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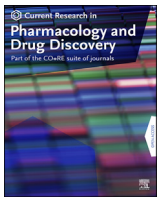

The potential roles of Nrf2/Keap1 signaling in anticancer drug interactions

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ABSTRACT

Nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2), together with its suppressive binding partner Kelch-like ECH-associated protein 1 (Keap1), regulates cellular antioxidant response and drug metabolism. The roles of Nrf2/Keap1 signaling in the pathology of many diseases have been extensively investigated, and small molecules targeting Nrf2/Keap1 signaling have been developed to prevent or treat diseases such as multiple sclerosis, chronic kidney disease and cancer. Notably, Nrf2 plays dual roles in cancer development and treatment. Activation of Nrf2/Keap1 signaling in cancer cells has been reported to promote cancer progression and result in therapy resistance. Since cancer patients are often suffering comorbidities of other chronic diseases, anticancer drugs could be co-administrated with other drugs and herbs. Nrf2/Keap1 signaling modulators, especially activators, are common in drugs, herbs and dietary ingredients, even they are developed for other targets. Therefore, drug-drug or herb-drug interactions due to modulation of Nrf2/Keap1 signaling should be considered in cancer therapies. Here we briefly summarize basic biochemistry and physiology functions of Nrf2/Keap1 signaling, Nrf2/Keap1 signaling modulators that cancer patients could be exposed to, and anticancer drugs that are sensitive to Nrf2/Keap1 signaling, aiming to call attention to the potential drug-drug or herb-drug interactions between anticancer drugs and these Nrf2/Keap1 signaling modulators.

1. Introduction

When two or more drugs are concomitantly administrated or sequentially within a short period, there are risks of drug-drug interactions (DDIs). DDIs can be grouped in two classes, namely pharmacokinetic and pharmacodynamic DDIs (Beijnen and Schellens, 2004). Pharmacokinetic DDIs refer to influences on the absorption, distribution, metabolism, or elimination of a drug. Drug metabolizing enzymes or transporters are often involved in these processes (Gay et al., 2017). Pharmacodynamic DDIs occur when two or more concomitantly used drugs have complementary, similar or competitive mechanisms of action, which lead to synergistic, additive or antagonistic effect, respectively (Niu et al., 2019).

Since cancer is a typical age-related disease, cancer patients are frequently suffering from comorbidities such as diabetes, cardiovascular diseases, neuro-degenerative diseases, and infectious diseases (Sarfati et al., 2016). Drugs to treat these comorbidities are often co-administrated with anticancer drugs. Indeed, polypharmacy (with five or more concurrent medications) is common among elder cancer patients (Mohamed et al., 2020). On the other hand, anticancer drugs are one of the most toxic classes of medications with narrow therapeutic window, and they are generally prescribed in combinations to maximize therapeutic efficacy and minimize adverse effects. Furthermore, many cancer patients turn to complementary and alternative therapies such as traditional Chinese medicine or other ethnopharmacy, as well as certain functional foods or dietary supplements (Goss et al., 2014). All the above contribute to the high risk of drug-drug or herb-drug interactions in cancer patients. These interactions may result in therapeutic failure or serious adverse events and exert important impacts on the prognosis, mortality and life quality of cancer patients (Ismail et al., 2020; Sharma et al., 2019; Jermini et al., 2019).

Nuclear factor erythroid-derived 2-related factor 2 (Nrf2, gene symbol NFE2L2), together with its suppressive binding partner, Kelch-like ECH-associated protein 1 (Keap1), regulates the expression of many drug metabolizing and cyto-protective genes, including those involved in redox homeostasis, drug metabolism and transport, mitochondrial functions and DNA repair (Yamamoto et al., 2018; Bai et al., 2016). Nrf2/Keap1 signaling plays important and complicated roles in the

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initiation and progression of cancer, and has been implied in both the resistance to and the toxicities of anticancer drugs (Rojo de la Vega et al., 2018; Sporn and Liby, 2012). Thus, Nrf2/Keap1 signaling may play important roles in both pharmacokinetic and pharmacodynamic anticancer DDIs. Nevertheless, its potential roles in drug interaction during cancer treatment attracted little attention. Here we briefly summarize the involvement of Nrf2/Keap1 signaling in cancer treatment, and call attention to potential drug-drug or herb-drug interactions of anticancer drugs due to modulation of Nrf2/Keap1 signaling.

2. Nrf2/Keap1 signaling in cancer and other diseases

Nrf2 is a cap'n'collar (CNC) basic-leucine zipper (bZIP) transcription factor which regulates the transcriptional response of cells to oxidative stress and electrophilic substances. It has been more than 20 years since the first report of Nrf2-mediated induction of phase II drug metabolizing enzymes (Itoh et al., 1997). Then the molecular regulation and physiological functions of Nrf2 have been extensively investigated and reviewed (Yamamoto et al., 2018; Baird and Yamamoto, 2020; Tonelli et al., 2018). Therefore, it will only be briefly summarized in the present review. Under basal conditions, Nrf2 is bound to Keap1 through the DLG and ETGE motifs and located in cytoplasm at a low level with a short half-life time. Keap1 is an E3 ubiquitin ligase adaptor which targets Nrf2 for rapid ubiquitination and proteasomal degradation. When the cells are subjected to oxidative or electrophilic substances including reactive oxygen/nitrogen species (ROS/RNS), the highly reactive cysteine residues on Keap1 protein are directly modified, disrupting the binding between Keap1 and Nrf2. The released Nrf2 accumulates in the nucleus and forms heterodimers with small musculoaponeurotic fibrosarcoma oncogene homologue (Maf) proteins, then the heterodimers bind to specific antioxidant response elements (AREs) in the regulatory regions of Nrf2 target genes and boost their transcription. In addition to the cysteine modification- and Keap1-dependent mechanisms, Nrf2 activity could be regulated by β-TrCP-, HRD1-or p62/SQSTM1-dependent protein degradation (Rojo de la Vega et al., 2018), or by epigenetic mechanisms (Guo et al., 2015). Post-translational modifications of Nrf2 such as acetylation and phosphorylation by various kinases also modulate Nrf2 transcriptional activity under some conditions (Baird and Yamamoto, 2020). The regulatory network of Nrf2/Keap1 signaling is schematically depicted in Fig. 1.

