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A Review on Some Dietary Phytochemicals as Potential Cancer Chemoprevention and Chemotherapeutic Agents

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Abstract

Cancer is a disease with multiple etiologies and has gained the interest of researchers in search for its prevention and therapeutic targets. Mammalian cells are constantly exposed to electrophilic/oxidative stresses that are considered to be part of the most essential and pervasive causes of cancer. The Nuclear factor erythroid 2-related factor 2 (Nrf2) is crucial in either inducing or suppressing angiogenesis. As a result, it has been implicated in numerous stages of carcinogenesis through association with several signaling pathways and molecules. This transcription factor may be regarded as key target for chemoprevention of cancer. As a transcription factor, Nrf2 exert a great function in ARE-driven genes expression. More so, it plays an important role in the up-regulation of these genes towards oxidative challenges. Numerous phytochemicals especially in fruits as well as edible vegetables have shown to activate Nrf2 and elicit antioxidant response. Inducing the synthesis of antioxidant/phase II detoxifying enzymes (UDP-glucuronyltransferase, Heme oxygenase-1, NAD(P)H: quinone oxidoreductase and Glutathione-s-transferase) by natural compounds present in diet is among the most efficient approaches for cancer prevention in human. This review discusses Keap1-Nrf2-ARE pathway as a prime target for cancer chemoprevention, its underlying mechanisms and modulation by dietary phytochemicals as well as effects of combination of phytochemicals.

Keywords: Phytochemicals, Cancer, Plants, Nrf2, Chemoprevention, oxidative stress

INTRODUCTION

Cancer chemoprevention entails the use of synthetic or natural compounds to prevent the danger of cancer initiation and development (Hu *et al*., 2006). A large number of foods founds in our typical diet, such as vegetables, fruits grains, seeds and spices have been demonstrated to be effective in cancer prevention (Dinkova-Kostova *et al*., 2005). Numerous findings have reported that different naturally-occurring dietary compounds possess significant cancer preventive effects and numerous experimental approaches have described the mechanisms by which they elicit these actions (Surh *et al*., 2003). Several animal models and cancer cell lines have been used to assess chemopreventive potentials of many phytochemicals and evaluate the mechanisms by which they prevent cancer (Shen *et al*., 2006). These researches have unveiled a large number of potential phytochemicals with cancer-preventive properties, such as, polyphenols from flavonoids from soybeans green and black tea, and isothiocyanates from cruciferous vegetables (Chen *et al*., 2005).

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These dietary phytochemicals have abroad anti-cancer effect mediated by various cellular mechanisms. These includes electrophilic or oxidative stresses that can lead to the stimulation of a wide range of cellular processes like increase in expression of phase II detoxifying/antioxidant enzymes [GST, HO-1, UGT] (Shen *et al*., 2006; Hu *et al*., 2006). Therefore, it can be concluded that these chemopreventive agents exhibited pleiotropic effects which can be deduce to be as a result of careful modulation of many signaling cascades within the cell by dietary phytochemicals (Dinkova-Kostova *et al*., 2005).

The majority of dietary phytochemicals presumably combine a number of different approaches to achieve their chemopreventive benefits. These include preventing carcinogens from binding to DNA and/or activating metabolic processes, promoting detoxification, stopping proliferation and angiogenesis or metastasis of cell, inducing apoptosis or differentiation of precancerous or malignant cells, repairing DNA damage, among other things (Silva-Islas *et al*., 2018).

Several findings have associated phytochemicals with the induction of synthesis of antioxidant enzymes /detoxifying for cellular defense, however, additional useful phytochemicals are found in dietary plants which have capacity to cause apoptotic death of the cell in neoplastic or even pre-neoplastic cells via different growth inhibitory mechanisms (Dinkova-Kostova *et al*., 2002).

The activity of these phytochemicals was assessed mainly as single compounds but also in the natural food matrix. Recently, attempts were made to select the best combination of naturally occurring compounds for chemoprevention or therapeutic purposes, including modulation of Nrf2 pathway. This review presents the current knowledge of the modulatory effect of selected phytochemicals in cancer prevention and treatment, with a particular focus on their combinatorial effect on Nrf2 activities in relation to their possible chemopreventive or therapeutic applications.

