cancer cells (DBCCs) and breast cancer stem cells (BCSCs). Both *in vitro* and *in vivo* analyses showed the DTX and SFN combined NPs have enhanced cytotoxicity toward both DBCCs and BCSCs compared with the free drugs. In addition, the self-renewal ability of BCSCs was strongly inhibited by the SFN-loaded NPs *in vivo*, and the inhibition of BCSCs *in vitro* was probably caused by down-regulating beta-catenin expression. The combination of SFN and DTX loaded NPs demonstrates their great therapeutic potential in the treatment of breast cancer.

Manjili *et al* fabricated novel SFN encapsulated gold-coated iron oxide nanoparticles [149]. The surface of gold-coated iron oxide NPs was functionalized with thiolate polyethylene glycol-folic acid and thiolate polyethylene glycol-FITC for SFN loading. The average diameter of the synthesized NPs was approximately 38 nm. The SFN loaded NPs were more cytotoxic than the no-loading NPs in MCF-7 cells as proved by cell viability and apoptosis assay. In addition, the expression rates of the anti-apoptotic genes (bcl-2 and bcl-xL) in MCF-7 cells were significantly decreased by exposure to SFN NPs. Overall, this study has exhibited a novel design of gold-coated iron oxide NPs, which could be developed as a potential nanodelivery system to improve the efficiency and stability of SFN as an anti-cancer therapy.

Danafar *et al.*, have established a micellar nanodelivery system using monomethoxypoly (ethylene glycol)-poly (varepsilon-caprolactone) (mPEG-PCL) [150]. SFN was encapsulated within mPEG-PCL micelles through a single-step nano-precipitation method. The obtained micelles have spherical shapes with size of 107 nm. The encapsulation efficiency of SFN was 86±1.58% and they also achieved a remarkable level of sustained release *in vitro*. The SFN loaded nanomicelles significantly inhibited viability and induced apoptosis in MCF-7 cells, which suggests that SFN loaded nanomicelles could be an effective breast cancer treatment strategy in the clinic. The same group have developed another micellar NP using a tri-block copolymer poly (caprolactone)-poly (ethylene glycol)-poly (caprolactone) (PCL–PEG–PCL) [151]. Micelle characterization and stability, the particle size and their morphology were determined by DLS and AFM. The loading efficiency of SF was 19.33 ± 1.28%. The resultant micelles were the same size as the mPEG-PCL micelles. The results of *in vivo* experiments indicated the SFN loaded micelles prolong the circulation period and increase the therapeutic efficacy of SFN. Later, this group has developed a combined anti-cancer nanodelivery strategy using curcumin (CUR), sulforaphane and PEGylated gold coated Fe_3O_4 magnetic nanoparticles (PEGylated Fe_3O_4@Au NPs) [152]. Both CUR and SFN have been entrapped in the metallic NPs to improve their bioavailability and solubility. The resultant NPs were around 20 nm, mono-dispersed in water, and with a high drug-loading capacity. The combined CUR and SFN NPs have demonstrated an enhanced synergistic antitumor effect in SK-BR-3 cells when compared to free CUR

and free SFN. The nanodelivery systems can increase therapeutic effects of SFN and CUR by apoptosis and necrosis induction as well as inhibiting migration in SK-BR-3 cells. The CUR and SFN combined NPs have been developed further using four times larger carrier NPs to increase their drug-loading capacity [153]. The resultant NPs also exhibited enhanced cytotoxicity and therapeutic effects toward MCF-7 cells.

Soni and Kohli have reported sulforaphane-loaded gold nanoparticles (SFN-GNPs) as a potential nanomedicine against solid tumors [154]. The size of SFN-GNPs has been optimized by four-factor three-level Box-Behnken experimental design. The optimized SFN-GNPs had a spherical shape with an average particle size of 147.23±5.321 nm, the zeta potential of -12.7±1.73 mV, EE value of 83.17±3.14% and drug loading of 37.26±2.33%. The SFN-GNPs have demonstrated enhanced retention at tumor sites as well as significant inhibition of tumor growth as compared to free SFN. In another study, Krug *et al.* synthesized sulforaphane-modified selenium nanoparticles in a simple aqueous-phase redox reaction through reduction of selenite with ascorbic acid [155], with the SFN presence on the selenium NP surface forming an adlayer. The cytotoxicity, biodistribution and excretion of resultant conjugate NPs have been investigated *in vivo* on male Wistar rats. The results suggest conjugated NPs did not induce observable negative symptoms in the rats. After 24 h, about 46% of the administered NPs were eliminated from the body in urine and feces, with the remainder mainly accumulated in the liver. The results from *in vitro* cytotoxicity assays suggested that SFN-conjugated NPs have considerable anti-cancer activity as well as selectivity toward cancer cells, which could be beneficial for the cancer treatment.

Mielczarek *et al.,* have evaluated a novel combination of SFN and doxorubicin entrapped in nanosized liposomes [81]. The SFN and DOX nanoliposomes were quickly taken up by MDA-MB-231 cells, followed by the release of the drug combination from the lysosomes. The *in vitro* interaction analysis using the Chou-Talalay approach suggested a high synergistic activity had been achieved by the drug combination, which enabled a favorable reduction in cytostatic dosage and an increase in cancer treatment efficiency.

Lu *et al.,* have built a multifunctional nanosystem based on SFN-conjugated carbon dots (SFN-CDs) for targeted imaging and inhibiting of EGFR-overexpressing cancer cells [156]. The SFN-CDs are synthesized by grafting SFN onto the amino-rich yellow fluorescent carbon dots. The obtained SFN-CDs have an average size of 5.33 nm. The *in vitro* toxicity experiments demonstrated that the SFN-CDs could significantly inhibit the proliferation of EGFR-overexpressing A549 lung cancer cell compared to BEAS-2B normal lung cells. As a result, SFN-CDs can be used as a potential nanodelivery system for both diagnostic and therapeutic functions in cancer management.

A recent study performed by Xu *et al.,* utilized a novel combination of CDDP and SFN encapsulated in mPEG-PLGA polymersome [157]. The CDDP was modified with poly (gamma-l-glutamic acid) (γ-PGA) to produce a water-soluble CDDP derivative. SFN was encapsulated in the outer layer of polymersome which could be used to achieve an efficient glutathione (GSH) depletion, to improve the accumulation of CDDP in cancer cells. The CDDP and SFN combined NPs were more effectively internalized and could significantly reduce GSH content in breast cancer cells as compared to the free drugs, which resulted in a significant increase in DNA damage-induced apoptosis. Moreover, in an orthotopic breast cancer model, the nanoparticles achieved a significantly higher tumor accumulation and exhibited a more powerful antitumor activity. Overall, this SFN-based nanodelivery system holds great potential to enhance the sensitivity and therapeutic efficacy of Pt-based chemotherapy.

In summary, natural ITCs are not only the important anti-cancer therapeutic candidates but also can interact with other chemotherapies and phytochemicals to achieve synergistic antitumor effects. All above that different materials and forms of nanodelivery systems have many positive effects on ITCs biomedical applications. Nanoformulations could significantly improve the solubility, stability, and bioavailability of native ITCs, as well as minimizing their shortcomings (adverse effects). The anti-cancer nanodelivery system of natural ITCs is summarized in Table 2.

660 Table 2. A summary of nanodelivery system for natural isothiocyanates

Type	Isothiocyanates	Carrier	Preparation method	Size(nm)	Encapsulation efficiency (EE)/Drug loading (DL) (%)	Cancer type	*In vitro*/*In vivo* model	Ref.
Micelle	AITC	mineral oil/Tween 80/Span 80 zein/caseinate	Emulsion inversion point (EIP) method self-assembling liquid–liquid process	137–215 nm	/	/	/	[116]
Polymeric nanoparticle	AITC	PLGA	Emulsion-solvent evaporation	200 ± 3 nm	EE 65.8% DL 24.9%	Cervical cancer Breast cancer	HeLa, MDA-MB-231 and ARPE cells	[117]
Polymeric nanoparticle	AITC	PLGA	Emulsion-solvent evaporation	200 nm	/	Cervical cancer Skin cancer	HeLa and A431 cells	[118]
Quantum dot	AITC	silicon quantum dots	Reacting the hydrogen terminated SiQDs with allyl bromide and then potassium thiocyanate	4nm		Liver cancer	HepG2 cells	[119]
Nanoemulsion	AITC	alkali-treated gelatin, polysaccharides and ***κ***-carrageenan	Oil-in-water microemulsion	9.5 ± 0.3 nm	/	Bladder cancer	HT1376 and RAW 264.7 cells	[121]
Nanoemulsion	BITC	medium-chain	self-emulsification	242 ± 3 nm	EE 77%	Colon cancer	Caco-2, SKOV-3,	[125]