In response to oxidative/electrophilic stresses, Nrf2 is known to regulate the expression of more than 500 cytoprotective genes and this number is likely to increase in the future (Tonelli et al., 2018). These genes are profoundly involved in cellular redox homeostasis (Yamamoto et al., 2018), drug detoxification (Bai et al., 2016), energy metabolism (Vomhof-Dekrey and PickloSr, 2012) and other stress responses such as DNA damage response (Sun et al., 2020; Kim et al., 2012). Specifically, Nrf2 is a major transcription factor regulating the expression of phase II drug metabolizing enzymes that are important for conjugation and detoxification of many drugs or carcinogens. Nrf2 protects the cells against a wide range of endogenous and exogenous insults, helps to maintain cellular homeostasis and offers the cells advantages to survive

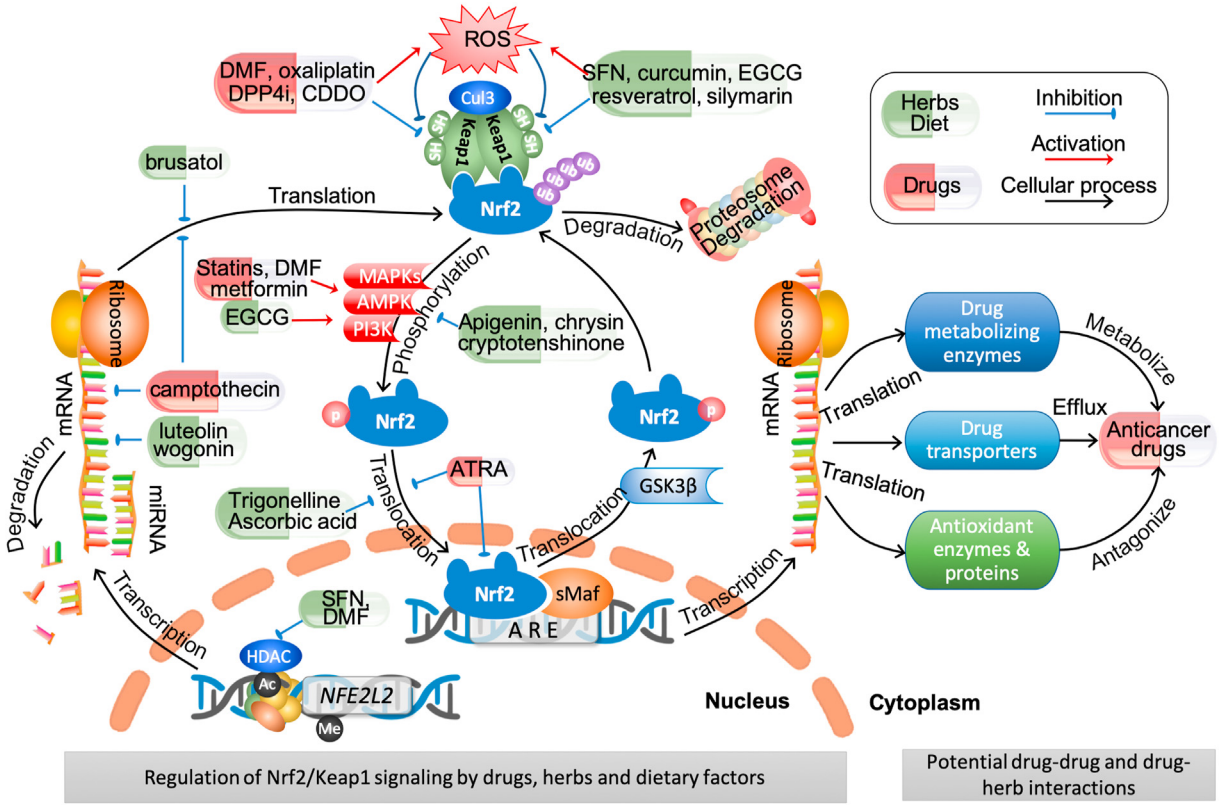

Fig. 1. Regulation of Nrf2/Keap1 signaling by drugs, herbal phytochemicals and dietary factors and its potential roles in anticancer drug-drug and drug-herb interactions. Under basal conditions, Nrf2 is bound to Keap1 through the DLG and ETGE motif, ubiquitinated by Cul3-E3 ubiquitin ligase and subjected for rapid proteasomal degradation. Upon oxidative or electrophilic stresses, the reactive cysteine residues on Keap1 protein are modified by these stressors including ROS and Nrf2 is released and translocated into nucleus, at where it forms heterodimers with small Maf proteins and boosts the transcription of ARE-driven genes, including antioxidant proteins, drug metabolizing enzymes and transporters. These genes are well known players in anticancer drug-drug and drug-herb interactions. In addition to the above core regulatory mechanism, Nrf2/Keap1 signaling could be modulated through other Keap1-independent mechanisms. Nrf2 protein can be phosphorylated and activated by MAPKs, AMPK and PI3K/Akt, while GSK3β phosphorylation promotes the exportation of Nrf2 from nucleus. The transcription of Nrf2 mRNA is regulated by DNA methylation and histone acetylation, the stability and translation of Nrf2 mRNA can be inhibited by certain compounds such as brusatol, camptothecin, luteolin and wogonin.

under unfavorable environments. Some typical drug metabolizing and cytoprotective genes regulated by Nrf2/Keap1 signaling and potentialyinvolved in the DDIs of anticancer drugs are summarized in Table 1 (Hayes and Dinkova-Kostova, 2014; Shen and Kong, 2009; Hirotsu et al., 2012; Ma, 2013).

