Cancer Chemopreventive Role of Dietary Terpenoids by Modulating Keap1-Nrf2-ARE Signaling System—A Comprehensive Update

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Abstract: ROS, RNS, and carcinogenic metabolites generate excessive oxidative stress, which changes the basal cellular status and leads to epigenetic modification, genomic instability, and initiation of cancer. Epigenetic modification may inhibit tumor-suppressor genes and activate oncogenes, enabling cells to have cancer promoting properties. The nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that in humans is encoded by the NFE2L2 gene, and is activated in response to cellular stress. It can regulate redox homeostasis by expressing several cytoprotective enzymes, including NADPH quinine oxidoreductase, heme oxygenase-1, UDP-glucuronosyltransferase, glutathione peroxidase, glutathione-S-transferase, etc. There is accumulating evidence supporting the idea that dietary nutraceuticals derived from commonly used fruits, vegetables, and spices have the ability to produce cancer chemopreventive activity by inducing Nrf2-mediated detoxifying enzymes. In this review, we discuss the importance of these nutraceuticals in cancer chemoprevention and summarize the role of dietary terpenoids in this respect. This approach was taken to accumulate the mechanistic function of these terpenoids to develop a comprehensive understanding of their direct and indirect roles in modulating the Keap1-Nrf2-ARE signaling system.

Keywords: Keap1; Nrf2; ARE; terpenoid; cancer; chemoprevention; reactive oxygen species (ROS)

1. Introduction

Today, cancer is considered one of the major global health crises. It is the second most prominent cause of death in the United States [1]. Globally, the cancer burden is estimated to double over the upcoming two decades [2]. This increasing global cancer incidence, associated with mortality along with spiraling treatment costs, is gradually increasing the interest in cancer prevention. Therefore, the FDA has approved several drugs for chemoprevention to minimize cancer incidence, morbidity, and mortality in the upcoming years [3]. In addition, it has been evidenced that an efficiently healthy diet containing plant-based foods with reduced intake of high-calorie meals, red meat, processed meat, etc., can contribute to chemoprevention [4]. Chemoprevention is a promising approach against a wide range of cancers for reversing, restraining or preventing different stages of carcinogenesis through the use of dietary supplements, as well as drugs from nature or synthetic sources [5].
Cancer chemopreventive agents are generally divided into two groups. First, blocking agents, which inhibit the mutagenic initiation of the carcinogenic activity, and second, suppressing agents, which inhibit the further advancement of an existing lesion [6]. Some agents are included in both categories. In addition, blocking agents are again sub-classified into three groups on the basis of their mechanism of action. The first group acts simply by preventing the activation of a carcinogen into its potential carcinogenic form, i.e., prevention of symmetrical dimethylhydrazine-induced neoplasia by disulfiram. The second group increases the activity of the enzyme systems involving the carcinogen detoxification process. The members of the third group act by scavenging and neutralizing the reactive forms of carcinogens, e.g., physiological nucleophile glutathione (GSH) [6]. Popularly known chemopreventive agents, e.g., traditional Chinese medicines, natural compounds, FDA approved drugs, etc., are selective and predisposed to interact with various protein targets with varied signaling pathways in living cells [7]. An increasing amount of evidence is accumulating in which cancer patients have been administered herbs using complementary therapies or dietary components that remarkably interfere with cell signaling [8]. Therefore, chemoprevention is effective with a molecular-level understanding of the factors that initiate and trigger cancer [9].

Over the last several decades, an increasing amount of focus has been put on the molecular origins of cancer. Reactive oxygen species (ROS) are greatly responsible for cancer development, either initiating tumor formation or facilitating cancer cell proliferation [10]. Specifically, increased ROS production accompanies hyperproliferation of tumor cells, and this process is aggravated when oxidative stress hampers the redox balance. Invasive tumor cells achieve this state by enhancing their antioxidant level to help ROS-mediated proliferation, while simultaneously evading ROS thresholds that would facilitate apoptosis, senescence, and ferroptosis [11,12]. Therefore, cancer cell proliferation can be managed through ROS modulation. The kelch like ECH associated protein 1 (Keap1)-nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant response element (ARE) signaling safeguards cells from carcinogenic invasion and restricts cancer development via ROS neutralization [13]. It has been observed in several studies that the Keap1-Nrf2 pathway is mutated in various cancers [14]. During oxidative stress, Nrf2 dissociates from Keap1 to be translocated into the nucleus; in turn, nuclear Nrf2 upregulates ARE-associated gene expression, i.e., heme oxygenase-1 (HO-1), NAD(P)H quinine oxidoreductase (NQO1), glutamate-cysteine ligase (GCL), GSH, GSH peroxidase (Gpx), etc., to maintain the cellular redox homeostasis [15]. As polyphenols from dietary sources are widely known for tackling oxidative stress, modulation of Keap1-Nrf2-ARE signaling by some of these compounds is expected to bring benefits in the prevention of oxidative-stress-mediated cancers.

Certain phytochemicals including dietary constituents that can decrease tumorigenesis both in vitro and in vivo experimental models. It has been well-established that the intake of these phytochemicals can either prevent cancer or slow down its growth and progression [16]. They play these roles either by decreasing metabolic activation of carcinogen, increasing the detoxification of carcinogens, or preventing them from binding with their cellular targets. Figure 1 demonstrates how certain groups of dietary nutraceuticals have been recognized or are thought to modulate specific pathways causing breast cancer development. This evidence, as well as additional information on naturally occurring food constituents and vitamins, has established the idea that diet modification can play vital role to prevent cancer [17].

Terpenoids, present largely in plants, animals, fungi and microbial species, are known for exhibiting potential effectiveness against cancers [18]. For example, betulinic acid, a triterpene compound extracted from birch tree, has shown cytotoxic activity in multiple cancer cells [19,20]. The cancer suppressing properties of terpenoids include inhibition of cell adhesion, migration and proliferation, specifically observed for a novel diterpene, tanshinone [21]. Limonene, a monoterpene, can be deposited in the fatty tissues due to its lipophilic nature in order to produce a long-term chemopreventive effect by mediating cell cycle arrest and eventually apoptosis [22]. Recently, multiple terpenoid compounds
have been found to be effective in activating the Keap1-Nrf2-ARE pathway, where the downstream target genes of Nrf2 were enhanced in a process that involved phosphoinositide 3-kinases (PI3K), protein kinase C (PKC), etc., [23]. In this review, we summarize the information of dietary terpenoids demonstrating a cancer chemopreventive role by direct or indirect modulation of the Keap1-Nrf2-ARE signaling system. The chemopreventive mechanisms of the associated up- and downstream signaling molecules of Keap1-Nrf2-ARE signaling are also discussed.