		triglycerides/ Tween 80: Transcutol flaxseed oil/egg PC	homogenization–sonication	117 ± 27 nm	EE 70%	Ovarian cancer Lung cancer	A549 cells	
Nanoemulsion	BITC	lemon oil + miglyl 812	Ultrasonication assisted cavitation	44.13 ± 3.22 nm	EE 99%	Breast cancer	MDA-MB 231	[126]
Metallic nanoparticle	BITC	cerium oxide	Ultrasonic nanoemulsion and then drug loading by incubation	5.1 ± 0.8 nm	EE 89.06 ± 2.3% DL 19.80 ± 1.54%	/	/	[129]
Nanoemulsion	BITC	rhamnolipid:Tween -80:miglyol-812:PE G200	Heating stirring-sonication method with GRAS ingredients	65.85 ± 1.34 nm	EE 99.92 ± 0.3% DL 1.26 ± 0.02%	Breast cancer	MDA MB 231 cells	[130]
Liposome	PEITC plus cisplatin	Dipalmitoylphospha tidylcholine (DSPC) and L-α-phosphatidylgl ycerol (EPG)	Film hydration	120-140 nm	DL ~1%	Non-small cell lung cancer	H596 cells	[137]
Liposome	PEITC	DOTMA/cholestero l/TPGS	Ethanol injection	70.0±5.8nm	/	Lung cancer	H727 cells	[139]
Nanocomposite	PEITC	graphene oxide	Drug loading by incubation	6nm	/	Liver cancer	HepG2 and 3T3 cells	[140]
Liposome	PEITC plus cisplatin	DSPC	Film hydration	173.4 ± 26.8 nm	EE 3.24 ± 0.47% DL 34.7 ± 3.2%	Non-small cell lung cancer	A549, H596, WI-38 and BEAS-2B cells	[138]
Nanosheet	PEITC plus doxorubicin	black phosphorus	Liquid exfoliation, dopamine	312 nm	/	Breast cancer	MCF-7 and MCF-7/ADR cells	[141]

			polymerization and π-π stacking				female nude mice	
Polymeric nanoparticle	SFN plus docetaxel	PLGA/hyaluronic acid	Modified solvent-dialysis method	179.3 ± 2.8 nm	DL 5.68 ± 0.96%	Breast cancer	MCF-7 cells Female Balb/c nude mice	[148]
Magnetic nanoparticle	SFN	gold-coated iron oxide nanoparticle	Co-precipitation method followed by coating with gold NPs, then drug loading by sonication and overnight incubation	34.59 ± 0.8 nm	DL 56%	Breast cancer	MCF-7 cells	[149]
Micelle	SFN	mPEG–PCL	Nanoprecipitation	~118 nm	EE 86 ± 1.58% DL 20 ± 1.78%	Breast cancer	MCF-7 cells	[150]
Micelle	SFN	PCL-PEG-PCL	Nanoprecipitation	107 nm	EE 87.1 ± 1.58% DL 19.33 ± 1.28%	Breast cancer	MCF-7, 4T1 and MCF10A cell Female Balb/c nude mice	[151]
Magnetic nanoparticle	SFN	PEGylated gold coated iron oxide nanoparticle	Co-precipitation method followed by coating with gold NPs, then drug loading by sonication and overnight	<30 nm	EE 72.20 ± 0.18 % DL 15.74 ± 0.015 %	Breast cancer	SK-BR-3 cells	[152]

			incubation					
Magnetic nanoparticle	SFN plus Curcumin	PEGylated gold coated iron oxide nanoparticle	Co-precipitation method followed by coating with gold NPs, then drug loading by overnight incubation	80.57 nm	EE 81.20 ± 0.18% DL 16.74 ± 0.015%	Breast cancer	MCF-7 cells Balb/c mice	[153]
Metallic nanoparticle	SFN	gold nanoparticle	Electrolysis, then drug loading by incubation	147.23 ± 5.321 nm	EE 83.17 ± 3.14% DL 37.26 ± 2.33%	Breast cancer Colon cancer	B16-F10, MCF-7, SW-620 and Caco-2 cells Male mice	[154]
Solid nanoparticle	SFN	selenium nanoparticle	Nanoprecipitation	80.2 ± 18.6 nm	DL 2.5%	Breast cancer Colon cancer Prostate cancer	MCF-7, Caco-2, HT-29, PC-3, MCF-10A and CRL-1790 cells	[155]
Liposome	SFN plus doxorubicin	1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC)	Film hydration	115 ± 8 nm	487.5 mg/g	Breast cancer	MDA-MB-231 and MCF-7 cells	[81]
Carbon dot	SFN	carbon dot	Hydrothermal synthesis, then drug loading by conjugation	5.33 nm	/	Lung cancer	A549 and BEAS-2B cells	[156]
Polymersome	SFN plus CDDP	mPEG-PLGA	Double emulsion	~98.2 nm	EE 58.7 ± 4.5%	Breast cancer Liver cancer	MCF-7 and HepG2 cells BALB/c nude mice	[157]

661

6 Therapeutic advantages of nanodelivery systems

Nanotechnology has been widely used in the development of new strategies for cancer management. It is playing an important role in providing both diagnostics and therapeutics for cancer. Nanodelivery systems have several therapeutic advantages over conventional administration of therapeutic agents including: an increased half-life, extended circulation time in the human body, enhanced penetration to the disease site, and improved pharmacokinetic clearance [158]. A successful nanodelivery system can be characterized by optimized encapsulation and drug loading features, sustained release of therapeutic agent at the delivery site, long storage life, and high therapeutic efficacy with no or minimized side effects [159]. In this review there are a number of featured nanodelivery system have been developed for delivery of natural ITCs as potential anti-cancer therapies. There are both solid systems such as quantum dots, carbon dots, and metallic and magnetic nanoparticls, as well as liquid systems such as liposomes, nanoemulsions, and polymersomes. Compared to the traditional forms of ITC administration, nanoparticle delivery systems offer many advantages in terms of cancer prevention and therapeutics which are described in more detail in subsections below.

6.1 Increase solubility and bioavailability

Several research groups have developed polymeric systems to encapsulate AITC and SFN [117, 118, 148, 150, 157]. Nanodelivery systems are formed by amphiphilic PLGA or PCL consisting of both hydrophilic and hydrophobic monomers, which self-assemble into a spherical structure in aqueous solution. ITCs are either dispersed into the polymer matrix or encapsulated in polymer. The resultant NPs are in the range of 100-200 nm with good drug loading capacities. Oil-in-water nanoemulsion has also been used to increase solubility and bioavailability of AITC and BITC [121, 125, 126, 130]. The obtained droplet size fall in the range of 10-250 nm and an encapsulation efficiency of 99% has been achieved using this nanodelivery method. Liposomes are another highly versatile nanodelivery system widely used in cancer treatment. Nanoliposomes represents nanosized self-assembled lipid vesicles which consist of phospholipid bilayers entrapping one or more therapeutic agents. The solubility and bioavailability PEITC have been significantly improved by this method [137, 138].

6.2 Enhanced stability

Another major advantage that nanotechnology offers is the ability to improve the stability of therapeutic agents which are sensitive, for example, to light, temperature, or pH. ITCs can be absorbed or conjugated onto the surface of a solid NP, which provides a strong scaffold to support them. They can also be encapsulated inside a NP, or dissolved within the NP matrix, which can shield them from degradation and protect them from a critical environment thus enhancing their potential pharmaceutical properties. ITC nanodelivery systems are reported to have low polydispersity and good colloidal stability that can last for several weeks [116, 117]. For example, AITC NPs have been reported to be stable when heated up to 110 °C and could also withstand three freeze-thawing cycles [121]. BITC NPs showed good long-term stability in a physiological environment and at a range of pH [125, 130]. Notably, most ITC NPs are stable at physiological conditions (pH 7.4), but release ITCs readily under acidic conditions, and thus they can be more efficiently made available in cancerous cell environments [152].

6.3 Improved tumor targeting

Due to the leaky vasculature of the tumor tissue, long-circulating NPs can accumulate more readily at tumor sites than in normal tissues [160]. Meanwhile, impaired lymphatic drainage also hinders NPs excretion from tumor tissue, resulting in further enhancement of NP accumulation in tumor tissues [161]. This is called the enhanced permeability and retention (EPR) effect [162], which has now been widely applied in the design of NP based drug delivery system for cancer treatment. EPR is widely considered to be a major driving force for NPs to reach and accumulate in the tumor tissue, through either passive or active targeting [163]. In general, EPR is most effective with NPs in the size range of 20-200 nm, which are more likely to show improved tumor targeting. Notably, the penetration of NPs in tumors depends on the size of the NP. The smaller the size of the NP, the greater the penetration throughout the tumor. It has been demonstrated that 100 nm NPs remain close to vasculature whereas 20 nm NPs distribute throughout the tumor [164]. Moreover, NP uptake based on EPR may also vary depending on the type of tumors [165, 166]. Most of the lipid nanodelivery systems developed for ITCs such as polymeric NP, micelle and liposome, range in size from 100 nm to 200 nm, and thus have enhanced tumor accumulation, resulting in significantly improved anti-cancer efficacy with minimized side effects, e.g. SFN loaded PLGA NP [148, 157].