Nrf2-deficient mice were more susceptible to oxidative injuries and chemical carcinogenesis, while Nrf2 activators protect against them (Sinha et al., 2013; Slocum and Kensler, 2011). Therefore, Nrf2 activators were initially considered as promising chemopreventive agents against various carcinogenesis (Hayes et al., 2010). However, Nrf2 was soon found to be aberrantly activated in many tumors by oncogenes or Keap1 mutations (DeNicola et al., 2011). Neoplastic cells can "hijack" Nrf2/Keap1 signaling to reprogram cellular metabolism, promote tumor survival and proliferation, drive tumorigenesis and result in chemo- and radio-resistance (Rojo de la Vega et al., 2018; Sporn and Liby, 2012). Thus, Nrf2/Keap1 signaling inhibitors as anticancer drugs have attracted increasing academic and industrial interests (Telkoparan-Akillilar et al., 2019; Zhu et al., 2016). To date, the roles of Nrf2/Keap1 signaling in cancer development and treatment are still controversial and highly sensitive to the context.

As a multifaceted transcription factor, Nrf2 has also been implied in the pathogenesis of many other chronic diseases including diabetes, respiratory disease, cardiovascular disease, inflammatory disease, neurodegenerative disease and autoimmune disease (Michalickova et al., 2020; Cuadrado et al., 2019). Unlike the case in cancer, the protective role of Nrf2 is generally favored for prevention or treatment of these diseases. Indeed, the first US FDA-approved Nrf2 activator, dimethyl fumarate (DMF), has been successfully marketed as multiple sclerosis (MS) treatment with impressive performance, and more Nrf2 activators are in phase II/III clinical trials and are expected to enter the market within a few years (Michalickova et al., 2020; Cuadrado et al., 2019). Furthermore, Nrf2 has been reported to be involved in pathogen infection, and activation of Nrf2 has been proposed as a host-directed therapeutic strategy to treat infectious diseases including COVID-19 (Deramaudt et al., 2013; Olagnier et al., 2020).

Table 1
Drug-metabolizing enzymes and cytoprotective genes regulated by Nrf2/keap1 signaling [references 11, 16, 21–24, 35].

	Gene symbol	Name
Phase I metabolism: oxidation, reduction and hydrolysis	CYP1B1	Cytochrome P450, family 1, subfamily B, polypeptide 1
	CBR1	Carbonyl reductases1 (and 3)
	mEH	Microsomal epoxide hydrolase
	ALDH1A1	Aldehyde dehydrogenase 1 family, member A1
	ALDH3A1	Aldehyde dehydrogenase 3 family, member A1 (and A2)
	AKR1B1	Aldo-keto reductase family 1, member B1 (and 1B8 and 1B10)
	AKR1C1	Aldo-keto reductase family 1, member C1 (and 1C2 and 1C3)
	AKR1B10	Aldo-keto reductase family 1, member B10
Phase II metabolism: drug conjugation	NQO1	NAD(P)H:quinone oxidoreductase 1
	GSTA1,2,3,5	Glutathione S-transferase class A1,2,3,5
	GSTM1,2,3	Glutathione S-transferase class M1,2,3
	GSTP1	Glutathione S-transferase class Pi 1
	γGCS	γ-glutamylcystein synthetase
	MGST1	microsomal glutathione S-transferase 1 (and 2)
	UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1
	UGT2B7	UDP glucuronosyltransferase 2 family, polypeptide B7 (and 2B34)
	SULT1A1	Sulfotransferase family, cytosolic, 1 A, member 1 (and 2)
	ABCB1	ATP Binding Cassette Subfamily B Member 1 (MDR1/*P*-glycoprotein)
	ABCC2,3,6	ATP Binding Cassette Subfamily C Member 1/Multidrug resistance associated protein 1 (MRP1)
	ABCG2	ATP Binding Cassette Subfamily G Member 2 (MXR/BCRP transporter)
	OATP2B	organic anion-transporting polypeptide
Cytoprotective: antioxidant	SOD3	Extracellular superoxide dismutase
	GCLC	glutamate-cysteine ligase, catalytic subunit
	GCLM	glutamate-cysteine ligase, modifier subunit
	GPX2	glutathione peroxidase 2
	GPX4	glutathione peroxidase 4
	GSR1	glutathione reductase
	TXNRD1	thioredoxin reductase 1

3. Nrf2/Keap1 signaling modulators that cancer patients could be exposed to

As discussed above, Nrf2 is an attractive drug target for treating many chronic and even infectious diseases, and several Nrf2/Keap1 signaling modulators are under active development or even been marketed (Telkoparan-Akillilar et al., 2019; Cuadrado et al., 2019; Panieri et al., 2020). On the other hand, some other drugs or drug candidates, though initially were developed for targets other than Nrf2/Keap1, have also been found to modulate Nrf2/Keap1 signaling. These drugs, no matter anticancer reagents or not, could be concurrently administrated to cancer patients due to comorbidities. Moreover, plants are the most abundant resource of Nrf2 activators, and cancer patients could be exposed to these phytochemicals through ingestion of herbs and dietary plants as complementary and alternative therapies. Some typical Nrf2/Keap1 signaling modulators including both activators and inhibitors that could be co-administrated to cancer patients are summarized in Table 2, and the regulatory mechanisms of Nrf2/Keap1 signaling by these drugs, herbal phytochemicals and dietary factors, and their potential roles in anticancer drug-drug and drug-herb interactions are presented in Fig. 1. A few examples will be discussed in more details below.