2. Terpenoids

Terpenoids, also known as terpenes, are the largest group of phytochemicals, and are present in many different plants, playing an array of biological and biochemical roles within living systems. Green plants, especially flowering plants, possess an incredibly large number of terpenoid compounds in comparison with other living organisms [24]. More than 80 thousand terpenoid secondary metabolites have been isolated from different sources in nature [25]. However, interestingly, there are a few hundred terpenoids that are present in almost all plant species, which are designated as primary metabolites and are involved in several biological activities, such as antioxidant, electron transfer, hormone and protein modification, membrane fluidity determination, etc., [24]. ‘Terpenoids’ are organic compounds commonly known as hydrocarbons. Their oxygenated, hydrogenated and dehydrogenated derivatives contain the general formula of \((C_{5}H_{8})n\), where \(n\) suggests the number of isoprene units [26]. Natural products containing terpenoids are rich in “isopentenyl pyrophosphate”, which is the active isoprene unit present in almost all living organisms as a common biosynthetic origin [27]. They are commonly classified as monoterpenoids (\(C_{10}\)), sesquiterpenoids (\(C_{15}\)), diterpenoids (\(C_{20}\)), sesterterpenoids (\(C_{25}\)), triterpenoids (\(C_{30}\)), tetraterpenoids (\(C_{40}\)), and polyterpenoids. Mono-, sesqui-, di-, tri-, and tetraterpenes are composed of two, three, four, six, and eight isoprene units, respectively.

The unique structural diversity of terpenoids is employed in coupling chemistry, which essentially links \(C_{5}\) isoprenoid precursors; \(C_{5}\) dimethylallyl diphosphate and \(C_{5}\) isopentenyl diphosphate become linked in a regular manner to generate \(C_{10}\) geranyl diphosphate (GPP), which can be condensed with supplementary isopentenyl diphosphate entities to generate \(C_{15}\) farnesyl diphosphate (FPP), \(C_{20}\) geranylgeranyl pyrophosphate (GGPP), and \(C_{25}\) geranylfarnesyl diphosphate, and this process continues [25]. For monoterpene synthesis, a distinct presence of geranyl pyrophosphate synthase enzyme is found in plants, although this enzyme is present in very low amounts in animals [28]. Terpene cyclases act directly on GPP, FPP and GGPP to yield mono-, sesqui-, and diterpenes; “head-to-head” linkage between FPP and GGPP yields tri- and tetraterpene presqualene diphosphate and prephytoene diphosphate, respectively [29]. Within human physiological systems, the formation of these important terpene metabolites is significant for cellular protein modification through the process of glycosylation and energy generation [30,31].

Several epidemiological studies have suggested that increased intakes of vegetables, fruits, whole-grains and pulses, and reduced intakes of red and processed meats and salt, are associated with minimized cancer risk [32]. As daily diets are responsible for the pathogenesis of multiple cancers, diets rich in plant-derived secondary metabolites can support the prevention of cancers. Terpenoids have been reported to possess several pharmacological activities, including against cancer (i.e., taxanes from *Taxus brevifolia* and vincristine and vinblastine from *Catharanthus roseus*) [33,34], malaria (i.e., artemisinin from *Artemisia annua*), and HIV (i.e., calanolide A from *Calophyllum lanigerum*) [35], etc., In particular, in the case of breast cancer development, terpenoids play chemopreventive roles by abrogating cancer initiation, promotion, and oxidative damage (Figure 1). Some terpenoid pigments including astaxanthin, bixin, and lycopene are widely used in various food industries. Additionally, the human body uses some of the terpenoids to yield essential compounds; for example, vitamin A is synthesized from \(\beta\)-carotene, a widely known plant terpene. The list and structures of dietary terpenes that modulate the Keap1-
Nrf2-ARE system are mentioned below, along with their chemical class (Table 1, Figure 2). The common dietary sources of these terpenes are listed as well (Table 2).

![Diagram](image)

**Figure 1.** Nutraceuticals can alter and inhibit the specific cellular and metabolic pathways associated with breast cancer development [36–38].

**Table 1.** Dietary terpenoid phytochemicals which can modulate the Keap1-Nrf2-ARE signaling system and their chemical classes.

| Compound Number | Compound Name       | Chemical Formula | Sub-Chemical Class   | Major Chemical Class |
|-----------------|---------------------|------------------|----------------------|---------------------|
| 1               | Zerumbone           | C_{15}H_{22}O    | Sesquiterpenoid      | Sesquiterpenoid     |
| 2               | Khayandirobilide A  | C_{22}H_{27}O_{11} | Andirobin-type limonoid | Triterpenoid     |
| 3               | Brusatol            | C_{26}H_{32}O_{11} | Quassinoid compound  | Triterpenoid     |
| 4               | Withaferin A        | C_{28}H_{38}O_{6} | Steroid              | Triterpenoid     |
| 5               | Betulin             | C_{30}H_{50}O_{2} | Steroid              | Triterpenoid     |
| 6               | Ganodermanondiol    | C_{30}H_{48}O_{3} | Steroid              | Triterpenoid     |
| 7               | Oleic acid          | C_{30}H_{48}O_{3} | Steroid              | Triterpenoid     |
| 8               | Ursolic acid        | C_{30}H_{48}O_{3} | Steroid              | Triterpenoid     |
| 9               | Dioscin             | C_{30}H_{72}O_{16} | Saponin              | Triterpenoid     |
| 10              | Corosolic acid      | C_{30}H_{48}O_{4} | Steroid              | Triterpenoid acid|
| 11              | Lycopene            | C_{40}H_{56}     | Carotenoid           | Tetraterpenoid    |
| 12              | Astaxanthin         | C_{42}H_{56}O_{6} | Carotenoid           | Tetraterpenoid    |

**Table 2.** Common dietary sources of terpenoid phytochemicals that can modulate the Keap1-Nrf2-ARE signaling system.

| Compound Number | Compound Name | Common Dietary Sources | Scientific Name | References |
|-----------------|---------------|------------------------|-----------------|------------|
| 1               | Zerumbone     | Ginger                 | *Zingiber zerumbet* Smith. | [39] |
Table 2. Cont.