Nuclear factor-erythroid 2-related factor 2 (Nrf2)

Nrf2 is a basic region-leucine zipper (bZIP) proteins belonging to the family of Cap "n" collar (CNC). It performs a vital role in mediating gene expression through ARE-dependent pathway (Zhang, 2006). Furthermore, earlier studies have revealed that Nrf2 plays a great role in the regulation of carcinogens-driven carcinogenesis.

The effect of activated Nrf2 in cytoprotection has been reported in the Nrf2 knockout mice susceptible to cancers (Fahey, 2006); thus, the Nrf2 signaling activation and subsequent induction of its target genes identifies its importance as potential therapeutic target for chemoprevention of cancer.

Evidences exist from both epidemiological and experimental studies reporting the importance of products from dietary sources in disease chemoprevention. It is recommended that consumption of these dietary products is a new reliable strategy in the prevention of carcinogenesis.

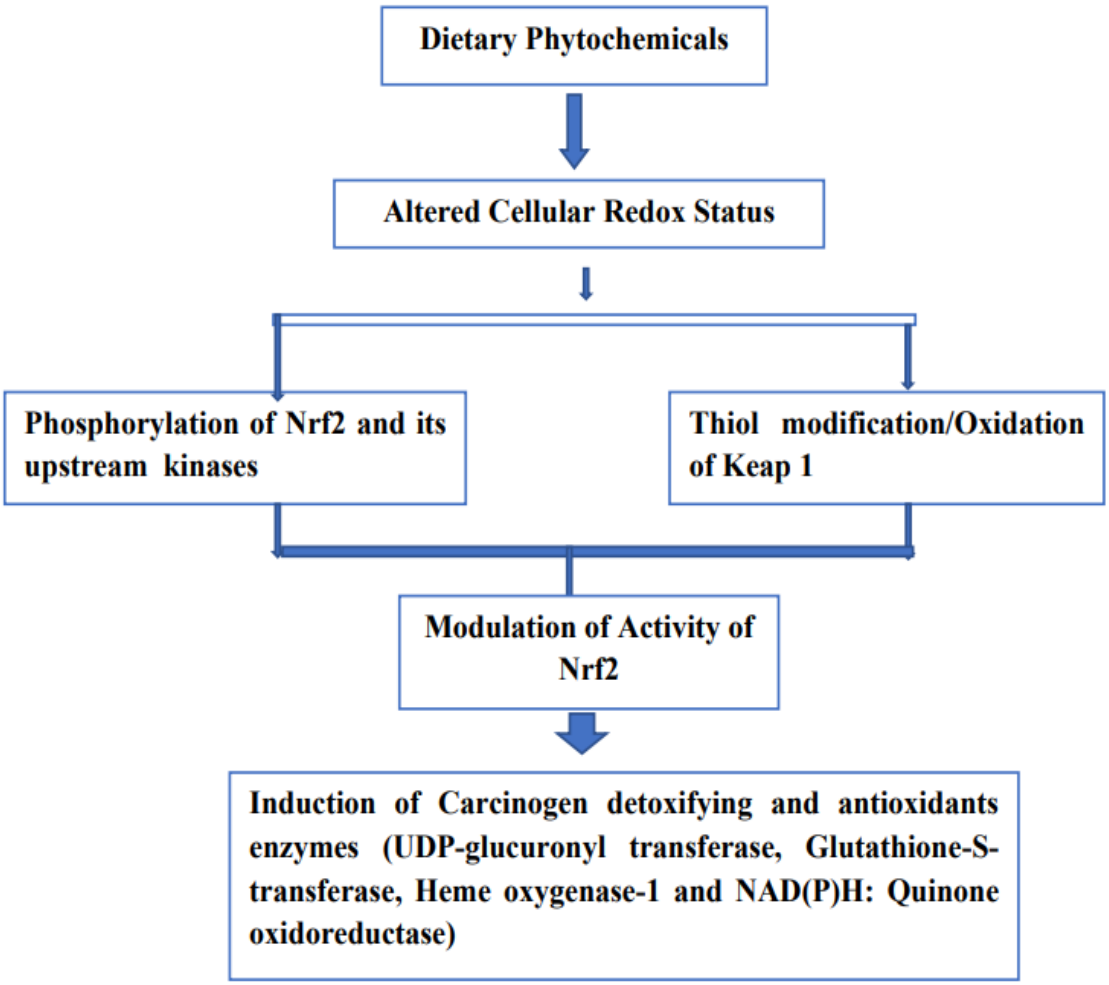

Figure 1: Scheme of Nrf2-ARE signaling pathway regulation by phytochemicals

Kelch-like ECH-associated protein 1 (Keap1)