3.1. *Nrf2 activators*

Nrf2 can be activated through Keap1-dependent or independent mechanisms (Baird and Yamamoto, 2020). Most Keap1-dependent activators are electrophilic compounds that covalently modifying the sulfhydryl group of reactive cysteine residues in Keap1 protein, while some others can modulate the protein-protein interactions in Keap1-Nrf2 or Keap1-Cul3 complexes, and finally stabilize Nrf2 protein (Yamamoto et al., 2018; Baird and Yamamoto, 2020; Tonelli et al., 2018). Some protein-protein interaction inhibitors of Keap1–Nrf2, like tetrahydroisoquinoline, thiopyrimidine and naphthalene have been discovered using virtual screening methods, but their therapeutic potential need to be further investigated (Lu et al., 2016; Robledinos-Antón et al., 2019). Nrf2 could also be activated through post-translational modifications independent of Keap1. For example, Nrf2 can be phosphorylated and activated by kinases such as AMP-activated protein kinase (AMPK), protein kinase C (PKC), phosphatidylinositol-3-kinase/protein kinase B (PI3K/PKB or PI3K/Akt) and mitogen-activated protein kinases (MAPKs) (Xu et al., 2006). The sulfhydryl-dependent Keap1 modifications are often sensitive to other sulfhydryl groups abundant in cellular context such as GSH and thioredoxin, while the selectivity of Keap1-independent activation is lower than Keap1-dependent activation.

DMF (commercial name Tecfidera®) is the first Nrf2-targeting drug approved by FDA in 2013 to treat multiple sclerosis (MS). Before that DMF is used to treat psoriasis (approved in Germany as Fumaderm®) (Kourakis et al., 2020). DMF and its metabolite monomethyl fumarate (MMF) modulate inflammatory and immune responses through both Nrf2-dependent and independent mechanisms, especially in central nervous system (Michalickova et al., 2020; Schulze-Topphoff et al., 2016; Gillard et al., 2015; Zaro et al., 2019). And multiple molecular targets of DMF have been proposed and identified (Piroli et al., 2019; Fox et al.,

Table 2
Nrf2/Keap1 signaling modulators that cancer patients could be exposed to.

Name	Indications	Status	References or NCT Identifier
Nrf2 activators			
Dimethyl fumarate	Multiple sclerosis, Psoriasis	Approved	Lu et al. (2016)
	Cutaneous T cell lymphoma, Adult brain glioblastoma, Chronic lymphocytic leukemia	Phase I/II	(Gillard et al., 2015; Zaro et al., 2019), NCT02546440/02337426/02784834
Bardoxolone methyl (RTA-402)	Diabetes and CKD	Phase II/III	(Fox et al., 2014), NCT02316821/03550443/03366337
	Pulmonary hypertension	Phase III	NCT02657356/03068130
	Advanced Solid Tumors	Phase I	(Piroli et al., 2019), NCT00529438/00508,807
	Lymphoid Malignancies		
	COVID-19	Phase II/III	NCT04494646
Statins	Dyslipidemia	Approved	(Zhu et al., 2017; Aubets et al., 2019; Loft et al., 2020)
Saxagliptin, sitagliptin	T2DM	Approved	Zecca et al. (2020)
Metformin	T2DM	Approved	(Ghajarzadeh et al., 2020; Booth et al., 2014)
Sulforaphane	Breast cancer, Prostate Cancer, lung cancer	Phase II	(Nicolay et al., 2016; Al-Jaderi and Maghazachi, 2016; Hong et al., 2012), NCT00843167/01228084/03232138
	schizophrenia	Phase II	NCT04521868
	Autism	Phase III	NCT02654743
	cystic fibrosis	Phase II	NCT01315665
	Helicobacter Pylori Infection	Phase IV	NCT03220542
Silymarin	NAFLD, NASH	Phase II	NCT00680407
	Metastatic Colorectal Cancer	Phase IV	(Loft et al., 2020) NCT03130634
Epigalocatechin 3-gallate (EGCG)	Prostate cancer	Phase II	(Chian et al., 2014), NCT00676780
	Obese, Hyperlipidemia	Phase III	NCT02116517
	Multiple System Atrophy	Phase III	NCT02008721
Curcumin	Prostate Cancer, Pancreatic cancer	Phase II/III	(Niedzielski et al., 2020), NCT02064673/00192,842/02336087
	Type 2 diabetes, Prediabetes	Phase IV	NCT01052025/03917784
	Major depression	Phase IV	NCT01750359
Resveratrol	Colon Cancer	Phase I	(Niedzielski et al., 2020), NCT00256334/00433,576
	Nonischemic cardiomyopathy	Phase III	NCT01914081
Rapamycin	Diabetes Mellitus, Type 1	Phase III	NCT01060605
Nrf2 inhibitors			
Brusatol	Antitumor effects	Preclinical	(Jang et al., 2016; Cuadrado et al., 2018; Wang et al., 2016)
Camptothecin	Advanced Solid Tumors	approved	Tschop et al. (2016)
Metformin	T2DM	approved	(Ashabi et al., 2015; Jiang et al., 2018)
	Endometrial Cancer	early phase I	NCT01205672
All trans-retinoic acid	Adenoid Cystic Carcinoma	Phase II	NCT03999684
	Acute Promyelocytic Leukemia	Phase IV	NCT01987297
Ascorbic acid	COVID-19	Phase II	NCT04363216
	•Acute Kidney Injury	Phase IV	NCT03921099
Ursolic acid	Prostate Cancer	early phase I	NCT04403568
	Sarcopenia	Phase II/III	NCT02401113
Luteolin	Autism Spectrum Disorders	Phase II	NCT01847521