| Compound Number | Compound Name     | Common Dietary Sources                                      | Scientific Name                | References |
|-----------------|-------------------|-------------------------------------------------------------|--------------------------------|------------|
| 2               | Khayandirolide A  | Stem barks, fruits, and leaves of African mahogany           | Khaya senegalensis             | [40]       |
| 3               | Brusatol          | Dried ripe fruits of *Brucea javanica*                       | *Brucea javanica*              | [41]       |
|                 |                   | Seeds of *Brucea sumatrana*                                  |                                 | [42]       |
| 4               | Withaferin A      | Ashwagandha                                                  | Withania somnifera              | [43]       |
| 5               | Betulin           | Silver Birch tree bark                                       | *Betula pendula*                | [44]       |
| 6               | Ganodermanondiol  | Lingzhi mushrooms                                            | *Ganoderma lucidum*            | [45]       |
|                 |                   | Olive leaves                                                 | *Olea europaea*                 |            |
|                 |                   | Jujube                                                       | *Ziziphus jujube Mill.*         | [46]       |
|                 |                   | Ginseng                                                       | *Panax sp.*                     |            |
| 7               | Oleanolic acid    | Apple peels                                                  | *Malus domestica*               | [47]       |
| 8               | Ursolic acid      | Leaves and rhizomes of plants from Dioscoreaceae family     | *Dioscorea opposita*            | [48]       |
| 9               | Dioscin           | *Dioscorea alata*                                            |                                 |            |
|                 |                   | *Dioscorea japonica*                                         |                                 |            |
|                 |                   | *Lagerstroemia speciosa L.*                                  |                                 | [49]       |
|                 |                   | Java tea                                                     | *Orthosiphon aristatus*         |            |
|                 |                   | Java tea                                                     |                                 |            |
|                 |                   | Korean weigela                                               | *Weigela subsessilis*           |            |
| 10              | Corosolic acid    | Kosam                                                        | *Schisandra chinensis*          |            |
|                 |                   | Loquat                                                       | *Eriobotrya japonica*           |            |
|                 |                   | Banaba                                                       | *Lagerstroemia speciosa L.*     |            |
|                 |                   | Java tea                                                     | *Orthosiphon aristatus*         | [49]       |
|                 |                   | Java tea                                                     |                                 |            |
|                 |                   | Korean weigela                                               |                                 |            |
|                 |                   | Papaya                                                       | *Carica papaya*                 | [50]       |
| 11              | Lycopene          | Tomato                                                       | *Solanum lycopersicum*          |            |
|                 |                   | Watermelon                                                   | *Citriullus lanatus*            |            |
| 12              | Astaxanthin       | Salmon                                                       | *Salmo salar*                   | [51]       |
|                 |                   | Trout                                                        | *Oncorhynchus mykiss*           |            |
| 13              | Fucoxanthin       | Microalgae                                                   | *Phaeodactylum tricornutum*     | [52]       |
|                 |                   | seaweeds                                                      | *Undaria pinnatifida*           |            |
Figure 2. Chemical structures of the dietary terpenoids that can modulate the Keap1-Nrf2-ARE signaling system. (1) zerumbone, (2) khayandirobilide A, (3) brusatol, (4) withaferin A, (5) betulin, (6) ganodermanondiol, (7) oleanolic acid, (8) ursolic acid, (9) dioscin, (10) corosolic acid, (11) lycopene, (12) astaxanthin, and (13) fucoxanthin.
3. Keap1-Nrf2-ARE Signaling System

Nrf2 is a member of the Cap ‘n’ collar transcription factor family that contains a distinct CNC domain that is connected to the N-terminal side of a greatly protected leucine zipper (bZIP) motif. Nrf2 performs its function through pairing with other bZip proteins, such as small MAF proteins, facilitating dimerization, DNA binding, and nuclear export-import. Nrf2 modulates antioxidant and detoxification gene expression and has been established as a tumor suppressor [53]. In different experiments, Nrf2-knockout mice demonstrated enhanced carcinogen susceptibility and increased metastasis of the lung, which was guided by elevated ROS levels [54,55]. Keap1, the major Nrf2 repressor, is an adaptor subunit of Cullin3-based E3 ubiquitin ligase that works as a sensor element for oxidative stresses [56]. The Keap1-Nrf2-ARE signaling system is critical for maintaining a healthy balance between the ROS and the redox state of cells [57]. Nrf2 binds to the endogenous AREs to form the Nrf2-ARE complex, which needs to be activated when needed. Activity of this complex is restricted during the period in which it binds with Keap1 [58]. Under basal conditions, the Nrf2-Keap1 complex is anchored to cytosolic actin [59] and allows the Nrf2 to react with ubiquitin. Ubiquitination subsequently hydrolyzes it to its subcellular organelles and halt DNA transcription [60]. On the contrary, the ubiquitination can be prevented by breaking down the Nrf2-Keap1 complex [58–60]. This usually happens when cells undergo oxidative stress due to the presence of excessive intracellular ROS. Here, Keap1 works as a redox sensor, as it contains a sulfhydryl group in the cysteine residues that can sense oxidative stress. Due to the electrophilic nature of ROS, they tend to react with the cysteine residues of Keap1 protein, and subsequently break the Keap1-Nrf2 complex. Free Nrf2 becomes phosphorylated at Ser40 and translocates into the nucleus from cytosol to bind with the ARE region of DNA [61]. Thus, it activates the transcription of genes encoding for antioxidant elements and accordingly triggers several downstream enzymes including HO-1, thioredoxin (TXN), thioredoxin reductase (TXNRD), superoxide dismutase (SOD), NQO1, glutathione reductase (GR), GCL, glutathione-S-transferase (GST), superoxide dismutase (SOD), NQO1, glutathione reductase (GR), GCL, glutathione-S-transferase (GST), etc., [62,63]. Therefore, this overall system is known as the Keap1-Nrf2-ARE signaling system. Over 500 genes are regulated by the Nrf2-ARE complex, including phase I and II detoxification enzymes, proteasome subunits, transport proteins, growth factors and some other transcription factors [64].