6.4 Minimize the risk of hormesis

In toxicology, hormesis is defined as a biphasic dose response to an exogenous or endogenous stimuli with low dose stimulation and high dose inhibition. Many drugs have been reported to exhibit such contradictory effects, also known as “biphasic dose responses” [167], which has shown significance in establishing the modality of a drug. Several studies have reported that ITCs kill cancer cells at high doses but promote cancer cell proliferation and survival at low doses [168-170]. Thus, it is crucial to optimize the anti-cancer effects and minimize the potential risks of ITCs in cancer prevention and treatment. NP based delivery systems featuring targeted delivery of ITCs could achieve high dose ITC accumulation at tumor sites, which can eliminate the unfavorable low dose stimulation effect in cancer treatments [119].

6.5 Combinational therapy

Simultaneous delivery of different therapeutic agents to the same tumor cells are known as co-delivery systems [171]. Such co-delivery systems could be easily achieved using recently developed nanotechnology. By the inclusion of extra components such as targeting motifs and imaging probes, an efficient multifunctional nanodelivery system could then be formed. Several combined nanodelivery systems have been developed so far incorporating ITCs and other phytochemicals e.g., curcumin or chemotherapeutics, e.g., CDDP in a single system. Combined SFN and CUR NPs showed significantly increased therapeutic effects toward breast cancer cells [153]. Combined SFN and DTX NPs simultaneously targeting DBCCs and BCSCs exhibited significantly improved antitumor efficacy compared to free drugs [148]. Encapsulating both SFN and DOX in nanoliposomes resulted in high synergistic activity towards triple negative breast cancer cells [81]. Co-delivery of SFN and CDDP by PLGA NPs largely improved the accumulation of CDDP at tumor tissue, which resulted in more powerful anti-tumor activity.

In summary, the application of nanotechnology in delivery of ITCs for the prevention and treatment of cancer could efficiently improve aqueous solubility and bioavailability of ITCs, extend their shelf life,

enhance the therapeutic efficacy by promoting their accumulation in tumors, and additionally have the advantage of eliminating hormetic effects. At the same time, combinational therapy of ITCs with other antitumor agents can also be achieved by these nanodelivery systems which can demonstrate synergistic effects on cancer treatment.

7 Conclusions and future perspectives

Cancer is one of the most common worldwide public health problems [24] and is in the world's top ten diseases which seriously affect human physical health. More than half of the anti-cancer drugs in clinical use are natural products or their derivatives [172] and many are plant-derived phytochemicals. Over two decades, natural ITCs from vegetableshave attracted extensive research interest for cancer prevention and treatment. Many studies have confirmed that ITCs have significant antioxidant, anti-inflammatory and anti-cancer effects *in vivo* and *in vitro*.However, the epidemiological evidence regarding the consumption of dietary ITCs as chemopreventive agents have been inconsistent, which presumably due to the hormetic effect of ITCs where high doses kill cancer cells, but low doses promote cancer cell proliferation. Apart from the aforementioned, low solubility, low bioavailability, low stability and short shelf lives; there are other factors which impede the clinical use of ITCs. T application of nanotechnology provides a new idea for further development and utilization of ITCs. Current research progress suggests that nanoformulation of ITCs can improve their solubility, enhance bioavailability, provide protection against degradation, and achieve controlled and targeted release of ITCs at tumor sites.

One important challenge infuture design of ITC nanodelivery systems is in the development of novel multifunctional nanomaterials that possess properties allowing them to deliver therapeutics across biological barriers and able to target specific types of tumor tissues in the body. Most of the studies took a passive nanodelivery approach controlled by the phenomenon of EPR. Only a few studies utilized targeting ligands, also known as ‘active targeting,’ to selectively deliver ITCs to tumor sites through ligand-receptor interactions. In the active delivery mode, certain RNAs, peptides, carbohydrates, and small metabolite molecules could be used as biomarkers to reach particular target sites [173]. In addition, stimuli-responsive components that can be triggered by specific stimuli (e.g., temperature, pH, or enzymes) could also be incorporated into the nanodelivery system to achieve the controlled release of the therapeutic agents at targeted sites [174]. Apart from surface features, particle size is also an important parameter of NPs which determine its pharmacokinetics, cell entry route, and interaction with the immune system [175]. In this review, we found that the size of ITC NPs varied from 4 nm up to over 300 nm. In principle, NPs in the size range of 20-200 nm can be delivered to the tumor site through the EPR effect. However, the *in vivo* delivery of NPs also depends on the types of tumor and their local conditions [165, 166]. Tumors with increased interstitial fluid pressure (IFP) are harder to permeate by passive targeting. It is also reported that the smaller the size of NP, the greater the penetration throughout the tumor. NPs with a mean size less than 100 nm are ideal for even distribution throughout the tumor. Thus, special attention should be paid to control the NP size for efficient drug delivery. Most of the reported studies lack *in vivo* evaluation of the pharmacokinetic and pharmacodynamic properties of ITC NPs. So far, none of the ITC nanodelivery systems have proceeded into the clinical trials, which suggests more preclinical work is needed to verify the safety and efficacy of nano formulated ITCs as a new cancer therapy.

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References

[1] C. Kala, S.S. Ali, N. Ahmad, S.J. Gilani, N.A. Khan, Isothiocyanates: A review, Pharmacogn. Res. 5(2) (2018) 71-89.

[2] P. Gupta, B. Kim, S.H. Kim, S.K. Srivastava, Molecular targets of isothiocyanates in cancer: Recent advances, Mol. Nutr. Food Res. 58(8) (2014) 1685-1707.

[3] D. Angelino, E. Jeffery, Glucosinolate hydrolysis and bioavailability of resulting isothiocyanates: Focus on glucoraphanin, J. Funct. Foods 7 (2014) 67-76.

[4] Y. Zhang, P. Talalay, C.G. Cho, G.H. Posner, A major inducer of anticarcinogenic protective enzymes from broccoli: Isolation and elucidation of structure, Proc. Natl. Acad. Sci. USA. 89(6) (1992) 2399-2403.

[5] Y. Uematsu, K. Hirata, K. Suzuki, K. Iida, T. Ueta, K. Kamata, Determination of isothiocyanates and related compounds in mustard extract and horseradish extract used as natural food additives, Shokuhin Eiseigaku Zasshi 43(1) (2002) 10-7.

[6] T. Sultana, G.P. Savage, D.L. McNeil, N.G. Porter, R.J. Martin, B. Deo, Effects of fertilisation on the allyl isothiocyanate profile of above-ground tissues of new zealand-grown wasabi, J. Sci. Food Agric. 82(13) (2002) 1477-1482.

[7] N.S. Giallourou, I.R. Rowland, S.D. Rothwell, G. Packham, D.M. Commane, J.R. Swann, Metabolic targets of watercress and peitc in mcf-7 and mcf-10a cells explain differential sensitisation responses to ionising radiation, Eur. J. Nutr. 58(6) (2019) 2377-2391.

[8] F.L. Chung, M.A. Morse, K.I. Eklind, J. Lewis, Quantitation of human uptake of the anticarcinogen phenethyl isothiocyanate after a watercress meal, Cancer Epidemiol. Biomarkers Prev. 1(5) (1992) 383-8.

[9] G. Kumar, H.S. Tuli, S. Mittal, J.K. Shandilya, A. Tiwari, S.S. Sandhu, Isothiocyanates: A class of bioactive metabolites with chemopreventive potential, Tumor Biol. 36(6) (2015) 4005-4016.

[10] K.L. Cheung, A.-N. Kong, Molecular targets of dietary phenethyl isothiocyanate and sulforaphane for cancer chemoprevention, AAPS J. 12(1) (2010) 87-97.

[11] N. Miyoshi, Chemical alterations and regulations of biomolecules in lifestyle-related diseases, Biosci. Biotechnol. Biochem. 80(6) (2016) 1046-1053.

[12] A.E. Wagner, C. Boesch-Saadatmandi, J. Dose, G. Schultheiss, G. Rimbach, Anti-inflammatory potential of allyl-isothiocyanate--role of nrf2, nf-(κ) b and microrna-155, J. Cell Mol. Med. 16(4) (2012) 836-43.

[13] R. Hu, C. Xu, G. Shen, M.R. Jain, T.O. Khor, A. Gopalkrishnan, W. Lin, B. Reddy, J.Y. Chan, A.N. Kong, Identification of nrf2-regulated genes induced by chemopreventive isothiocyanate peitc by oligonucleotide microarray, Life Sci. 79(20) (2006) 1944-55.

[14] A.T. Dinkova-Kostova, J.W. Fahey, R.V. Kostov, T.W. Kensler, Keap1 and done? Targeting the nrf2 pathway with sulforaphane, Trends Food Sci. Technol. 69(Pt B) (2017) 257-269.

[15] H.K. Bryan, A. Olayanju, C.E. Goldring, B.K. Park, The nrf2 cell defence pathway: Keap1-dependent and -independent mechanisms of regulation, Biochem. Pharmacol. 85(6) (2013) 705-17.

[16] C.E. Guerrero-Beltrán, M. Calderón-Oliver, J. Pedraza-Chaverri, Y.I. Chirino, Protective effect of sulforaphane against oxidative stress: Recent advances, Exp. Toxicol. Pathol. 64(5) (2012) 503-8.

[17] Z. Zhao, G. Liao, Q. Zhou, D. Lv, H. Holthfer, H. Zou, Sulforaphane attenuates contrast-induced nephropathy in rats via nrf2/ho-1 pathway, Oxid. Med. Cell Longev. 2016 (2016) 9825623.