Keap1, a protein (69-kDa) that possess certain homology similar to protein of actin-binding Kelch and acts to suppresses Nrf2. In human, the sequence of Keap1 protein is made up of 627 residues of amino acid arranged into 5 different domains, these domains are *N*-terminal region (NTR), Broad complex, Tramtrack, and Bric-a-Brac (BTB), linker intervening region (IVR), the Kelch domain, and *C*-terminal region (CTR). The BTB domain linked to actin-binding proteins carried out Nrf2 ubiquitination through homodimerization and interaction with a complex containing cullin (Cul3)-based ubiquitin E3 ligase. IVR possessing cysteine residues are responsive to oxidation and nuclear export signal (NES) motif.

The Kelch domain contain 6 repeats of kelch with numerous protein binding sites that facilitate interaction of Keap1 and Nrf2 (the Kelch domain binds with Nrf2's Neh2 domain) as well as proteins of cytoskeleton (with myosin or actin or both). In human Keap1, there are twenty seven (27) cysteine residues and only seven (Cys^{613}, Cys^{434}, Cys^{297}, Cys^{288}, Cys^{273}, Cys^{257}

and Cys[151]) were very reactive towards electrophiles and ROS and participated in redox reaction (Uruno and Motohashi, 2011).
Keap1 functions to modulate the activity of Nrf2. This Keap1 was screened and obtained as protein inhibitor of Nrf2 (Itoh *et al*., 1999). Since Keap1 interacts in the cells with F-actin, binds in the cytoplasm to Nrf2 via attachment to the Nrf2's Neh2 domain.

At resting state, Nrf2 bound to Keap1 as a result of linkage between Nrf2 single protein and a dimer of Keap1. Keap1 acts as a protein that facilitates the interaction of Nrf2 with Cul3-based E2-ubiquitin ligase complex which leads to a progressive Nrf2 ubiquitination and its subsequent degradation by proteasome (Kobayashi *et al*., 2004).

In mice, breakdown of Keap1 gene provide a mechanistic insight on the central role of Keap1 in Nrf2 modulation (Wakabayashi *et al*., 2003). Hepatic protein levels of NQO1 and GSTs in young Keap1-attenuated mice were significantly elevated compared to same aged wild-type mice. Similar reports were obtained in knockout mice tissues were Nrf2 nuclear levels and levels of transcript of its target genes were significantly increased.The present model of interactions between KEAP1–Nrf2 is established by the presence of two different binding sites known as ETGE and DLG motifs in the Neh2 domain of Nrf2 (Uruno and Motohashi, 2011).
According to reviews in Tong *et al*., 2006 and Hayes *et al*., 2009, ubiquitin acceptor sites on Nrf2 seems to be immobilized by Keap1 via attaching the transcription factor across the two repeat domains of Kelch, putting them near to Cul3–Rbx1 in a state that promotes ubiquitination. Due higher affinity exhibited by ETGE motif for Keap1 than DLG motif, a proposed mechanism called 'hinge and latch' has been made, which involved a process of sequential interaction where Keap1 dimers first binds Nrf2 through the ETGE motif before the DLG motif docks onto the nearby vacant repeat domain of Kelch.

Either one or both the Nrf2-interacting motifs separate from Keap1 after exposure to a variety of inducers and stressors thereby prevent NRF2 protein from degradation by proteasome and enabling translocation into the nucleus. The inducers and stressors include endogenous activators, like lipid aldehydes, reactive oxygen species (ROS), reactive nitrogen species, 14-prostaglandin J2 and 15-deoxy-D12, as well as number of exogenous agents.

Although, Keap1 have more than twenty cysteine residues, out of them, only small number have been demonstrated to elicit biological activity thus far (Yamamoto *et al*., 2008; Holland *et al*., 2008).

It is hypothesized that these activators (exogenous and endogenous) of the Nrf2 signaling pathway interact with the cysteine residues to induce changes in the conformation that prevent Nrf2 from being ubiquitinated or potentially cause its dissociation from Keap1. As seen in the previous scenerio, newly synthesized Nrf2 would short circuit the Keap1–Cul3–Rbx1 complex and translocate into the nucleus. Once translocated into the nucleus, the Nrf2 undergo dimerization with small Maf proteins resulting to the activation of multiple genes involved cytoprotection. The promoter regions of these genes have one or more antioxidant response elements (AREs).