2014). DMF activates Nrf2/Keap1 signaling at lower concentrations mainly by direct modification of sulfhydryl groups on Keap1 protein, while HDAC inhibition and casein kinase 2-mediated Nrf2 phosphorylation also contribute to DMF-induced Nrf2 activation (Iniaghe et al., 2015; Kalinin et al., 2013). On the other hand, higher concentrations of DMF (>25 mmol/L) may inhibit Nrf2 and induces oxidative stresses in several cancer cell lines (Saidu et al., 2017).

There are at least two publications investigated the potential drug-drug interactions between DMF and other drugs. In a clinical investigation (Zhu et al., 2017), the potential DDI between DMF and an oral contraceptive (OC, norgestimate/ethinyl estradiol) was tested in healthy women, and no impact of DMF on the DM/PK of OC was identified. Another publication (Aubets et al., 2019) examined the direct impact of DMF on cytochrome P450 (CYP) enzymes and P-glycoprotein (P-gp) activities *in vitro*, and the results indicate that DMF is unlikely to interfere with CYP or P-gp activities at clinically relevant concentrations. However, it is well recognized that DMF activates Nrf2 which regulates the expression of phase II metabolizing enzymes, but this issue was not considered. Moreover, the potential interactions between DMF and anticancer drugs were not investigated.

It is noteworthy that psoriasis is associated with increased risks of cancer, especially non-melanoma skin cancer, lymphoma, and lung cancer (Loft et al., 2020). Although the prevalence of cancer in MS patients is similar to or less than that in general populations, the frequency of cancer diagnosis increased over time among MS patients but not in controls (Zecca et al., 2020; Ghajarzadeh et al., 2020). There are unneglectable chances for cancer patients to be exposed to DMF, the potential DDIs between DMF and anticancer drugs deserve attention. Indeed, DMF has been tested as anticancer agents *in vitro*, and has been shown to interact with proteasome inhibitors (Booth et al., 2014) or synergize with ruxolitinib (Tavallai et al., 2016). Moreover, several clinical trials are undergoing to test different formulations of DMF and fumarate derivatives in cancer therapies, like cutaneous T cell lymphoma, adult brain glioblastoma and chronic lymphocytic leukemia (Nicolay et al., 2016; Al-Jaderi and Maghazachi, 2016). The outcomes of these trials may help to further clarify the potential DDIs of DMF with anticancer drugs.

Bardoxolone methyl (CDDO-Me or RTA402) is a synthetic potent Nrf2-activating triterpenoid initially developed for cancer prevention and treatment (Hong et al., 2012). Similar to the situation of DMF, multiple molecular targets including PPARγ, PML-RARα and IKKβ have been proposed for bardoxolone, but Nrf2/Keap1 is recognized as its major target. After the phase I clinical trial in lymphoma patients, bardoxolone was re-purposed for end-stage renal disease treatment, but unfortunately failed in phase III trial due to safety issues (de Zeeuw et al., 2013). Currently bardoxolone is in phase II/III clinical trials for pulmonary hypertension, polycystic kidney disease, type 2 diabetes mellitus (T2DM), chronic kidney disease and most recently COVID-19 (NCT02657356, NCT03068130, NCT03366337, NCT03550443, NCT04494646, respectively). In addition, the anticancer activities of bardoxolone and its derivatives are under experimental or pre-clinical

investigations. Obviously, bardoxolone has a good chance to interact with other anticancer drugs in clinical trials or clinical use if approved by FDA, and the potential DDIs between bardoxolone and other anticancer drugs due to activation of Nrf2/Keap1 signaling must be taken into account.

Some other FDA-approved drugs, including anticancer drugs, have been reported to activate Nrf2/Keap1 signaling. An ARE-luciferase reporter-based screening identified cisplatin, carmustine and acrolein (an active metabolite of cyclophosphamide) as Nrf2 activators (Wang et al., 2006). Oxaliplatin, a third-generation platinum-based drug used to treat colorectal and ovarian cancer, activates Nrf2/Keap1 signaling conferring protection against the cytotoxicity of anticancer drugs (Wang et al., 2014; Chian et al., 2014). Statins are the most prescribed lipid-lowering drugs to prevent cardiovascular diseases. Some statins such as simvastatin, lovastatin and fluvastatin can activate Nrf2 through extracellular signal-regulated kinase (ERK) or PI3K/Akt pathway (Niedzielski et al., 2020; Jang et al., 2016; Cuadrado et al., 2018). Second line hypoglycemic dipeptidyl peptidase-4 inhibitors (DPP-4i) saxagliptin and sitagliptin have been reported to upregulate Nrf2 signaling and promoted tumor metastasis (Wang et al., 2016). The mechanisms of metformin to treat T2DM are not completely understood, and it has been found to activate Nrf2/Keap1 signaling in neurons, liver and skeletal muscle in an AMPK-dependent manner (Tschop et al., 2016; Ashabi et al., 2015). However, some other reports proposed metformin as a Nrf2 inhibitor and will be discussed later.