The indirect activation of the Nrf2 signaling pathway involves stress-response protein kinases including PKC, mitogen activated protein kinase (MAPK) cascade, PI3K, extracellular signal regulated kinase (ERK), c-Jun N-terminal kinase (JNK), etc., [65–69]. Transcription factors like heat shock factor 1 (Hsf1), p30, p65, nuclear factor-κB (NF-κB), peroxisome proliferator activated receptor γ (PPARγ), etc., are either positively or negatively involved in the regulation of Nrf2 activity [70–74]. A new but poorly studied Nrf2 activation mechanism has been established of late, the non-canonical pathway, where proteins like p62, p21, dipeptidyl-peptidase III (DPP3), wilms tumor gene on X chromosome (WTX), etc., abrogate the Nrf2-Keap1 complex by directly interacting with Keap1, which in turn disrupts Nrf2 ubiquitination and thereby facilitates Nrf2 nuclear translocation and its subsequent activation [75]. Figure 3 represents how Nrf2 works intracellularly under both basal and stress conditions, and Figure 4 summarizes the factors that are involved in Nrf2 regulation.
Various factors participate in Nrf2 regulation. The yellow color suggests the suppression of Nrf2 expression and the green color suggests the elevation on Nrf2 expression. The diagram was adapted and modified from Basak, P. et al., 2017 [56].

**Figure 3.** The basic Keap1-Nrf2-ARE signaling system. (A) Hydrolyzation of Nrf2 under basal conditions by ubiquitination. (B) Breakdown of Keap1-Nrf2 complex under stress conditions and nuclear translocation of Nrf2.

Various factors participate in Nrf2 regulation. The yellow color suggests the suppression of Nrf2 expression and the green color suggests the elevation on Nrf2 expression. The diagram was adapted and modified from Basak, P. et al., 2017 [56].

**Figure 4.** Various factors participate in Nrf2 regulation. The yellow color suggests the suppression of Nrf2 expression and the green color suggests the elevation on Nrf2 expression. The diagram was adapted and modified from Basak, P. et al., 2017 [56].

4. Role of Dietary Terpenoids in Modulating the Keap1-Nrf2-ARE Signaling System

4.1. Zerumbone (ZB)

Zerumbone (I) is a sesquiterpene that naturally occurs in the herbal plant *Zingiber zerumbet* Smith and its rhizome ginger. ZB scavenges different cell lines from oxidation-induced injury via its antioxidant effects [39, 76]. One of the antioxidant roles of ZB arises mainly because of the presence of an α,β-unsaturated carbonyl moiety in its skeleton, serving as an electrophile [39].
The α,β-unsaturated carbonyl group in ZB forms a covalent bond with Keap1 to activate Nrf2 [77].

ZB suppressed the migration and invasion of colorectal cancer cells in vitro by inhibiting the focal adhesion kinase (FAK)/PI3K/NF-κB signaling pathway [78]. The FAK-dependent signaling pathway helps tumor progression and consequent metastasis by causing cell migration, invasion, transition, and angiogenesis [79,80]. In addition, the antioxidative action of Nrf2 and its associated detoxifying enzymes is dependent on the inhibition of the NF-κB signaling pathway [81]. Therefore, the capacity of ZB to combat colorectal cancer might be indirectly related to the Nrf2 signaling pathway. The suppression of NF-κB activity by ZB was also observed in AGS gastric cancer cells; the vascular endothelial growth factor (VEGF) expression was also downregulated [82]. A recent review gathered the accumulated evidence supporting the role of ZB in the amelioration of cancer in various cancer cells [83]. Here, ZB showed significant cytotoxicity against Raji (Epstein–Barr virus), promyelocytic leukemia HL-60, CCL-240, murine lymphoid neoplasm P-388D1, CCL-46, liver cancer HepG2, breast cancer MCF-7, MDA-MB231, lung cancer A549, ovarian cancer Caov-3, cervix cancer HeLa, etc., cells. In HEK 293 cells, ZB exhibited cytoprotective action by enhancing the protein levels of Nrf2 and ARE-dependent transcriptional activity, which in turn increased the expression of NQO1 and HO-1 [84]. In THP-1 cell-derived macrophages, ZB mediated anti-inflammatory action by abrogating the induction of NF-κB p65 and toll-like receptor 2/4 (TLR-2/4) [85].

ZB prevented ultraviolet (UV)-induced photoaging and skin carcinogenesis by increasing the nuclear translocation of Nrf2 and enhancing the ARE luciferase activity, whereby the Nrf2/ARE signaling pathway was accompanied by HO-1 and γ glutamate cysteine ligase catalytic subunit (γ-GCLC) gene induction [86]. Protection of skin keratinocytes and fibroblasts requires the action of Nrf2 signaling against UVA-induced oxidative insult [87,88]. Nrf2 safeguards cells from oxidative injury by means of its target genes, such as HO-1, and suppresses cellular malignant transformation [89]. ZB-induced Nrf2 transcriptional activation was mediated by upregulated expression of p38 MAPK, PI3K/protein kinase B (AKT), and PKC signaling pathways [86]. According to another study, ZB upregulated the expressions of antioxidant enzymes HO-1 and γ-GCLC via increased nuclear accumulation of Nrf2, and decreased cytosolic Keap1 content by means of the ERK, JNK, PI3K/AKT, PKC, and AMP-activated protein kinase (AMPK) signaling pathways [90]. The chemical adduction, oxidation or glutathionylation of single or several important cysteine residues in Keap1 disturbs the association between Keap1 and Nrf2, making it possible for Nrf2 nuclear translocation to activate cytoprotective genes [86,91]. In response to oxidant injuries, Nrf2 binds to cis-acting AREs in the promoter site of phase II antioxidant encoding genes, leading to the expression of their respective proteins [90]. Acute lung injury was ameliorated by ZB as well, whereby it abolished lipopolysaccharide (LPS)-induced lipid peroxidation and promoted the activation of antioxidant defense system [92]. Here, nuclear expression of Nrf2 was markedly enhanced, and therefore the expressions of HO-1, catalase (CAT), SOD and Gpx were upregulated. Mechanistically, inhibition of two specific signaling pathways namely TLR4/NF-κB/cyclooxygenase-2 (COX-2) and p38 MAPK/JNK-1xB/NF-κB by ZR were implicated in the amelioration of acute lung injury [93,94]. Moreover, ZB markedly enhanced the expressions of antioxidant enzymes SOD, Gpx, and GSH and suppressed the production of malondialdehyde (MDA). Finally, it induced an anti-skin carcinogenic effect in female mice, wherein Nrf2 and its downstream target gene HO-1 were upregulated after topical administration of ZB on the dorsal skin of mice [95]. Figure 5 presents the mechanism of Nrf2 activation by ZB.