Antioxidant response element (ARE)

Antioxidant Response Element known as ARE, contains a unique sequences of DNA that are present in the upstream regulatory regions of genes that direct the synthesis of enzymes involve in detoxification and proteins with cytoprotective function. It is the *cis*-regulatory element. Because AREs needed for specific genes are different from those required for other genes, the consensus ARE sequence cannot be recognised as a single sequence (Nioi *et al.*, 2003).

The regulation of Phase II enzymes such as, γ-glutamate cysteine ligase, glutathione S-transferase (GST), NAD(P)H:quinone- oxidoreductase (NQO1) and hemeoxygenase-1(HO-1) is being done at level of transcription by the interaction between Nrf2 (a transcriptional factor) and antioxidant response element (ARE), a base sequence common to these genes. The ARE (5-A/G TGA C/T NNNGC A/G-3) is present in the promoter regions of more than 200 genes (Lau *et al.*, 2003; Osburn and Kensler, 2008).

Nrf2 Signaling Pathway

The Nrf2 pathway performed a cytoprotective function. Evidence exist that its activation results in the expression of numerous cytoprotective enzymes and proteins associated with protection of cell from attack by electrophilic species and reactive oxygen species (ROS) (Jung *et al*., 2018). Thus, it serves as the first line of defense against agents that initiate and promotes the development of cancer. Normally, Nrf2 is linked to its repressor Keap1 confined in the cytoplasm. Keap1 is a protein rich in cysteine residues having five domains (Saha *et al*., 2020). Keap1/Cul3 ubiquitin ligase catalyzed the polyubiquitination of Nrf2 and this accelerates its degradation by proteasomes (Krajka-Kuzniak *et al*., 2017).

The activators of Nrf2 mainly phytochemicals such as isothiocynates binds to sulfuhydryl groups of the Keap1 protein causing a conformational change that prevents Nrf2 from degrading and enables the movement of Nrf2 into the nucleus. Through its bZip domains, Nrf2 attach to small Maf proteins such as MafF, MafG, and MafK to form heterodimers in the nucleus where it binds to the ARE sequence of 50-GTCACAGTGACTCAGCAGAATCTG-30 in the target DNA (Silva-Islas *et al*., 2018).

A part from activation via the canonical pathway, phosphorylation is another mechanism by which Nrf2 can be regulated. Several protein kinases facilitate the release of Nrf2 from the complex with Keap1, stabilizes and its translocation to the nucleus through post-translational modification (Krajka-Kuzniak *et al*., 2017).

The p62 (SQSTM1) protein play a role in one of the mechanisms in the non-canonical pathway of Nrf2 activation, this particular protein functions as an autophagy receptor for breakdown of mitochondria and proteins. The KIR domain in p62 allows it to interact with Keap1 much like does Keap1 with Nrf2. In HEK293 and MEF cells, the interaction of Keap1 with p62 resulted in the stabilization as well as activation of Nrf2, which in turn causes Keap1 degradation by autophagy (Shah *et al*., 2018).

The activation of Nrf2 rely on p62 ability to promotes anti-apoptotic proteins expression like B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma- extra-large (Bcl-xL), NAD(P)H:quinone

oxidoreductase (NQO1) and glutathione -S-transferases (GSTs), thus, lowering the levels of ROS and sheilding the cell from oxidative challenge (Silva-Islas *et al*., 2018).

The persistent Nrf2 activation brought on by a reduction in autophagy and an enhanced phosphorylation of p62 facilitate the proliferation of cancer cells. A rise in ROS production is linked with mutations in the KIR domain of p62 protein, which hinders the interaction between Keap1 and p62 (Sun *et al*., 2016; Silva-Islas *et al*., 2018). MicroRNA and other epigenetic mechanisms, like methylation of Keap1or Nrf2 promoter have also been linked to the intricate control of activity of Nrf2 pathway (Krajka-Kuzniak *et al*., 2017).