[18] E. Kubo, B. Chhunchha, P. Singh, H. Sasaki, D.P. Singh, Sulforaphane reactivates cellular antioxidant defense by inducing nrf2/are/prdx6 activity during aging and oxidative stress, Sci. Rep. 7(1) (2017) 14130.

[19] Y. Shan, X. Wang, W. Wang, C. He, Y. Bao, P38 mapk plays a distinct role in sulforaphane-induced up-regulation of are-dependent enzymes and down-regulation of cox-2 in human bladder cancer cells, Onco.l Rep. 23(4) (2010) 1133-8.

[20] R.A. Dick, M.K. Kwak, T.R. Sutter, T.W. Kensler, Antioxidative function and substrate specificity of nad(p)h-dependent alkenal/one oxidoreductase. A new role for leukotriene b4 12-hydroxydehydrogenase/15-oxoprostaglandin 13-reductase, J. Biol. Chem. 276(44) (2001) 40803-10.

[21] E.H. Kobayashi, T. Suzuki, R. Funayama, T. Nagashima, M. Hayashi, H. Sekine, N. Tanaka, T. Moriguchi, H. Motohashi, K. Nakayama, M. Yamamoto, Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription, Nat. Commun. 7 (2016) 11624.

[22] E. Heiss, C. Herhaus, K. Klimo, H. Bartsch, C. Gerhäuser, Nuclear factor kappa b is a molecular target for sulforaphane-mediated anti-inflammatory mechanisms, J. Biol. Chem. 276(34) (2001) 32008-15.

[23] P. Soundararajan, J. Kim, Anti-carcinogenic glucosinolates in cruciferous vegetables and their antagonistic effects on prevention of cancers, Molecules 23(11) (2018) 2983.

[24] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2020, CA: Cancer J. Clin. 70(1) (2020) 7-30.

[25] G.D. Stoner, M.A. Morse, Isothiocyanates and plant polyphenols as inhibitors of lung and esophageal cancer, Cancer Lett. 114(1) (1997) 113-119.

[26] F.L. Chung, D. Jiao, C.C. Conaway, T.J. Smith, C.S. Yang, M.C. Yu, Chemopreventive potential of thiol conjugates of isothiocyanates for lung cancer and a urinary biomarker of dietary isothiocyanates, J. Cell. Biochem. (1997) 76-85.

[27] S.S. Hecht, Inhibition of carcinogenesis by isothiocyanates, Drug Metab. Rev. 32(3-4) (2000) 395-411.

[28] C. Bonnesen, I.M. Eggleston, J.D. Hayes, Dietary indoles and isothiocyanates that are generated from cruciferous vegetables can both stimulate apoptosis and confer protection against DNA damage in human colon cell lines, Cancer Res. 61(16) (2001) 6120-6130.

[29] G. Murillo, R.G. Mehta, Cruciferous vegetables and cancer prevention, Nutr. Cancer 41(1-2) (2001) 17-28.

[30] P. Rose, M. Whiteman, S.H. Huang, B. Halliwell, C.N. Ong, Beta-phenylethyl isothiocyanate-mediated apoptosis in hepatoma hepg2 cells, Cell Mol. Life Sci. 60(7) (2003) 1489-503.

[31] E. Tseng, E.A.S. Ramsay, M.E. Morris, Dietary organic isothiocyanates are cytotoxic in human breast cancer mcf-7 and mammary epithelial mcf-12a cell lines, Exp. Biol. Med. 229(8) (2004) 835-842.

[32] S. Shukla, S. Gupta, Dietary agents in the chemoprevention of prostate cancer, Nutr. Cancer 53(1) (2005) 18-32.

[33] J.D. Clarke, R.H. Dashwood, E. Ho, Multi-targeted prevention of cancer by sulforaphane, Cancer Lett. 269(2) (2008) 291-304.

[34] C. Fimognari, P. Hrelia, Sulforaphane as a promising molecule for fighting cancer, Mutation Research/Reviews in Mutation Research 635(2-3) (2007) 90-104.

[35] M. Lenzi, C. Fimognari, P. Hrelia, Sulforaphane as a promising molecule for fighting cancer, Cancer Treat Res 159 (2014) 207-23.

[36] D. Hanahan, Robert, Hallmarks of cancer: The next generation, Cell 144(5) (2011) 646-674.

[37] S. Wu, H. Lu, Y. Bai, Nrf2 in cancers: A double‐edged sword, Cancer Med. 8(5) (2019) 2252-2267.

[38] R. Yu, W. Lei, S. Mandlekar, M.J. Weber, C.J. Der, J. Wu, A.N. Kong, Role of a mitogen-activated protein kinase pathway in the induction of phase ii detoxifying enzymes by chemicals, J. Biol. Chem. 274(39) (1999) 27545-52.

[39] J.R. Bacon, Sulforaphane and quercetin modulate phip-DNA adduct formation in human hepg2 cells and hepatocytes, Carcinogenesis 24(12) (2003) 1903-1911.

[40] K. Singletary, C. Macdonald, Inhibition of benzo[a]pyrene- and 1,6-dinitropyrene-DNA adduct formation in human mammary epithelial cells bydibenzoylmethane and sulforaphane, Cancer Lett. 155(1) (2000) 47-54.

[41] A. Singh, S. Venkannagari, K.H. Oh, Y.-Q. Zhang, J.M. Rohde, L. Liu, S. Nimmagadda, K. Sudini, K.R. Brimacombe, S. Gajghate, J. Ma, A. Wang, X. Xu, S.A. Shahane, M. Xia, J. Woo, G.A. Mensah, Z. Wang, M. Ferrer, E. Gabrielson, Z. Li, F. Rastinejad, M. Shen, M.B. Boxer, S. Biswal, Small molecule inhibitor of nrf2 selectively intervenes therapeutic resistance in keap1-deficient nsclc tumors, ACS Chem. Biol. 11(11) (2016) 3214-3225.

[42] T.W. Kensler, N. Wakabayashi, Nrf2: Friend or foe for chemoprevention?, Carcinogenesis 31(1) (2010) 90-99.

[43] S.K. Niture, R. Khatri, A.K. Jaiswal, Regulation of nrf2—an update, Free Radical Biology and Medicine 66 (2014) 36-44.

[44] M. La Marca, P. Beffy, C. Della Croce, P.G. Gervasi, R. Iori, E. Puccinelli, V. Longo, Structural influence of isothiocyanates on expression of cytochrome p450, phase ii enzymes, and activation of nrf2 in primary rat hepatocytes, Food Chem. Toxicol. 50(8) (2012) 2822-30.

[45] Y. Yoshigae, C. Sridar, U.M. Kent, P.F. Hollenberg, The inactivation of human cyp2e1 by phenethyl isothiocyanate, a naturally occurring chemopreventive agent, and its oxidative bioactivation, Drug Metab. Dispos. 41(4) (2013) 858-869.

[46] G. Kumar, H.S. Tuli, S. Mittal, J.K. Shandilya, A. Tiwari, S.S. Sandhu, Isothiocyanates: A class of bioactive metabolites with chemopreventive potential, Tumour Biol 36(6) (2015) 4005-16.

[47] F. Geng, L. Tang, Y. Li, L. Yang, K.-S. Choi, A.L. Kazim, Y. Zhang, Allyl isothiocyanate arrests cancer cells in mitosis, and mitotic arrest in turn leads to apoptosis via bcl-2 protein phosphorylation, The Journal of biological chemistry 286(37) (2011) 32259-32267.

[48] T.O. Khor, W.K. Cheung, A. Prawan, B.S. Reddy, A.N. Kong, Chemoprevention of familial adenomatous polyposis in apc(min/+) mice by phenethyl isothiocyanate (peitc), Mol. Carcinog. 47(5) (2008) 321-5.

[49] Y.C. Hsu, S.J. Chang, M.Y. Wang, Y.L. Chen, T.Y. Huang, Growth inhibition and apoptosis of neuroblastoma cells through ros-independent mek/erk activation by sulforaphane, Cell Biochem Biophys 66(3) (2013) 765-74.

[50] E. Bergantin, C. Quarta, C. Nanni, S. Fanti, A. Pession, G. Cantelli-Forti, R. Tonelli, P. Hrelia, Sulforaphane induces apoptosis in rhabdomyosarcoma and restores trail-sensitivity in the aggressive alveolar subtype leading to tumor elimination in mice, Cancer Biol Ther 15(9) (2014) 1219-25.

[51] K. Rudolf, M. Cervinka, E. Rudolf, Sulforaphane-induced apoptosis involves p53 and p38 in melanoma cells, Apoptosis 19(4) (2014) 734-47.

[52] X. Zou, Z.Y. Qu, Y.N. Fang, X. Shi, Y.B. Ji, Endoplasmic reticulum stress mediates sulforaphane-induced apoptosis of hepg2 human hepatocellular carcinoma cells, Mol. Med. Rep. 15(1) (2017) 331-338.

[53] C. Xu, G. Shen, X. Yuan, J.-H. Kim, A. Gopalkrishnan, Y.-S. Keum, S. Nair, A.-N.T. Kong, Erk and jnk signaling pathways are involved in the regulation of activator protein 1 and cell death elicited by three isothiocyanates in human prostate cancer pc-3 cells, Carcinogenesis 27(3) (2006) 437-445.