4.2. Khayandirobilide A (KLA)

Khayandirobilide A (2) is an andirobin-type limonoid compound, characterized by a modified furan ring present in its structure. It was first isolated and purified from the stem barks of K. senegalensis [40].
KLA exhibited anti-inflammatory activity by abrogating the production of LPS-induced nitric oxide in BV-2 microglial cells. Moreover, it downregulated interleukin (IL)-6, inducible nitric oxide synthase (iNOS), and COX-2 expression [40]. KLA also inhibited the activation of NF-κB and activator protein-1 (AP-1), and upregulated HO-1 expression by Keap1 autophagic degradation and Nrf2 nuclear translocation. Several reports suggest overexpression of NF-κB activity is associated with the progression of breast and colon carcinoma [96–98]. It is also evident that AP-1 activation is required for tumor promotion and progression [99]. Oxidative stress mediated several inflammatory pathway proteins, i.e., NF-κB, AP-1, iNOS, COX-2, IL-6, etc., leading to the transformation of normal cells into tumor cells [100], suggesting the role of anti-inflammatory agents like KLA in potential chemoprevention. Figure 6 presents the mechanism of Nrf2-ARE activation by KLA.

Figure 5. Mechanism of Nrf2 activation by ZB. The diagram was adapted and modified from Yang, H.-L. et al., 2018 [86].

4.3. Brusatol (BT)

Brusatol (3), a quassinoid present in *Brucea sumatrana* and *B. javanica*, exhibits a potent tumor suppressing effect [42]. It suppresses Nrf2 expression by upregulating protein ubiquitination, disrupting intracellular redox balance.

In many cancer types, it has been observed that high constitutive expression of Nrf2 builds up a conducive environment for the survival and proliferation of cancer cells [101]. Therefore, specific Nrf2 inhibitors are a must in such circumstances in order to tackle these cancer cells. BT sensitized a broad spectrum of cancer cells, including A549 xenografts to cisplatin, where it selectively decreased the protein levels of Nrf2 via increased ubiquitination and degradation of Nrf2 [101]. Consequently, the expressions of Nrf2-downstream genes were reduced, and the Nrf2-dependent cellular response was suppressed. This co-treatment of BT and cisplatin reduced cell proliferation, inhibited tumor growth, and induced apoptosis more substantially than cisplatin treatment alone. Combinatorial therapy of BT with chemotherapeutic drugs has demonstrated better outcomes than using BT alone. It synergistically enhanced the antitumor activity of trastuzumab against human epidermal
growth factor receptor 2 (HER2)-positive SKOV3 and BT-474 cells, which was modulated by the inhibition of the Nrf2/HO-1 and HER2-AKT/ERK1/2 signaling pathways [102]. Combination of BT and metformin overcame progestin resistance by downregulating Nrf2/aldo-keto reductase family 1 member C1 (AKR1C1) in endometrial cancer [103]. BT also improved sensitivity to taxol as a result of Nrf2 suppression and ROS level upregulation in MCF-7 and MDA-MB-231 breast cancer cells [104]. BT and sorafenib in combination ameliorated hepatitis C virus-associated hepatocellular carcinoma and increased the efficacy of the anticancer drug [105]. This combinatorial therapy inhibited Nrf2 expression and enhanced NF-κB, tumor necrosis factor (TNF), and MAPK pathways in order to exert its effect. BT treatment in combination with UVA inhibited A375 melanoma cell growth via G1 phase cell cycle arrest and apoptosis induction which involved partial suppression of Nrf2 and its target gene, HO-1, through the PI3K/AKT signaling pathway [106]. A quite similar mechanism was found for the amelioration of nasopharyngeal carcinoma [107]. Here, BT mediated the mitochondrial apoptosis and cell cycle arrest that followed the suppression of the AKT/mammalian target of rapamycin (mTOR) signaling. BT and cytarabine in combination exerted an anti-tumor effect in acute myeloid leukemia by inhibiting Nrf2, which in turn downregulated the expression of glycolysis-related proteins and reduced glucose uptake and lactate production [108]. In Hepa-1c1c7 hepatoma cells, BT imparted improved chemoresistance by inhibiting Keap1-independent Nrf2 signaling [109]. Again based on Nrf2 inhibition, BT remarkably suppressed the viability of A549 cells and promoted apoptotic processes [110]. The Nrf2 inhibitory action of BT is correlated with its capacity to suppress tumorigenicity and tumor cell migration and invasion [111]. For instance, in PATU-8988 and PANC-1 pancreatic cancer cells, it mediated apoptosis by inactivating NF-κB/sp1 signal transducer and activator of transcription 3 (STAT3) and activating JNK/p38 MAPK signaling [112]. As a potential inhibitor of Nrf2 and STAT3, BT actively suppressed tumor formation and progression in head and neck squamous cell carcinoma, as well [113].

Disruption of PI3K/AKT/NF-κB signaling by BT caused inhibition of epithelial mesenchymal transition (EMT) in order to exert its potent anti-gastric cancer effect [114].

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**Figure 6.** Mechanism of Nrf2-ARE activation by KLA. The diagram was adapted and modified from Zhou, M.-M. et al., 2018 [40].
Involvement of the EMT inhibition by BT was recently reported in another study, wherein, in combination with Paclitaxel, it abolished triple-negative breast cancer [115]. It ameliorated laryngeal carcinoma by disrupting the metastasis and EMT of invasive cells, mediated by downregulation of Janus kinase 2 (JAK2)/STAT3 signaling [116]. However, some chemotherapeutic roles of BT were accompanied by upregulation of STAT3 expression. For example, suppression of metastasis by BT was recently reported in hepatocellular carcinoma, whereby EMT was abrogated by an enhanced level of STAT3 expression [117]. Nano-molar concentrations of BT, as an Nrf2 inhibitor, caused DNA damage and reactivated NR4A3 gene expression to heal acute myeloid leukemia [118]. Several other reports have demonstrated the effective Nrf2 inhibitory role of BT in the management of pancreatic and colorectal cancers [119,120]. A recent review also reported BT to be a specific Nrf2 inhibitor and described its anticancer role in the amelioration of various cancers [121]. However, a recent report demonstrated the role of enhanced Nrf2/HO-1 signaling in mediating the tumor suppressing effect of BT in U-251 glioma cells [122]. Here, the PI3K/AKT/mTOR signaling was inhibited during the exertion of the anti-neurotoxic effect. As far as the dual role of Nrf2 in cancer chemoprevention is concerned, targeted inhibition of Nrf2 signaling has attracted a great deal of focus in the last decade for certain cancer cell types [123], suggesting the promising role of BT in cancer prevention.