Many herbal or dietary ingredients are strong Nrf2 activators. Sulforaphane (SFN), an isothiocyanate found in cruciferous vegetables, has been reported as a very potent Nrf2 activator through direct modification of Keap1 or by inhibiting HDAC. SFN has been well documented to prevent the initiation and development of several cancers and has been recommended as a chemopreventive agent against various cancers (Jiang et al., 2018). Several clinical trials have been carried out to test the therapeutic efficacy of SFN on breast cancer (Atwell et al., 2015) [NCT03934905], prostate cancer (Traka et al., 2019), melanoma (Tahata et al., 2018), and other diseases such as schizophrenia [NCT04521868], autism [NCT02654743] and cystic fibrosis [NCT01315665]. On the other hand, SFN modulates the enzymatic drug metabolizing system and interacts with drugs (Lubelska et al., 2012), and has been found to increase tumor growth once the tumor is already formed (Tao et al., 2018). Silymarin has been widely used to treat liver diseases, and activation of Nrf2/Keap1 signaling is one of its major mechanisms of action (Xie et al., 2019). Epigallocatechin-3-gallate (EGCG) from green tea extract, curcumin from turmeric, resveratrol from grape seeds, and many other phytochemicals, are known as Nrf2 activators potentially involved in cancer care (Zhu et al., 2020; T et al., 2020). According to epidemiological, laboratory and clinical studies, these phytochemicals have been regarded as cancer-preventive or curative agents, with activation of Nrf2 as one of their mechanisms of action. Nevertheless, they could also interact with anticancer therapies due to activation of Nrf2/Keap1 signaling.

3.2. *Nrf2 inhibitors*

As the "dark side" of Nrf2 in cancer progression and therapy resistance is being revealed, Nrf2 inhibitors receive more and more interests for their potential applications in reversing chemoresistance or suppressing tumor growth. Though Nrf2 inhibitors are relatively rare and the underlying mechanisms are elusive, several promising Nrf2 inhibitors have been identified and some of them have progressed to clinical development. Notably, a few approved drugs have been found to inhibit Nrf2/Keap1 signaling, thus potential DDIs between these drugs and anticancer drugs should be considered in cancer treatment.

Brusatol, a quassinoid from *Brucea javanica* seeds, might be the best characterized Nrf2 inhibitor to the date. It rapidly decreases Nrf2 protein levels in a wide array of cancer cells and sensitizes the cells to chemotherapy or radiotherapy (Ren et al., 2011). Brusatol is located to the endoplasmic reticulum and inhibits both cap-dependent and cap-independent protein translation, especially those short-lived proteins, like Nrf2 (Harder et al., 2017). Inhibition of Nrf2 by brusatol in hepatocytes also sensitized the cells to chemical toxicity, highlighting the involvement of Nrf2 inhibition in evaluation of potential adverse events resulted from non-target cells (Olayanju et al., 2015). Several other natural compounds, such as apigenin, chrysin, cryptotanshinone, luteolin, trigonelline, triptolide, wogonin, etc., have been reported to inhibit Nrf2/Keap1 signaling in cancer cells at different concentrations through various mechanisms like accelerating mRNA degradation, down-regulating PI3K/Akt and ERK pathways to decrease Nrf2 phosphorylation, and reducing nuclear import of Nrf2, etc. (reviewed in (Telkoparan-Akillilar et al., 2019; Zhu et al., 2016; Panieri et al., 2020)). These compounds, though none have progressed to clinical development yet, have attracted significant research interests for their potential applications in cancer therapy.

Several prescription drugs and vitamins have been reported to inhibit Nrf2/Keap1 signaling in cancer cells. Camptothecin, a chemotherapeutic DNA topoisomerase inhibitor, can suppress Nrf2 activity in hepatocellular carcinoma cells and sensitize them to chemotherapies (Chen et al., 2017). Camptothecin is an anticancer drug approved to treat a broad spectrum of cancers, inhibition of Nrf2 could be one of the mechanisms underlying the synergistic effects between camptothecin and other therapeutic agents. Metformin has also been found to inhibit Nrf2 and reverse chemoresistance in various cancer cell lines (Cai et al., 2020; Bai et al., 2018). More importantly, metformin diminished the deleterious impacts of Nrf2/Keap1 signaling on the prognosis of breast cancer patients with T2DM (Urpilainen et al., 2019). All trans-retinoic acid (ATRA) inhibits Nrf2 activity in cancer cells via the crosstalk between RARalpha and Nrf2, but not in normal tissues (Wang et al., 2007). Ascorbic acid was reported to sensitize cervical carcinoma and leukemia cells to anticancer drugs while protecting normal cells and tissues, and Nrf2/Keap1 signaling was involved in both effects (Wu et al., 2020; Tarumoto et al., 2004). Identification of more Nrf2/Keap1 signaling inhibitors from approved drugs is an attractive strategy to improve therapeutic efficacy.