[54] E.-S. Hwang, G.H. Kim, Allyl isothiocyanate influences cell adhesion, migration and metalloproteinase gene expression in sk-hep1 cells, Exp. Biol. Med. 234(1) (2009) 105-111.

[55] K.C. Lai, C.C. Lu, Y.J. Tang, J.H. Chiang, D.H. Kuo, F.A. Chen, I.L. Chen, J.S. Yang, Allyl isothiocyanate inhibits cell metastasis through suppression of the mapk pathways in epidermal growth factor-stimulated ht29 human colorectal adenocarcinoma cells, Oncol. Rep. 31(1) (2014) 189-196.

[56] M. Kim, H.J. Cho, G.T. Kwon, Y.H. Kang, S.H. Kwon, S. Her, T. Park, Y. Kim, Y. Kee, J.H. Park, Benzyl isothiocyanate suppresses high-fat diet-stimulated mammary tumor progression via the alteration of tumor microenvironments in obesity-resistant balb/c mice, Mol. Carcinog. 54(1) (2015) 72-82.

[57] P. Gupta, C. Adkins, P. Lockman, S.K. Srivastava, Metastasis of breast tumor cells to brain is suppressed by phenethyl isothiocyanate in a novel in vivo metastasis model, PLoS One 8(6) (2013) e67278.

[58] C.S. Lee, H.J. Cho, Y.J. Jeong, J.M. Shin, K.K. Park, Y.Y. Park, Y.S. Bae, I.K. Chung, M. Kim, C.H. Kim, F. Jin, H.W. Chang, Y.C. Chang, Isothiocyanates inhibit the invasion and migration of c6 glioma cells by blocking fak/jnk-mediated mmp-9 expression, Oncol. Rep. 34(6) (2015) 2901-2908.

[59] A. Mondal, R. Biswas, Y.H. Rhee, J. Kim, J.C. Ahn, Sulforaphene promotes bax/bcl2, mapk-dependent human gastric cancer ags cells apoptosis and inhibits migration via egfr, p-erk1/2 down-regulation, Gen. Physiol. Biophys. 35(1) (2016) 25-34.

[60] C. Bao, M.C. Kim, J. Chen, J. Song, H.W. Ko, H.J. Lee, Sulforaphene interferes with human breast cancer cell migration and invasion through inhibition of hedgehog signaling, J. Agric. Food Chem. 64(27) (2016) 5515-5524.

[61] P.S. Steeg, Targeting metastasis, Nat. Rev. Cancer 16(4) (2016) 201-18.

[62] L. Wang, Z. Tian, Q. Yang, H. Li, H. Guan, B. Shi, P. Hou, M. Ji, Sulforaphane inhibits thyroid cancer cell growth and invasiveness through the reactive oxygen species-dependent pathway, Oncotarget 6(28) (2015) 25917-31.

[63] B.E. Cavell, S.S. Syed Alwi, A. Donlevy, G. Packham, Anti-angiogenic effects of dietary isothiocyanates: Mechanisms of action and implications for human health, Biochem. Pharmacol. 81(3) (2011) 327-36.

[64] Z. Zhang, L.L. Atwell, P.E. Farris, E. Ho, J. Shannon, Associations between cruciferous vegetable intake and selected biomarkers among women scheduled for breast biopsies, Public Health Nutrition 19(7) (2016) 1288-1295.

[65] L.L. Atwell, Z. Zhang, M. Mori, P.E. Farris, J.T. Vetto, A.M. Naik, K.Y. Oh, P. Thuillier, E. Ho, J. Shannon, Sulforaphane bioavailability and chemopreventive activity in women scheduled for breast biopsy, Cancer Prev. Res. (Phila) 8(12) (2015) 1184-1191.

[66] J.J. Alumkal, R. Slottke, J. Schwartzman, G. Cherala, M. Munar, J.N. Graff, T.M. Beer, C.W. Ryan, D.R. Koop, A. Gibbs, L. Gao, J.F. Flamiatos, E. Tucker, R. Kleinschmidt, M. Mori, A phase ii study of sulforaphane-rich broccoli sprout extracts in men with recurrent prostate cancer, Investigational New Drugs 33(2) (2015) 480-489.

[67] Z. Zhang, M. Garzotto, E.W. Davis, 2nd, M. Mori, W.A. Stoller, P.E. Farris, C.P. Wong, L.M. Beaver, G.V. Thomas, D.E. Williams, R.H. Dashwood, D.A. Hendrix, E. Ho, J. Shannon, Sulforaphane bioavailability and chemopreventive activity in men presenting for biopsy of the prostate gland: A randomized controlled trial, Nutr Cancer 72(1) (2020) 74-87.

[68] L.A. Emens, F.J. Esteva, M. Beresford, C. Saura, M. De Laurentiis, S.B. Kim, S.A. Im, Y. Wang, A. Mani, J. Shah, H. Liu, S. De Haas, M. Patre, S. Loi, Overall survival (os) in kate2, a phase ii study of programmed death ligand 1 (pd-l1) inhibitor atezolizumab (atezo)+trastuzumab emtansine (t-dm1) vs placebo (pbo)+t-dm1 in previously treated her2+ advanced breast cancer (bc), Annals of Oncology 30(Supplement_5) (2019) v104.

[69] Z. Bahadoran, M. Tohidi, P. Nazeri, M. Mehran, F. Azizi, P. Mirmiran, Effect of broccoli sprouts on insulin resistance in type 2 diabetic patients: A randomized double-blind clinical trial, Int J Food Sci Nutr 63(7) (2012) 767-71.

[70] Z. Bahadoran, P. Mirmiran, F. Hosseinpanah, A. Rajab, G. Asghari, F. Azizi, Broccoli sprouts powder could improve serum triglyceride and oxidized ldl/ldl-cholesterol ratio in type 2 diabetic patients: A randomized double-blind placebo-controlled clinical trial, Diabetes Res Clin Pract 96(3) (2012) 348-54.

[71] A.S. Axelsson, E. Tubbs, B. Mecham, S. Chacko, H.A. Nenonen, Y. Tang, J.W. Fahey, J.M.J. Derry, C.B. Wollheim, N. Wierup, M.W. Haymond, S.H. Friend, H. Mulder, A.H. Rosengren, Sulforaphane reduces hepatic glucose production and improves glucose control in patients with type 2 diabetes, Science Translational Medicine 9(394) (2017) eaah4477.

[72] K. Singh, S.L. Connors, E.A. Macklin, K.D. Smith, J.W. Fahey, P. Talalay, A.W. Zimmerman, Sulforaphane treatment of autism spectrum disorder (asd), Proc. Natl. Acad. Sci. 111(43) (2014) 15550-15555.

[73] M.H. Traka, A. Melchini, J. Coode-Bate, Omar, S. Saha, M. Defernez, P. Troncoso-Rey, H. Kibblewhite, C.M. O'Neill, F. Bernuzzi, L. Mythen, J. Hughes, P.W. Needs, J.R. Dainty, G.M. Savva, R.D. Mills, R.Y. Ball, C.S. Cooper, R.F. Mithen, Transcriptional changes in prostate of men on active surveillance after a 12-mo glucoraphanin-rich broccoli intervention—results from the effect of sulforaphane on prostate cancer prevention (escape) randomized controlled trial, The American Journal of Clinical Nutrition 109(4) (2019) 1133-1144.

[74] J.M. Yuan, I. Stepanov, S.E. Murphy, R. Wang, S. Allen, J. Jensen, L. Strayer, J. Adams-Haduch, P. Upadhyaya, C. Le, M.S. Kurzer, H.H. Nelson, M.C. Yu, D. Hatsukami, S.S. Hecht, Clinical trial of 2-phenethyl isothiocyanate as an inhibitor of metabolic activation of a tobacco-specific lung carcinogen in cigarette smokers, Cancer Prev. Res. (Phila) 9(5) (2016) 396-405.

[75] T.A. Yap, A. Omlin, J.S. de Bono, Development of therapeutic combinations targeting major cancer signaling pathways, J. Clin. Oncol. 31(12) (2013) 1592-1605.

[76] R. Bayat Mokhtari, T.S. Homayouni, N. Baluch, E. Morgatskaya, S. Kumar, B. Das, H. Yeger, Combination therapy in combating cancer, Oncotarget 8(23) (2017) 38022-38043.

[77] C. He, J. Lu, W. Lin, Hybrid nanoparticles for combination therapy of cancer, J. Control. Release 219 (2015) 224-236.

[78] L. Hunakova, P. Gronesova, E. Horvathova, I. Chalupa, D. Cholujova, J. Duraj, J. Sedlak, Modulation of cisplatin sensitivity in human ovarian carcinoma a2780 and skov3 cell lines by sulforaphane, Toxicol. Lett. 230(3) (2014) 479-486.

[79] X. Ling, D. Westover, F. Cao, S.S. Cao, X. He, H.R. Kim, Y.S. Zhang, D.C.F. Chan, F.Z. Li, Synergistic effect of allyl isothiocyanate (aitc) on cisplatin efficacy in vitro and in vivo, Am. J. Cancer Res. 5(8) (2015) 2516-2530.