4.4. Withaferin A (WFA)

Withaferin A (4) was isolated from traditional Indian medicinal herb Withania somnifera roots and has been studied extensively for its anti-inflammatory, and cardioprotective effects [124]. It has been found to be effective in ameliorating a wide variety of cancers including breast, cervical, ovarian, prostate, oral, glioblastoma, and pancreatic cancer [125,126]. The chemical structure of WFA contains α,β-unsaturated carbonyl moieties [127]. Therefore, it might work as a Michael acceptor and a thiol modifier; in particular, WFA might have an interesting role in the modification of Keap1-cysteine thiol residues. This modification might help Nrf2 to disassociate from Keap1, thus allowing it to be activated.

The Nrf2-induced oxidative stress response pathway was implicated in the anticancer action of WFA [128]. According to this model, under oxidative stress, WFA bound with Keap1, freeing Nrf2 to be translocated into the nucleus. Thus, the enhanced Nrf2 bound with AREs in order to upregulate its downstream antioxidant enzymes. Robust induction of Nrf2 by WFA was recently reported in the treatment of human breast cancer cells [129]. This study concluded that Nrf2 helped in the mediation of apoptosis and autophagy in several breast cancer cells. Induction by WFA of Nrf2 and its associated detoxifying enzymes was also reported to produce an effective cytoprotective response in both in vitro and in vivo models [130]. This withaferin A-mediated Nrf2 and ARE induction followed a unique Keap1-independent phosphatase and tensin homolog (PTEN)/PI3K/AKT signaling pathway. In this case, the Nrf2-dependent cytoprotective genes were significantly induced even under Keap1-deprived conditions. WFA upregulated the mRNA expression of Nrf2 and its downstream antioxidant genes HO-1, glutathione-disulfide reductase (GSR), and NQO1 in Ca9-22 oral cancer cells [131]. In addition, it facilitated mild phosphorylation of the MAPK family proteins including ERK1/2, JNK, and p38. The same study reported a migration inhibitory role of WFA against oral cancer, where it abolished matrix metalloproteinase (MMP)-2 and MMP-9 activities. In J82 bladder cancer cells, WFA responded remarkably to oxidative stress by upregulating the expression of Nrf2 and its antioxidant enzymes CAT, SOD1, TXN, GSR, NQO1, and HO-1 [132]. Moreover, WFA mediated DNA strand breaks and oxidative DNA damage to the bladder cancer cells. Withania somnifera containing WFA demonstrated antioxidant and anti-inflammatory activity in BV-2 microglial cells, wherein upregulated Nrf2/HO-1 and downregulated NF-κB expression played the key role [133]. The apoptosis-inducing role of WFA has also been reported, in which ERK, JNK, and p38 MAPK signaling pathways are involved, resulting in the phosphorylation of Nrf2 and enhancement of HO-1 levels [134].
WFA suppressed necrotic hepatocyte injury by enhancing Nrf2, GCLC and NQO1, and abrogating IL-6, TNF-α and IL-1β expression [135]. In the same study, mitochondrial Bax translocation, JNK expression and nitrotyrosine generation were reduced in WFA-treated mice. A review on the anticancer action of WFA reported that WFA upregulated Nrf2 protein expression, thereby enhancing the expressions of HO-1, SOD, CAT, Gpx and NQO1 [127]. The accumulated evidence supporting the chronic inflammation ameliorating role of WFA was gathered in a recent review [136]. Here, reduced NF-κB and increased Nrf2 expression were implicated in the anti-inflammatory role of WFA. Additionally, signaling pathways like AKT/mTOR, MAPK, and JAK/STAT were involved in exerting this effect. In a recent study, inhibition of NF-κB expression was implicated in the anti-hepatocellular carcinoma effect mediated by WFA [137]. The anti-angiogenic pathway of WFA against lung cancer involved the inhibition of transforming growth factor β1 (TGF-β1), TNF-α, and nuclear translocation and phosphorylation of NF-κB [138]. WFA also exerted antiangiogenic activity in endothelial cells by inhibiting the activation of NF-κB [124]. Suppression of inflammatory cytokines like IL-6, TNF-α and NF-κB/STAT1/STAT3 signaling was implicated in the anti-colorectal cancer effect of WFA [139].

4.5. Betulin (BE)

Betulin (5) is a triterpene, usually found in birch tree Betulaeae sp. bark. It possesses anti-inflammatory, antibacterial and antiviral properties [44].

A review article presented the accumulated evidence of the anticancer and chemopreventive role of BE in various cancer cells, including myeloid leukemia, glioblastoma, neuroblastoma, thyroid, ovarian, breast, skin, colorectal, hepatic, prostate, oral, gastric, pancreatic, and lung carcinoma [140]. This review reported that the anticancer role of BE was mechanized either by extrinsic (TNF, Fas, etc.) or intrinsic (DNA damage, nuclear fragmentation, etc.) apoptotic factors. Evidence was found for BE’s suppressive role on various cancer cells via an intrinsic apoptotic mechanism [141]. Induction of apoptosis was also implicated in the anticancer action of BE in multidrug-resistant renal carcinoma [142]. BE, extracted from Betula platyphylla demonstrated promising cytotoxicity against A549, H1264, and Calu-6 lung adenocarcinoma cells [143]. In addition, it ameliorated the side effects of chemotherapy in the same study, i.e., gastric and renal cell damage. A brief review described BE to be a direct acting agent on mitochondria [144]. Agents that act on mitochondria directly in order to exert chemotherapeutic action receive special consideration in the field of cancer studies, because they can cause cell death under conditions in which conventional chemotherapeutic agents might fail. BE exhibited anti-inflammatory activity through the dose-dependent induction of Nrf2 and its detoxifying enzymes NQO1, HO-1, GCLC and glutamate cysteine ligase modifier subunit (GCLM) [145]. This Nrf2-dependent anti-inflammatory signaling of BE followed the AMPK/AKT/glycogen synthase kinase 3β (GSK 3β) signaling pathway. Nrf2 becomes phosphorylated with serine and threonine residues through AKT, AMPK, and PI3K in order to promote the discharge of Nrf2 from Keap1 and its consequent nuclear translocation for the initiation of antioxidant action to protect the cells against cancerous invasion [146]. In addition, inflammatory mediators, e.g., iNOS, COX-2, that are involved in the carcinogenic process were significantly abolished by BE [145]. Some other pro-inflammatory cytokines and chemokines that are responsible for oncogenesis, like IL-1, TNF-α, etc., were reportedly inhibited by BE via disruption of NF-κB and MAPK signaling [147].