Interestingly, many of these Nrf2/Keap1 signaling inhibitors, including natural compounds such as apigenin, chrysin and luteolin, drugs like metformin and ATRA, have also been reported to activate Nrf2 at different concentrations or in different tissues or cell lines. Such phenomena underpin the importance of clinically relevant dosages when talking about potential DDIs related to Nrf2/Keap1 signaling. The tissue-specific concentrations of specified drugs to activate or inhibit Nrf2/Keap1 signaling must be clinically relevant for patients, especially most of these drugs are not designed to target Nrf2/Keap1 signaling. ATRA at 1 μM was found to suppress tBHQ, β-naphthoflavone, or SFN-induced activation of Nrf2 in cancer cells (Wang et al., 2007), but itself was also reported to activate Nrf2 signaling in a dose-dependent manner *in vitro* and in vivo (Tan et al., 2008). The clinical dose of metformin as an oral hypoglycemic drug ranges between 500 and 2000 mg/d, which translates into about 60–260 mg/kg in mice, and this concentration has been reported to activate Nrf2 in mice (Wu et al., 2018; Prasad et al., 2017). Meanwhile, the drugs designed to target Nrf2/Keap1 signaling such as DMF or bardoxolone at their effective doses will activate Nrf2/Keap1 signaling, and supposedly the subsequent expression of drug metabolizing enzymes and antioxidant proteins. Cancer patients could also be exposed to some Nrf2/Keap1-targeting agents such as SFN through dietary supplements or herbs. SFN has not been formally approved for any medical usage, but broccoli sprouts or broccoli seed extract that can provide SFN are available as food additives or dietary supplements in many countries, and the allowed dosage is enough to activate Nrf2/Keap1 signaling in vivo. Thus, it is expected that these drugs could interact with anticancer drugs through modulation of Nrf2/Keap1 signaling at a clinically relevant dosage. In general, extra caution should be paid to the potential DDIs between these Nrf2 modulators and anticancer drugs, especially those are sensitive to Nrf2 modulators.

4. Anticancer drugs that could interact with Nrf2/Keap1 signaling modulators

Activation of Nrf2/Keap1 signaling due to mutations in NFE2L2/KEAP1 genes or aberrant upstream signaling in cancer is well known to promote cancer progression and lead to resistance to anticancer drugs through both pharmacokinetic and pharmacodynamic mechanisms. These mechanisms include upregulation of antioxidant and detoxification enzymes, activation of drug efflux transporters, inhibition of drug-induced cellular apoptotic responses and induction of Nrf2-dependent proteasome activity (Rojo de la Vega et al., 2018; Panieri et al., 2020). On the other hand, adverse events resulted from anticancer drugs could also be affected by Nrf2/Keap1 signaling in normal tissues (Yarmohammadi et al., 2020; Fang et al., 2020). Due to the broad participation of Nrf2/Keap1 signaling in the metabolism of and cellular defense against anticancer drugs in both cancerous and normal cells, it is expected that more and more anticancer drugs would be identified to be sensitive to Nrf2/Keap1 signaling. A plethora of anticancer drugs have already been confirmed to be sensitive to Nrf2/Keap1 signaling modulators, and some examples are summarized in Table 3 and discussed below.

4.1. Nrf2/Keap1 signaling in resistance to anticancer drugs

The aberrant activation of Nrf2 is an important reason accounting for the chemoresistance of platinum-based drugs. For example, Cisplatin can be detoxified by coordination to GSH and transported via MRP2, both are regulated by Nrf2/Keap1 signaling (Homma et al., 2009). A549 human lung adenoma cells, with somatic mutation at the Keap1-Kelch domain, is resistant to cisplatin treatment; while NCI H231 human lung cancer cells, with a mutation at the Keap1-LVR domain which increases Nrf2 degradation, is sensitive to cisplatin (Silva et al., 2019). In Keap1-deficient non-small cell lung cancer, constitutive Nrf2 activation conferred resistance to carboplatin (Singh et al., 2016). Oxaliplatin is sensitive to Nrf2 activity, and Nrf2/Keap1 signaling inhibitor could sensitize oxaliplatin-resistant cancer cells to chemotherapeutic drugs (Wang et al., 2014; Chian et al., 2014).

Nrf2 over-activation by Keap1 mutation reduced the sensitivity of biliary tract cancer cells to 5-fluorouracil (5-FU) (Shibata et al., 2008). Similar effect was seen in iASPP-overexpression/knockdown cancer cells, which is an antioxidant factor competing with Nrf2 for Keap1 binding (Ge et al., 2017). A clinical investigation on gastric cancer showed that Nrf2 could be a predictive marker for 5-FU resistance and prognosis (Hu et al., 2013). Nrf2 inhibition enhances the therapeutic efficacy of paclitaxel and docetaxel in ovarian cancer, non-small cell lung cancer and endometrial cancer (Chen et al., 2019; Manandhar et al., 2012; Jiang et al., 2010). Acquired resistance to anthracycline antibiotics doxorubicin is accompanied by Nrf2 over activation in various cancer cells, and inhibition of Nrf2 re-sensitized resistant cells to these drugs (Shim et al., 2009). In addition, the resistances to gemcitabine, temozolomide, bortezomib, arsenic trioxide, and some other chemotherapeutic drugs have all been reported to be regulated by Nrf2/Keap1 signaling (Wang et al., 2008).

Along with the increased prescription of targeted kinase/enzyme inhibitors such as tyrosine kinase inhibitors (TKIs), the potential roles of Nrf2/Keap1 signaling in targeted therapies are increasingly reported. Overexpression of Nrf2 target genes by acquired Keap1 mutation mediates resistance to gefitinib and cross-resistance to afatinib and osimertinib (Park et al., 2018). Nrf2 regulates the sensitivity of ovarian cancer cells to lapatinib and erlotinib through HER1 signaling (Kankia et al., 2017). Activation of Nrf2 signaling by hemin reduces cellular sensitivity to imatinib (Tarumoto et al., 2004; Nagai et al., 2008).

Table 3
Anticancer drugs that could interact with Nrf2/Keap1 signaling modulators.