[80] R. Gupta, L.K. Bhatt, M. Momin, Potent antitumor activity of laccaic acid and phenethyl isothiocyanate combination in colorectal cancer via dual inhibition of DNA methyltransferase-1 and histone deacetylase-1, Toxicol. Appl. Pharmacol. 377 (2019).

[81] L. Mielczarek, P. Krug, M. Mazur, M. Milczarek, Z. Chilmonczyk, K. Wiktorska, In the triple-negative breast cancer mda-mb-231 cell line, sulforaphane enhances the intracellular accumulation and anticancer action of doxorubicin encapsulated in liposomes, Int. J. Pharm. 558 (2019).

[82] M.K. Sundaram, R. Raina, N. Afroze, A. Dhupkar, N.P. Kaur, A. Arte, F.A. Khan, A. Hussain, Combinational use of phytochemicals and chemotherapeutic drugs enhance their therapeutic potential on human cervical cancer cells, Int. J. Cancer Manag. 12(6) (2019).

[83] M.M. Kamal, S. Akter, C.N. Lin, S. Nazzal, Sulforaphane as an anticancer molecule: Mechanisms of action, synergistic effects, enhancement of drug safety, and delivery systems, Arch. Pharm. Res. 43(4) (2020) 371-384.

[84] A. Hussain, J. Mohsin, S.A. Prabhu, S. Begum, Q.E.A. Nusri, G. Harish, E. Javed, M.A. Khan, C. Sharma, Sulforaphane inhibits growth of human breast cancer cells and augments the therapeutic index of the chemotherapeutic drug, gemcitabine, Asian Pac. J. Cancer Prev. 14(10) (2013) 5855-5860.

[85] J.P. Burnett, G. Lim, Y. Li, R.B. Shah, R. Lim, H.J. Paholak, S.P. McDermott, L. Sun, Y. Tsume, S. Bai, M.S. Wicha, D. Sun, T. Zhang, Sulforaphane enhances the anticancer activity of taxanes against triple negative breast cancer by killing cancer stem cells, Cancer Lett. 394 (2017) 52-64.

[86] B.M. Kaminski, A. Weigert, B. Brune, M. Schumacher, U. Wenzel, D. Steinhilber, J. Stein, S. Ulrich, Sulforaphane potentiates oxaliplatin-induced cell growth inhibition in colorectal cancer cells via induction of different modes of cell death, Cancer Chemother. Pharmacol. 67(5) (2011) 1167-1178.

[87] G. Kallifatidis, S. Labsch, V. Rausch, J. Mattern, J. Gladkich, G. Moldenhauer, M.W. Büchler, A.V. Salnikov, I. Herr, Sulforaphane increases drug-mediated cytotoxicity toward cancer stem-like cells of pancreas and prostate, Mol. Ther. 19(1) (2011) 188-195.

[88] L. Kelland, The resurgence of platinum-based cancer chemotherapy, Nat. Rev. Cancer. 7(8) (2007) 573-584.

[89] D.W. Shen, L.M. Pouliot, M.D. Hall, M.M. Gottesman, Cisplatin resistance: A cellular self-defense mechanism resulting from multiple epigenetic and genetic changes, Pharmacol. Rev. 64(3) (2012) 706-721.

[90] A.J. Di Pasqua, C. Hong, M.Y. Wu, E. McCracken, X. Wang, L. Mi, F.-L. Chung, Sensitization of non-small cell lung cancer cells to cisplatin by naturally occurring isothiocyanates, Chem. Res. Toxicol. 23(8) (2010) 1307-1309.

[91] X.T. Wang, S. Govind, S.P. Sajankila, L.X. Mi, R. Roy, F.L. Chung, Phenethyl isothiocyanate sensitizes human cervical cancer cells to apoptosis induced by cisplatin, Mol. Nutr. Food Res. 55(10) (2011) 1572-1581.

[92] C. Kerr, G. Adhikary, D. Grun, N. George, R.L. Eckert, Combination cisplatin and sulforaphane treatment reduces proliferation, invasion, and tumor formation in epidermal squamous cell carcinoma, Mol. Carcinog. 57(1) (2018) 3-11.

[93] Y.J. Lee, S.H. Lee, Sulforaphane potentiates growth-inhibiting and apoptosis-promoting activities of cisplatin following oxidative stress and mitochondrial dysfunction in malignant mesothelioma cells, Mol. Cell Toxicol. 12(3) (2016) 289-299.

[94] M.J. Nunez-Iglesias, S. Novio, C. Garcia, E. Perez-Munuzuri, P. Soengas, E. Cartea, P. Velasco, M. Freire-Garabal, Glucosinolate-degradation products as co-adjuvant therapy on prostate cancer in vitro, Int. J. Mol. Sci. 20(20) (2019).

[95] P. Desai, A. Thakkar, D. Ann, J. Wang, S. Prabhu, Loratadine self-microemulsifying drug delivery systems (smedds) in combination with sulforaphane for the synergistic chemoprevention of pancreatic cancer, Drug Deliv. Transl. Res. 9(3) (2019) 641-651.

[96] F. Liu, R.B. Lv, Y. Liu, Q. Hao, S.J. Liu, Y.Y. Zheng, C. Li, C. Zhu, M. Wang, Salinomycin and sulforaphane exerted synergistic antiproliferative and proapoptotic effects on colorectal cancer cells by inhibiting the pi3k/akt signaling pathway in vitro and in vivo, Oncotargets Ther. 13 (2020) 4957-4969.

[97] J. Santana-Galvez, J. Villela-Castrejon, S.O. Serna-Saldivar, L. Cisneros-Zevallos, D.A. Jacobo-Velazquez, Synergistic combinations of curcumin, sulforaphane, and dihydrocaffeic acid against human colon cancer cells, Int. J. Mol. Sci. 21(9) (2020).

[98] G.W. Watson, L.M. Beaver, D.E. Williams, R.H. Dashwood, E. Ho, Phytochemicals from cruciferous vegetables, epigenetics, and prostate cancer prevention, AAPS J. 15(4) (2013) 951-61.

[99] D.L. Palliyaguru, J.-M. Yuan, T.W. Kensler, J.W. Fahey, Isothiocyanates: Translating the power of plants to people, Mol. Nutr. Food Res. 62(18) (2018) e1700965-e1700965.

[100] R. Mithen, E. Ho, Isothiocyanates for human health, Mol. Nutr. Food Res. 62(18) (2018) 1870079.

[101] M. Ferrari, Cancer nanotechnology: Opportunities and challenges, Nat. Rev. Cancer. 5(3) (2005) 161-171.

[102] Y. Zhang, Y. Huang, S. Li, Polymeric micelles: Nanocarriers for cancer-targeted drug delivery, AAPS PharmSciTech. 15(4) (2014) 862-871.

[103] H. Chan, P. Král, Nanoparticles self-assembly within lipid bilayers, ACS Omega 3(9) (2018) 10631-10637.

[104] T.O.B. Olusanya, R.R. Haj Ahmad, D.M. Ibegbu, J.R. Smith, A.A. Elkordy, Liposomal drug delivery systems and anticancer drugs, Molecules 23(4) (2018).

[105] B.K. Nanjwade, H.M. Bechra, G.K. Derkar, F.V. Manvi, V.K. Nanjwade, Dendrimers: Emerging polymers for drug-delivery systems, Eur. J. Pharm. Sci. 38(3) (2009) 185-196.

[106] C.I.C. Crucho, M.T. Barros, Polymeric nanoparticles: A study on the preparation variables and characterization methods, Mater. Sci. Eng. C. Mater. Biol. Appl. 80 (2017) 771-784.

[107] A. Vaiserman, A. Koliada, A. Zayachkivska, O. Lushchak, Nanodelivery of natural antioxidants: An anti-aging perspective, Front. Bioeng. Biotechnol. 7(447) (2020).

[108] D. Bera, L. Qian, T.-K. Tseng, P.H. Holloway, Quantum dots and their multimodal applications: A review, Materials (Basel) 3(4) (2010) 2260-2345.

[109] Q. Wang, H. Ni, A. Pietzsch, F. Hennies, Y. Bao, Y. Chao, Synthesis of water-dispersible photoluminescent silicon nanoparticles and their use in biological fluorescent imaging, J. Nanoparticle Res. 13(1) (2011) 405-413.

[110] D.G. Zayed, A.S. AbdElhamid, M.S. Freag, A.O. Elzoghby, Hybrid quantum dot-based theranostic nanomedicines for tumor-targeted drug delivery and cancer imaging, Nanomedicine 14(3) (2019) 225-228.

[111] M.-X. Zhao, B.-J. Zhu, The research and applications of quantum dots as nano-carriers for targeted drug delivery and cancer therapy, Nanoscale Res. Lett. 11(1) (2016) 207.

[112] V.V. Mody, R. Siwale, A. Singh, H.R. Mody, Introduction to metallic nanoparticles, J. Pharm. Bioallied Sci. 2(4) (2010) 282-9.