BE ameliorated 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary cancer in rats by upregulating the Nrf2 expression [148]. Downstream antioxidant enzymes like HO-1, Gpx, SOD and CAT were markedly enhanced after BE treatment. This chemopreventive effect of BE was accompanied by downregulated expression of Keap1, MAPKs, aryl hydrocarbon receptor nuclear translocator (ARNT), aryl hydrocarbon receptor (AhR), and cytochrome p450 family 1 subfamily A member 1 (CYP1A1).
4.6. *Ganodermanondiol (GD)*

Ganodermanondiol (6) is generally found in the medicinally important mushroom *Ganoderma lucidum*. The main bioactive secondary metabolites of *G. lucidum* are triterpenoids (ganoderic acid), polysaccharides, and steroids [149].

Ethanol extract of *G. lucidum*, which contains GD, exhibited an effective response against H$_2$O$_2$-mediated oxidative cytotoxicity in C2C12 myoblast cells [150]. This cytotoxicity was mediated by induction of Nrf2 and HO-1. An anti-colon-cancer effect was recently reported for GD [151]. It markedly hampered SW620 cell viability by mediating apoptosis. GD was found to be cytotoxic against a wide number of cancer cell lines, including HL-60 human leukemia, MDA-MB-231 breast, HepG2 liver, HeLa cervical, HCT-116 and HT-29 colon cancer cells [152–155]. It also ameliorated nasopharyngeal carcinoma [156]. In human oral epidermoid carcinoma KBv200 cells, GD reversed multidrug resistance to the anti-tumor drug doxorubicin [157]. It demonstrated potent cytoprotective effect on human liver-derived HepG2 cells via Nrf2-dependent GSH, GCL, and HO-1 antioxidant enzyme upregulation [45]. This Nrf2-centered cytoprotective action of GD was mediated by AMPK signaling, GD effectively suppressed the pronouncement of cellular melanogenesis-related proteins, i.e., transient receptor potential channel (TRP)-1, TRP-2, and microphthalmia-associated transcription factor (MITF) in B16F10 cells, which was modulated by MAPK family proteins [158]. Specifically, the ERK and JNK phosphorylation was induced but the p38 phosphorylation was abrogated by GD.

4.7. *Oleanolic Acid (OA)*

Oleanolic acid (7) is a pentacyclic triterpenoid compound naturally existing in olive leaves, jujube, ginseng, etc., either as a free acid or as an aglycone precursor [46,159]. It has been demonstrated to possess a wide array of pharmacological potentials, including hepatoprotective, anti-inflammatory, anti-viral, anti-hyperlipidemic, anti-hyperglycemic, and anti-tumor activities [159]. OA is an active suppressor of cellular inflammatory pathways and an established enhancer of phase II antioxidant enzymes [46]. It has been reported to improve malignant glioma, leukemia, liver, lung, breast, colon, bladder, gallbladder, prostate, and pancreatic cancer [160–168].

OA, a known Nrf2 activator, reportedly upregulated the expression of Nrf2 and its target antioxidant enzymes, including NQO1, HO-1, GCLC, and GCLM, to exert cytoprotective effect in hepatocytes [169]. In A549 lung cancer cells, OA and ursolic acid activated the Nrf2/ARE signaling [170]. In addition, this combination enhanced the p62 expression in A549 cells. Conjugation of diclofenac with OA derivatives exhibited enhanced chemopreventive activity [171]. In immortalized normal THLE-2 hepatocyte cells, the OA conjugates activated Nrf2 and enhanced SOD-1 and NQO1 expression. However, in HepG2 hepatoma cells, the opposite effect was obtained, with the apoptotic pathway being induced due to increased ROS generation. In both THLE-2 and HepG2 cells, the expressions of NF-κB and COX-2 were suppressed. A quite similar effect was observed when OA derivatives were conjugated with indomethacin [172]. Here, the Nrf2-ARE pathway was inhibited in HepG2 cells, but not in THLE-2 hepatocytes. In another report, OA oxime derivatives provided chemopreventive response by activating Nrf2 in human hepatoma cells [173]. This study also showed that the conjugation of OA oximes with aspirin caused increased Nrf2 expression in normal THLE-2 cells, whereas the opposite effect was observed in HepG2 cells. Moreover, activation of AMPK signaling was observed in the OA-mediated anticancer effect in PC3 prostate and MCF-7 breast cancer cells [174]. OA improved tBHP-mediated oxidative insult via an Nrf2-dependent increase in antioxidant enzymes GSH, CAT, and peroxiredoxins (PRX1) in which the activated signaling of JNK and ERK were involved [175]. A review reported that OA and its derivatives influenced a wide range of signaling pathways including NF-κB, AKT, STAT3, mTOR, caspases, intercellular adhesion molecule 1 (ICAM-1), VEGF, and poly (ADP-ribose) polymerase (PARP) in different tumor cells [176]. VEGFR-2 activation was abolished by OA in HU-VECs in another study [177].
OA ameliorated DMBA-induced liver carcinogenesis through modulating the antioxidant level, causing apoptosis and autophagy [178]. Here, downregulation of VEGF, proliferating cell nuclear antigen (PCNA), NF-κB, TNF-α and COX-2 expression and upregulation of caspase-3, Bcl-2 and Beclin-1 expression were observed. Synergistic action of grafted chitosan and OA improved liver injury by enhancing the hepatic antioxidant capacity [179]. Here, the Nrf2/Keap1 pathway played the key role in enhancing the hepatic antioxidant capacity, while hepatic inflammation was tackled by the downregulation of NF-κB signaling. OA ameliorated hepatotoxicity and provided cytoprotection against oxidative stress via Nrf2 nuclear accumulation and enhancing its target enzymes, including NQO1, GLC, GCLC and HO-1 [180]. A recent review described the role of OA in hepatoprotection, wherein activation of the Nrf2/ARE pathway was reported [181]. Here, the activated Nrf2 upregulated the expressions of GSH, NQO1 and HO-1. One study suggested that the anti-tumor potential of OA involved the generation of cellular apoptotic signals, whereby ERK-mediated Nrf2 upregulation actively suppressed ROS generation in oncogenic cells [182]. Several signaling pathways, including AMPK, ERK1/2, AKT/PI3K, ROS/apoptosis signal-regulating kinase 1 (ASK1)/p38 MAPK, and NF-κB, were involved in modulating the anticancer activity of OA [46]. OA was demonstrated to possess promising anti-inflammatory activity, because it depleted pro-inflammatory cytokines and augmented antioxidant genes by inhibiting NF-κB expression and promoting Nrf2 nuclear translocation, suggesting the existence of long-discussed cross-talk between NF-κB and Nrf2 [183]. Indole derivatives OA exhibited anti-inflammatory action both in vivo and in vitro [184]. This action against inflammation was accompanied by inhibition of NO, pro-inflammatory cytokines, and chemokines, i.e., IL-1β, IL-6, TNF-α, etc., as well as enhancement of anti-inflammatory cytokine IL-10. Inhibition of NF-κB, MAPKs and PI3K/AKT signaling and upregulation of Nrf2/HO-1 signaling regulated these cytokine expressions.