Although, Nrf2 pathway is crucial in preserving electrophilic homeostasis and cellular redox, overexpression of Nrf2 in cancer cells has been reported, which may be a factor to enhance their proliferative, invasive, and chemoresistance characteristics (Raghunath *et al*., 2018).
A number of mechanisms, such as epigenetic alterations and genetic changes are involved in prooncogenic Nrf2 pathway activation in cancer cells (Panieri and Saso, 2019). Metabolic reprogramming has demonstrated that this pathway is linked with the uncontrolled growth of cancer cells via (Song *et al*., 2021).

Potential chemopreventive Phytochemicals targeting Nrf2

Curcumin
Curcumin is a pigment, obtained from *Curcuma longa* L. It is widely used in food preparation as a flavoring and coloring agent in most Asian countries. Several researches have demonstrated that curcumin exerts numerous biological effects like antioxidant, anti-inflammatory, chemotherapeutic and chemopreventive activities (Haroon *et al*., 2020). Curcumin possess anti-inflammatory and antioxidant capabilities; however, because of its low absorption potential, it is less effective against systemic diseases.

In human hepatic cells, report has shown that curcumin stimulates the expression of glutathione-s-transferase 1 through action of Nrf2, a transcription factor (Nishinaka *et al*., 2007). Also in retina-derived cell lines, curcumin pretreatment prevents cell death induced by H_2O_2 via increasing thioredoxin and heameoxygnase-1 levels, which is driven by Nrf2 transcription factor (Mandal *et al*., 2009).
Curcumin also stimulates upstream kinases to trigger Nrf2–ARE signaling. In mouse-β cell lines, curcumin can stimulate of heameoxygnase-1 expression through a signaling cascade involving transcription factor (Nrf2) and PI-3K/Akt-driven signaling pathway. Furthermore, through the actions of Nrf2, p38MAPK and PKC-δ, curcumin act by increasing antioxidant defense genes expression in human monocytes via ARE (Zhao *et al*., 2010).

Resveratrol
Resveratrol is a well-known phytoalexin, mostly found in red wine and grapes. It exhibits many important biological functions such as anti-aging anti-inflammatory, neuroprotective and antioxidant activities (Aqeel *et al*., 2012; Ballevar *et al*., 2014). Numerous studies have shown that resveratrol provide protection to PC12 cells from oxidative attack by inducing heme oxygenase-1 expression through Nrf2 regulatory pathway (Chen *et al*., 2005).

Epigallocatechin gallate (EGCG)
It is found in abundance in *Camellia sinensis* (green tea) and white tea as catechin, but detected in small amount in black tea (McKay and Blumberg, 2002). EGCG also increases antioxidant enzymes level through the activation of Nrf2-ARE pathway (Shen *et al*., 2005; Wu *et al*., 2006). A recent research has described the mechanism by which quercetin inhibit Nrf2 leading to cell death.

Quercetin
As the most extensively studied flavonoid, quercetin is present in many vegetables and fruits. It possesses numerous biological functions, such as, antioxidant, anti-tumor, and anti-inflammatory. Quercetin is also shown to lower the danger of cardiovascular disease (Anande *et al*., 2016). Numerous reports have demostrated that quercetin is capable of inducing apoptosis partly by reducing Nrf2 nuclear localization, inducing degradation of Nrf2 by proteasome and decreases histone deacetylase HDAC4, that resulted to increase the levels of pro-apoptotic miRNAs (Krajka-Ku´zniak and Baer-Dubowska, 2021). Several studies have shown that quercetin can trigger apoptosis, partially as result of its ability to demethylate DNA, via HDAC inhibition and alteration of histone (H3ac and H4ac). This initiates the transcription of genes to form products engaged in the apoptosis pathway (De Prax, *et al*., 2019). Consequently, epigenetic modulation of expression of Nrf2 and function may be regarded as crucial target of natural products (phytochemicals) that act as inhibitors or inducers of this pathway.

Isothiocyanates
Sulforaphane is a well-known isothiocyanate, predominantly found in cruciferous vegetables like cauliflower, cabbage and broccoli. It has capacity to activate to phase 2 detoxification enzymes (Juge *et al*., 2007; Surh and Na, 2008). Sulforaphane induces the activation of Nrf2, probably by altering the cysteine residues present in Keap1 (Dinkova-Kostova *et al*., 2002; Hong *et al*., 2005). A lot of attentions have been paid on sulforaphane for its role as a ''regulating'' agent, can alter Nrf2-Keap1 signaling (Myzak and Dashwood, 2006).