[113] T.-T. Liu, T.-S. Yang, Stability and antimicrobial activity of allyl isothiocyanate during long-term storage in an oil-in-water emulsion, J. Food Sci. 75(5) (2010) C445-C451.

[114] K. Cejpek, J. Valusek, J. Velisek, Reactions of allyl isothiocyanate with alanine, glycine, and several peptides in model systems, J. Agric. Food Chem. 48(8) (2000) 3560-3565.

[115] S. Kawakishi, M. Namiki, Decomposition of allyl isothiocyanate in aqueous solution, Agric. Biol. Chem. 33(3) (1969) 452-459.

[116] Y. Li, Z. Teng, P. Chen, Y.Y. Song, Y.C. Luo, Q. Wang, Enhancement of aqueous stability of allyl isothiocyanate using nanoemulsions prepared by an emulsion inversion point method, J. Colloid Interface Sci. 438 (2015) 130-137.

[117] D. Encinas-Basurto, J. Ibarra, J. Juarez, M.G. Burboa, S. Barbosa, P. Taboada, R. Troncoso-Rojas, M.A. Valdez, Poly(lactic-co-glycolic acid) nanoparticles for sustained release of allyl isothiocyanate: Characterization, in vitro release and biological activity, J. Microencapsul. 34(3) (2017) 231-242.

[118] D. Encinas-Basurto, J. Juarez, M.A. Valdez, M.G. Burboa, S. Barbosa, P. Taboada, Targeted drug delivery via human epidermal growth factor receptor for sustained release of allyl isothiocyanate, Curr. Top. Med. Chem. 18(14) (2018) 1252-1260.

[119] P. Liu, M. Behray, Q. Wang, W. Wang, Z. Zhou, Y. Chao, Y. Bao, Anti-cancer activities of allyl isothiocyanate and its conjugated silicon quantum dots, Sci. Rep. 8(1) (2018) 1084.

[120] Y. Chao, L. Šiller, S. Krishnamurthy, P.R. Coxon, U. Bangert, M. Gass, L. Kjeldgaard, S.N. Patole, L.H. Lie, N. O'Farrell, T.A. Alsop, A. Houlton, B.R. Horrocks, Evaporation and deposition of alkyl-capped silicon nanocrystals in ultrahigh vacuum, Nat. Nanotechnol. 2(8) (2007) 486-489.

[121] W.J. Chang, B.H. Chen, B.S. Inbaraj, J.T. Chien, Preparation of allyl isothiocyanate nanoparticles, their anti-inflammatory activity towards raw 264.7 macrophage cells and anti-proliferative effect on ht1376 bladder cancer cells, J. Sci. Food Agric. 99(6) (2019) 3106-3116.

[122] M. Zhu, W. Li, X. Dong, Y. Chen, Y. Lu, B. Lin, J. Guo, M. Li, Benzyl-isothiocyanate induces apoptosis and inhibits migration and invasion of hepatocellular carcinoma cells in vitro, J. Cancer 8(2) (2017) 240-248.

[123] Y. Liu, M. Yamanaka, N. Abe-Kanoh, X. Liu, B. Zhu, S. Munemasa, T. Nakamura, Y. Murata, Y. Nakamura, Benzyl isothiocyanate ameliorates acetaldehyde-induced cytotoxicity by enhancing aldehyde dehydrogenase activity in murine hepatoma hepa1c1c7 cells, Food Chem. Toxicol. 108 (2017) 305-313.

[124] S. Uppal, K. Kaur, R. Kumar, N.D. Kaur, G. Shukla, S.K. Mehta, Chitosan nanoparticles as a biocompatible and efficient nanowagon for benzyl isothiocyanate, Int. J. Biol. Macromol 115 (2018) 18-28.

[125] H.S.S. Qhattal, S. Wang, T. Salihima, S.K. Srivastava, X. Liu, Nanoemulsions of cancer chemopreventive agent benzyl isothiocyanate display enhanced solubility, dissolution, and permeability, J. Agric. Food Chem. 59(23) (2011) 12396-12404.

[126] R. Kumar, K. Kaur, S.K. Pandey, R. Kumar, S. Uppal, S.K. Mehta, Fabrication of benzylisothiocynate encapsulated nanoemulsion through ultrasonication: Augmentation of anticancer and antimicrobial attributes, J. Mol. Liq. 263 (2018) 324-333.

[127] J. Rao, D.J. McClements, Lemon oil solubilization in mixed surfactant solutions: Rationalizing microemulsion & nanoemulsion formation, Food Hydrocoll. 26(1) (2012) 268-276.

[128] Z.T. Jiang, Q.F. Zhang, H.L. Tian, R. Li, The reaction of allyl isothiocyanate with hydroxyl/water and β-cyclodextrin using ultraviolet spectrometry, Food Technol. Biotechnol. 44(3) (2006) 423-427.

[129] S. Uppal, Aashima, R. Kumar, S. Sareen, K. Kaur, S.K. Mehta, Biofabrication of cerium oxide nanoparticles using emulsification for an efficient delivery of benzyl isothiocyanate, Appl. Surf. Sci. 510 (2020).

[130] S. Uppal, P. Sharma, R. Kumar, K. Kaur, A. Bhatia, S.K. Mehta, Effect of benzyl isothiocyanate encapsulated biocompatible nanoemulsion prepared via ultrasonication on microbial strains and breast cancer cell line mda mb 231, Colloids Surf. A Physicochem. Eng. Asp. 596 (2020).

[131] H.M. Wang, L.M. Wang, L.M. Cao, Q.C. Zhang, Q.Q. Song, Z.W. Meng, X. Wu, K. Xu, Inhibition of autophagy potentiates the anti-metastasis effect of phenethyl isothiocyanate through jak2/stat3 pathway in lung cancer cells, Mol. Carcinog. 57(4) (2018) 522-535.

[132] P. Thejass, G. Kuttan, Inhibition of endothelial cell differentiation and proinflammatory cytokine production during angiogenesis by allyl isothiocyanate and phenyl isothiocyanate, Integr. Cancer. Ther. 6(4) (2007) 389-99.

[133] L.G. Wang, X.M. Liu, J.W. Chiao, Repression of androgen receptor in prostate cancer cells by phenethyl isothiocyanate, Carcinogenesis 27(10) (2006) 2124-2132.

[134] L.D. Huong, J.-H. Shim, K.-H. Choi, J.-A. Shin, E.-S. Choi, H.-S. Kim, S.-J. Lee, S.-J. Kim, N.-P. Cho, S.-D. Cho, Effect of β-phenylethyl isothiocyanate from cruciferous vegetables on growth inhibition and apoptosis of cervical cancer cells through the induction of death receptors 4 and 5, J. Agric. Food Chem. 59(15) (2011) 8124-8131.

[135] P. Bansal, S. Medhe, N. Ganesh, M.M. Srivastava, In vitro anticancer activity of dietary bioagent (isothiocyanates) on hepg2 and b16f10 cell lines: A comparative study, Ann. Pla. Sci. 2(07) (2013) 4.

[136] P. Rose, J.S. Armstrong, Y.L. Chua, C.N. Ong, M. Whiteman, Beta-phenylethyl isothiocyanate mediated apoptosis; contribution of bax and the mitochondrial death pathway, Int. J. Biochem. Cell Biol. 37(1) (2005) 100-19.

[137] Y.T. Yang, Y. Shi, M. Jay, A.J. Di Pasqua, Enhanced toxicity of cisplatin with chemosensitizer phenethyl isothiocyanate toward non-small cell lung cancer cells when delivered in liposomal nanoparticles, Chem. Res. Toxicol. 27(6) (2014) 946-948.

[138] M.W. Sun, Y. Shi, U.J. Dang, A.J. Di Pasqua, Phenethyl isothiocyanate and cisplatin co-encapsulated in a liposomal nanoparticle for treatment of non-small cell lung cancer, Molecules 24(4) (2019).

[139] A. Pulliero, Y. Wu, D. Fenoglio, A. Parodi, M. Romani, C.P. Soares, G. Filaci, J.L. Lee, P.N. Sinkam, A. Izzotti, Nanoparticles increase the efficacy of cancer chemopreventive agents in cells exposed to cigarette smoke condensate, Carcinogenesis 36(3) (2015) 368-377.

[140] D.M.J. Seema, B. Saifullah, M. Selvanayagam, S. Gothai, M.Z. Hussein, S.K. Subbiah, N.M. Esa, P. Arulselvan, Designing of the anticancer nanocomposite with sustained release properties by using graphene oxide nanocarrier with phenethyl isothiocyanate as anticancer agent, Pharmaceutics 10(3) (2018) 12.

[141] F. Wu, M. Zhang, X.H. Chu, Q.C. Zhang, Y.T. Su, B.H. Sun, T.Y. Lu, N.L. Zhou, J. Zhang, J.X. Wang, X.Y. Yi, Black phosphorus nanosheets-based nanocarriers for enhancing chemotherapy drug sensitiveness via depleting mutant p53 and resistant cancer multimodal therapy, Chem. Eng. J. 370 (2019) 387-399.

[142] M.S. Donaldson, Nutrition and cancer: A review of the evidence for an anti-cancer diet, Nutr. J. 3(1) (2004) 19.