Drug	Effect	Type of study	References
Cisplatin	Drug resistance	In vitro, in vivo and TCGA database	(Zhu et al., 2020; T et al., 2020)
	Nephrotoxicity	In vivo	Yarmohammadi et al. (2020)
Carboplatin	Drug resistance	In vitro and in vivo	Ren et al. (2011)
Oxaliplatin	Drug resistance	In vitro	(Kalinin et al., 2013; Saidu et al., 2017)
	Peripheral neuropathy and hepatotoxicity	In vitro and in vivo	(Fang et al., 2020; Homma et al., 2009)
5-FU	Drug resistance	In vitro, in vivo and clinical trial	(Harder et al., 2017; Olayanju et al., 2015; Chen et al., 2017)
Paclitaxel, Docetaxel	Drug resistance	In vitro, in vivo and clinical specimens	(Cai et al., 2020; Bai et al., 2018; Urpilainen et al., 2019)
Doxorubicin	Drug resistance	In vitro	Wang et al. (2007)
	Cardiotoxicity	In vitro and in vivo	Prasad et al. (2017)
Gefitinib, afatinib, osimertinib	Drug resistance	In vitro, in vivo and patient tissue samples	Tarumoto et al. (2004)
Lapatinib, erlotinib	Drug resistance	In vitro and in vivo	Tan et al. (2008)
Imatinib	Drug resistance	In vitro and in vivo	(Lubelska et al., 2012; Wu et al., 2018)
Cyclophosphamide	Hematotoxicity	In vitro and in vivo	Silva et al. (2019)

4.2. Nrf2/Keap1 signaling in undesirable toxicity of anticancer drugs

Oxidative stress and mitochondrial damage are the most common mechanisms for the toxicity of chemotherapy drugs. Given the crucial roles of Nrf2 in oxidative stress, mitochondrial damage, drug metabolism and transport, it is expectable that the toxicities of anticancer drugs to normal cells are also regulated by Nrf2/Keap1 signaling, though less noticed and investigated than drug resistance.

The application of doxorubicin has been limited by its acute and chronic cardiotoxicity, with oxidative stress as the primary cause of this cardiotoxicity (Yarmohammadi et al., 2020). Nrf2 deficiency aggravated doxorubicin-induced oxidative stress and abnormal autophagic activities (Li et al., 2014). Cisplatin can induce Nrf2-dependent cytoprotective genes in wild type mice kidney, but this induction is blunted in Nrf2-deficient mice, accompanied by severe oxidative damage and inflammatory reaction in the kidney (Aleksunes et al., 2010). Nrf2-deficient mice are more susceptible to oxaliplatin-induced peripheral neuropathy (Yang et al., 2018) and hepatotoxicity (X.J.He et al., 2017). The hematological toxicity of cyclophosphamide and its active metabolite acrolein is deteriorated in Nrf2 deficient mice (Que et al., 2016). Nrf2 activators have been well-recognized to protect normal cells against electrophilic insults, thus it is reasonable to use Nrf2 activators to protect against the toxicity of anticancer drugs. A wide range of Nrf2 activators including natural compounds such as sulforaphane (Yarmohammadi et al., 2020; Bose et al., 2018) and silymarin (Rašković et al., 2011), and synthetic drugs such as bardoxolone (Atilano-Roque et al., 2016) and DMF (Miyagi et al., 2019) have been used to reduce the toxicities of chemotherapeutic drugs. Some of these chemo-protectants, such as SFN against doxorubicin-induced cardiotoxicity, have progressed to clinical trials [NCT03934905].

5. Conclusions and future perspectives

The important roles of Nrf2/Keap1 signaling in the prevention and treatment of cancers have been extensively demonstrated and recognized. It is well accepted that the resistance to and toxicities of certain

cancer therapies are profoundly impacted by Nrf2/Keap1 signaling, either good or bad. Therefore, the potential roles of Nrf2/Keap1 signaling in drug-drug, herb-drug or diet-drug interactions of anticancer drugs cannot be neglected. The occurrence of these interactions is an integrated result of dosage, tissue distribution, metabolism and excretion, as well as activities other than modulating Nrf2/Keap1 signaling, of the drugs and herbs in consideration. These interactions could be exploited to enhance therapeutic efficacy or reduce toxicity, which is the major focus of current literatures. For instance, Nrf2 inhibitors have been developed to reverse the chemoresistance of cancer cells, while Nrf2 activators have been examined as potential chemo-protectants to reduce the toxicities or side effects of chemotherapies.

On the other hand, the undesirable interactions of anticancer drugs and Nrf2/Keap1 signaling modulators, such as increased chemoresistance or deteriorated toxicities, are far less reported, possibly due to a publication bias. However, it does not mean such interactions are scarce or risk-free. As a matter of fact, Nrf2/Keap1 signaling modulators, especially activators, are widely presented in drugs in clinical application or development, herb medicines and diets. Indeed, many herbs that have been reported to interact with anticancer drugs have also been reported to activate Nrf2/Keap1 signaling. On the other hand, some of these herbs or herb ingredients have also been reported to be cancer preventive or curative under certain situations, and cancer patients could be exposed to these substances when concomitantly taking anticancer drugs. Therefore, greater attention should be paid to the potential roles of Nrf2/Keap1 signaling in interactions with anticancer drugs, in either clinical practices or drug development.

CRediT authorship contribution statement

Jingya Wang: Writing – original draft, Writing – review & editing, Visualization. **Jin Yang:** Writing – original draft, Writing – review & editing, Visualization. **Mingnan Cao:** Resources, Writing – review & editing. **Zhigang Zhao:** Resources, Writing – review & editing. **Baoshan Cao:** Resources, Writing – review & editing. **Siwang Yu:** Conceptualization, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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