Diallyl sulphide
Diallylsulfide (DAS), a flavouring agent obtained from garlic and an enzyme called cytochrome P4502E1 (CYP2E1) catalysed its transformation into diallylsulfone (DASO2) and diallylsulfoxide (DASO). Garlic is a bulbous root with a strong taste and smell. The diallyl sulphide detected in onion and garlic acts as a potent inhibitor of CYP2E1 enzyme. CYP2E1 catalyzed the metabolism of some carcinogens. DAS serves as a substrate of CYP2E1 and has a key role in the prevention of the occurrence of oncological diseases brought on by nitrosamines (Lii *et al*., 2006). According to animal and epidemiological research, regular consumption of garlic and other allium vegetables may reduce the risk of developing chemically-induced skin, gastric, cervical, colon, fore stomach and lung,cancers (Yang *et al*., 2001).

The involvement of diallyl sulphide in the expression of genes driven by AREs as well as Nrf2, NQO1, and HO-1 proteins have also been documented in another study (Jeong *et al*., 2006). Jointly, these investigations suggest that sulphur containing compounds can execute preventive functions for chemical-induced cancers not only by inhibiting the activation of carcinogens, but also by enhancing the detoxification of activated carcinogenic intermediates

through the induction of phase II enzymes (Yang *et al.,* 2001). These studies collectively imply that sulphur containing compounds can prevent cancers caused by chemicals by blocking carcinogens activation as well as increasing the detoxification of activated carcinogenic intermediates by inducing phase II enzymes.

Table 1: Regulatory Effect of Some Phytochemical constituents on Nrf2 Signaling Pathway

Phytochemical	Plant source	Common Name	Effect on Nrf2/ARE	Reference
Cucumin	*Curcuma longa rhizomes*	Crab's eye	Increase expression and protein of Nrf2.	Chen *et al*., 2014
Resveratrol	*Vitis vinifera*	European wine grape	Increase nuclear level of Nrf2 and GSTP protein level.	Krajka-Ku´zniak *et al*., 2014
Quercetin/Flavonoid	*Pinus banksiana*	Jack pine	Increase nuclear translocation of Nrf2 and hemooxygenase-1 expression.	Liu *et al.,* 2015
Phenethyl isothiocyanate/ Isothiocyanate	*Brassicaceae*	Mustards	Increase expression of Nrf2, binding Nrf2 to DNA.	Krajka-Ku´zniak *et al*., 2020
Sulforaphane/isothiocyanate	*Brassicaceae*		Increase of Nrf2 expression, and GHST1, NAD(P)H;QO levels.	Licznerska *et al*., 2021
Epigallocatechin gallate/flavonoid	*Camellia sinensis*	Tea plant/tea shrub	Increase expression and protein level of Nrf2 and hemooxygenase-1. Increase expression of Nrf2 and hemooxygenase-1.	Han *et al*., 2014
Genistein/isoflavone	*Genista tinctoria*	Dyer's greenweed	Increase expression of Nrf2 nuclear translocation of Nrf2. Increased Keap1 protein level.	Zhong *et al*.,2013
Wogonin/flavone	*Scutelaria baicalensis*	Chinese skullcap	Increased hemooxygenase-1 and NAD(P)H;QO level	Xu *et al*., 2017
Sappanone/Isoflavone	*Caesalpinia sappan*	Sappanwood/Indian redwood	Increase nuclear translocation of Nrf2 and expression of HO-1,NQO1	
Apigenin/Flavone	*Matricaria chamomilla*	German chamomilla	Increase mRNA and protein levels of Nrf2, hemooxygenase-1	Lee *et al*., 2015 Sahin *et al*., 2019

Effect of Combinations of Phytochemical on Nrf2 Signaling Pathway

Generally minimal toxicity as well as ability of inducing or inhibiting signaling pathway such as Nrf2, is a successful approach for cancer therapy and chemoprevention. Shortening feedback loops signaling, cellular cross communication between the signaling pathways and various cells types within the tumor may be beneficial (Krajka-Ku´zniak *et al*.,2020). The wide range of molecular approach exhibited by natural compounds encourages the development of synergistic combinatorial therapies (Lodi *et al*., 2017).