[143] C.A. Houghton, R.G. Fassett, J.S. Coombes, Sulforaphane: Translational research from laboratory bench to clinic, Nutr. Rev. 71(11) (2013) 709-726.

[144] M.R. Kim, L. Zhou, B.H. Park, J.R. Kim, Induction of g□/m arrest and apoptosis by sulforaphane in human osteosarcoma u2-os cells, Mol. Med. Rep. 4(5) (2011) 929-34.

[145] Y. Li, T. Zhang, Targeting cancer stem cells with sulforaphane, a dietary component from broccoli and broccoli sprouts, Future Oncol. 9(8) (2013) 1097-1103.

[146] X. Wang, Y. Li, Y. Dai, Q. Liu, S. Ning, J. Liu, Z. Shen, D. Zhu, F. Jiang, J. Zhang, Z. Li, Sulforaphane improves chemotherapy efficacy by targeting cancer stem cell-like properties via the mir-124/il-6r/stat3 axis, Sci. Rep. 6(1) (2016) 36796.

[147] Q.-Q. Li, Y.-K. Xie, Y. Wu, L.-L. Li, Y. Liu, X.-B. Miao, Q.-Z. Liu, K.-T. Yao, G.-H. Xiao, Sulforaphane inhibits cancer stem-like cell properties and cisplatin resistance through mir-214-mediated downregulation of c-myc in non-small cell lung cancer, Oncotarget 8(7) (2017) 12067-12080.

[148] J.B. Huang, C. Tao, Y. Yu, F.F. Yu, H. Zhang, J. Gao, D. Wang, Y. Chen, J. Gao, G.Q. Zhang, G.C. Zhou, J.J. Liu, Z.G. Sun, D.X. Sun, H. Zou, H. Xu, Y. Lu, Y.Q. Zhong, Simultaneous targeting of differentiated breast cancer cells and breast cancer stem cells by combination of docetaxel- and sulforaphane-loaded self-assembled poly(d, l-lactide-co-glycolide)/hyaluronic acid block copolymer-based nanoparticles, J. Biomed. Nanotechnol. 12(7) (2016) 1463-1477.

[149] H.K. Manjili, L. Ma'mani, S. Tavaddod, M. Mashhadikhan, A. Shafiee, H. Naderi-Manesh, D, l-sulforaphane loaded fe3o4@ gold core shell nanoparticles: A potential sulforaphane delivery system, PLoS One 11(3) (2016).

[150] H. Danafar, A. Sharafi, H. Kheiri Manjili, S. Andalib, Sulforaphane delivery using mpeg-pcl co-polymer nanoparticles to breast cancer cells, Pharm. Dev. Technol. 22(5) (2017) 642-651.

[151] H. Kheiri Manjili, A. Sharafi, E. Attari, H. Danafar, Pharmacokinetics and in vitro and in vivo delivery of sulforaphane by pcl-peg-pcl copolymeric-based micelles, Artif. Cells Nanomed. Biotechnol. 45(8) (2017) 1728-1739.

[152] H. Danafar, A. Sharafi, S. Askarlou, H.K. Manjili, Preparation and characterization of pegylated iron oxide-gold nanoparticles for delivery of sulforaphane and curcumin, Drug Res. 67(12) (2017) 698-704.

[153] H. Danafar, A. Sharafi, S. Kheiri, H. Kheiri Manjili, Co -delivery of sulforaphane and curcumin with pegylated iron oxide-gold core shell nanoparticles for delivery to breast cancer cell line, Iran J Pharm Res 17(2) (2018) 480-494.

[154] K. Soni, K. Kohli, Sulforaphane-decorated gold nanoparticle for anti-cancer activity: In vitro and in vivo studies, Pharm. Dev. Technol. 24(4) (2019) 427-438.

[155] P. Krug, L. Mielczarek, K. Wiktorska, K. Kaczynska, P. Wojciechowski, K. Andrzejewski, K. Ofiara, A. Szterk, M. Mazur, Sulforaphane-conjugated selenium nanoparticles: Towards a synergistic anticancer effect, Nanotechnology 30(6) (2019).

[156] W.J. Lu, F.F. Du, X.W. Zhao, L.H. Shi, S.M. Shuang, X.T. Cui, C. Dong, Sulforaphane-conjugated carbon dots: A versatile nanosystem for targeted imaging and inhibition of egfr-overexpressing cancer cells, ACS Biomater. Sci. Eng. 5(9) (2019) 4692-4699.

[157] Y. Xu, X. Han, Y. Li, H. Min, X. Zhao, Y. Zhang, Y. Qi, J. Shi, S. Qi, Y. Bao, G. Nie, Sulforaphane mediates glutathione depletion via polymeric nanoparticles to restore cisplatin chemosensitivity, ACS Nano 13(11) (2019) 13445-13455.

[158] S. Ravindran, J.K. Suthar, R. Rokade, P. Deshpande, P. Singh, A. Pratinidhi, R. Khambadkhar, S. Utekar, Pharmacokinetics, metabolism, distribution and permeability of nanomedicine, Curr. Drug Metab. 19(4) (2018) 327-334.

[159] A.R. Bilia, V. Piazzini, C. Guccione, L. Risaliti, M. Asprea, G. Capecchi, M.C. Bergonzi, Improving on nature: The role of nanomedicine in the development of clinical natural drugs, Planta. Med. 83(5) (2017) 366-381.

[160] H. Kang, S. Rho, W.R. Stiles, S. Hu, Y. Baek, D.W. Hwang, S. Kashiwagi, M.S. Kim, H.S. Choi, Size-dependent epr effect of polymeric nanoparticles on tumor targeting, Adv. Healthcare Mater. 9(1) (2020) 1901223.

[161] J.W. Nichols, Y.H. Bae, Epr: Evidence and fallacy, J. Control. Release 190 (2014) 451-464.

[162] E. Blanco, H. Shen, M. Ferrari, Principles of nanoparticle design for overcoming biological barriers to drug delivery, Nat. Biotechnol. 33(9) (2015) 941-951.

[163] N. Bertrand, J. Wu, X. Xu, N. Kamaly, O.C. Farokhzad, Cancer nanotechnology: The impact of passive and active targeting in the era of modern cancer biology, Adv. Drug. Deliv. Rev. 66 (2014) 2-25.

[164] S.D. Perrault, C. Walkey, T. Jennings, H.C. Fischer, W.C.W. Chan, Mediating tumor targeting efficiency of nanoparticles through design, Nano Lett. 9(5) (2009) 1909-1915.

[165] T.A. Denison, Y.H. Bae, Tumor heterogeneity and its implication for drug delivery, J. Control Release 164(2) (2012) 187-91.

[166] U. Prabhakar, D.C. Blakey, H. Maeda, R.K. Jain, E.M. Sevick-Muraca, W. Zamboni, O.C. Farokhzad, S.T. Barry, A. Gabizon, P. Grodzinski, Challenges and key considerations of the enhanced permeability and retention effect (epr) for nanomedicine drug delivery in oncology, Cancer Res. (2013) canres.4561.2012.

[167] E.J. Calabrese, L.A. Baldwin, Applications of hormesis in toxicology, risk assessment and chemotherapeutics, Trends Pharmacol. Sci. 23(7) (2002) 331-7.

[168] Y. Bao, W. Wang, Z. Zhou, C. Sun, Benefits and risks of the hormetic effects of dietary isothiocyanates on cancer prevention, PLoS One 9(12) (2014) e114764.

[169] T.G. Son, S. Camandola, M.P. Mattson, Hormetic dietary phytochemicals, Neuromolecular Med. 10(4) (2008) 236-46.

[170] A. Speciale, J. Chirafisi, A. Saija, F. Cimino, Nutritional antioxidants and adaptive cell responses: An update, Curr. Mol. Med. 11(9) (2011) 770-89.

[171] W. Xiao, X. Chen, L. Yang, Y. Mao, Y. Wei, L. Chen, Co-delivery of doxorubicin and plasmid by a novel fgfr-mediated cationic liposome, Int. J. Pharm. 393(1-2) (2010) 119-26.

[172] M. González-Vallinas, M. González-Castejón, A. Rodríguez-Casado, A. Ramírez de Molina, Dietary phytochemicals in cancer prevention and therapy: A complementary approach with promising perspectives, Nutr. Rev. 71(9) (2013) 585-99.

[173] R. Conte, V. Marturano, G. Peluso, A. Calarco, P. Cerruti, Recent advances in nanoparticle-mediated delivery of anti-inflammatory phytocompounds, Int. J. Mol. Sci. 18(4) (2017).

[174] M. Gu, X. Wang, T.B. Toh, E.K.-H. Chow, Applications of stimuli-responsive nanoscale drug delivery systems in translational research, Drug Discov. Today 23(5) (2018) 1043-1052.

[175] N. Hoshyar, S. Gray, H.B. Han, G. Bao, The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction, Nanomedicine 11(6) (2016) 673-692.

Highlights

- Natural isothiocyanates show significant antioxidant, anti-inflammatory and anti-cancer activities.
- Nano-formulation enhances delivery of isothiocyanates in cancer therapy.
- Combination of isothiocyanates and anti-cancer drugs exhibit synergistic therapeutic potential.