The reports from various *in vitro* investigations as well as *in vivo* to some extent, show that combinations of different phytochemical constituents may enhance their capacity for chemotherapeutic and chemopreventive, which can effectively target the signaling pathways associated with cell survival and proliferation (Cheung *et al*., 2014). In the cancer cells of pancrease, combinatorial effect of resveratrol and phenethyl isothiocyanate on the activation and expression of Nrf2 was studied. The combination of phenethyl isothiocyanate and resveratrol promotes Nrf2 activation as well as expression and consequently its target genes Glutathione peroxidase (GSTP), superoxide dismutase (SOD), and NQO1 (Krajka-Ku´zniak *et al*., 2020). A decrease in proliferation of pancreatic cancer (PANC-1) cells was achieved through alteration of these two signaling pathways. Furthermore, enhanced P-JNK and P-Nrf2 levels and a reduced P-GSK-3β level revealed that these two kinases participated in Nrf2 activation (Cykowiak *et al*., 2021). These results shows that combinations of different phytochemicals which are present in natural diets may effectively regulate Nrf2 signaling pathway and decrease the survival and spread of pancreatic cancer cell.

Table 2 present different combinations of phytochemicals that modulate Nrf2 and have more potent modulatory effects on this pathway than single compounds. It was reported that a combination of Phenylisothiocyanate and sulphorane increases Nrf2 expression and synthesis of HO-1, NQO1, similarly, suppresses the expression of COX-2, iNOS and PGE2 was reported in RAW 264.7 cells (Chueng *et al*., 2014).

A combination of phenylisothiocyanate, resveratrol and quercetin synergistically blocked ROS through the Nrf2 signalling activation in hepatic cells (Masuelli *et al*., 2014; Majumdar *et al*., 2009). In particular, treatment of human hepatoma cells (HepG2–8) with this combination of phytochemicals greatly induced binding of Nrf2 to ARE sequence and enhanced the expression of mRNA and protein of Nrf2-modulated genes. Consequently, this finding showed that the constituents in berry; resveratrol, phenyl isothiocyanate and quercetin are capable of activating Nrf2 signaling pathway and demonstrate synergy in eliciting anti-oxidative stress potential at specific concentrations (Saw *et al*., 2014). The examined phytochemicals were used in equimolar quantities in the majority of *in vitro* trial. Arbitrary selection applied only in a few instances.

Regarding the mechanism of action or type of interaction that exist between different phytochemicals, the only effects observed were synergy among different phytochemicals. But, determining the type of interaction based on Chou–Talalay method proves abortive. Combinations of different phytochemical constituents may be effective especially in chemoprevention (Hackman *et al*., 2020).

Table 2: Modulatory Potentials of Combination of Phytochemicals on Nrf2 Signaling Pathway

Phytochemical Combination	Interaction	Effect on Nrf2	Reference
Resveratrol + Cucumin	Synergism	Increase expression of Nrf2 and NQO1, HO-1	Masuelli *et al*., 2014; Majumdar *et al*., 2009
Phenylisothiocyanate + Sulforaphane	Synergism	Increase expression of Nrf2 and NQO1, HO-1	Cheung *et al*., 2014
Cucumin + Sulforaphane	Synergism	Increase expression of Nrf2 and NQO1, HO-1	Cheung *et al*., 2014
Epigallogachetin gallate + Cucumin	Synergism	Increase expression of Nrf2, protein level and HO-1	Wang *et al*., 2014
Resveratrol + Phenylisothiocyanate	Synergism	Increase Nrf2 expression and enhance the binding of Nrf2 to DNA, and expression of GSTP, NQO1, SOD	Krajka-Ku´zniak *et al*.,2020; Cykowiak *et al*., 2021

CONCLUSION

Nrf2 is a transcription factors concerned with the regulation of antioxidant genes. Numerous phytochemicals with antioxidant activity trigger Nrf2-driven production of phase 2 detoxification or antioxidant enzymes to enhance cellular defence potential against electrophilic or oxidative attack in addition to neutralizing reactive oxygen species.

It's interesting to note that most of the phytochemicals used in chemoprevention have antioxidant capacity. Cysteine thiols, which are found in Nrf2 and it regulator (Keap1) are known to act as redox sensors, changing transcriptional control of several genes necessary for preserving cellular homeostasis. As a result, molecular target-based cyto-protection and chemoprevention with antioxidant phytochemicals can be achieved by oxidizing or covalently modifying the thiol groups in redox-sensitive transcription factors and molecules that regulate them. Numerous phytochemicals showed synergistic effects when regulating Nrf2 signaling pathway. Therefore, their combinations may enhance this impact.

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