4.8. Ursolic Acid (UA)

Ursolic acid (8) is a naturally occurring pentacyclic triterpenoid acid found in apple peels, cranberries, blueberries, etc., which possesses a wide range of biological activities including antioxidant, antitumor and anti-inflammatory effects [185–187]. A low dose of UA effectively induced HO-1 expression in acute myeloid leukemia kasumi-1 cells [188]. However, the expression of HO-1 suppression increased the sensitization of Kasumi-1 cells to UA, which in turn mediated more efficient apoptosis. An important chemopreventive mechanism of UA observed in human mammary epithelial and hepatocellular carcinoma cells involved the inhibition of COX-2 [189,190]. Another study supported the same notion that UA effectively promoted apoptosis in gastric cancer cells by suppressing the expression of pro-inflammatory mediator COX-2 [191]. In LNCaP and PC-3 prostate cancer cells, UA enhanced the expression of SET domain-containing lysine methyltransferase 7 (Setd7), which in turn upregulated Nrf2/ARE signaling [192]. As a result, the Nrf2 downstream enzymes NQO1 and glutathione S-transferase theta 2 (GSTT2) were enhanced, and oxidative insult was attenuated. However, a recent finding demonstrated the Nrf2 inhibitory role of OA in treating breast cancer [193]. In MDA-MB-231 breast cancer cells, UA suppressed the expression of Nrf2, NQO1 and SOD1 and increased the expression of Keap1. The anti-migration and anti-invasive effects of UA in MDA-MB-231 human breast cancer cells were triggered by the downregulation of JNK, AKT, and NF-κB expressions [194]. UA and cisplatin combination sensitized HepG2/DDP cells to cisplatin by following an Nrf2 inhibitory mechanism, as well [195]. This combinatorial therapy worked against HepG2/DDP cells by inducing ROS generation, cell cycle arrest, and apoptosis. Moreover, UA induced apoptosis in SNG-II and HEC108 endometrial adenocarcinoma cells by inhibiting AKT/PI3K and MAPK signaling [61]. Apoptosis was also induced by UA in HCT116 and HT29 colorectal cancer cells via inhibition of JAK2/STAT3 phosphorylation [196]. UA nanoparticles ameliorated cervical cancer by
enhancing the expressions of p53 and caspases and abrogating the anti-apoptosis-related signals [197].

It improved CCl_4-induced fibrosis by modulating the Nrf2/ARE antioxidant signaling by elevating the expression of HO-1, NQO1, GST and downregulating the levels of inflammatory cytokines like TNF-α, prostaglandin, and iNOS [198]. One study correlated the link between upregulated phase II antioxidant enzymes and downregulated inflammatory cytokines expression with chemoprevention in an in vivo rat model [199]. Again, some reviews have summarized the essential role of activated Nrf2/ARE antioxidative signaling and anti-inflammatory action in the chemopreventive role of UA [200,201]. UA helped to actively prevent skin carcinogenesis by upregulating the expression of Nrf2-dependent antioxidant enzymes such as HO-1, NQO1 and UDP-glucuronosyltransferase 1A1 [202]. A quite similar effect was obtained for UA against skin cancer, implicating the epigenetic activation of Nrf2 [203]. It demonstrated a cytoprotective effect in lung cells by upregulating the expression of Nrf2 and its target genes NQO1 and GST [204]. Non-melanoma skin cancer was improved by UA treatment, whereby Nrf2 and NQO1 expression was upregulated [205]. Additionally, the expressions of inflammatory cytokines IL-8 and NF-κB were suppressed.

4.9. Dioscin (DC)

Dioscin (9) is a steroidal saponin that is abundantly present in *Dioscorea nipponica*, *D. zingiberensis*, *D. opposita*, *D. alata*, and *D. japonica* [48]. It has previously been reported to ameliorate prostate, lung, gastric and skin carcinogenesis [206–209].

In HL-60 leukemia cells, it produced anticancer action by activating p38 MAPK and JNK signaling [210]. DC ameliorated LPS-induced inflammation in mouse mammary epithelial cells by enhancing the level of total and nuclear Nrf2 and its downstream enzyme HO-1 [211]. Mechanistically, the AMPK signaling was activated and the expression levels of IL-1β, IL-6, TNF-α and NF-κB were suppressed. A study suggested ROS production to be an important event in DC-mediated apoptosis in human esophageal cancer Kyse510 cells [212]. This ROS-generating anticancer mechanism implied the Nrf2 inhibitory role of DC, where the cellular antioxidant defense enzymes like PRX1 and PRDX6 were downregulated [213]. The ROS-mediated apoptotic role of DC against colon cancer was accompanied by JNK/p38 MAPK signaling activation [214]. In another report, activation of ERK1/2 signaling was implicated in the DC-regulated apoptotic activity in human hepatoma Huh7 cells [215]. The anti-metastatic role of DC was evident in A549 lung cancer cells, where it suppressed EMT by downregulating TGF-β1 expression [216].

DC ameliorated hepatic fibrosis by facilitating the nuclear translocation of Nrf2, followed by its dissociation from Keap1 [217]. Consequently, by binding to the AREs, Nrf2 upregulated the expression of antioxidant enzymes HO-1, GST, GCLC and GCLM. DC improved doxorubicin-mediated liver damage by tackling oxidative stress and inflammation, and promoting apoptosis [218]. Here, it markedly increased silent information regulator 1 (Sirt1) and HO-1 expressions by mediating Nrf2 nuclear translocation and abrogating forkhead box protein 01 (FOXO1) and Keap1 expression. In addition, inflammation was inhibited by DC by reduced NF-κB, TNF-α, IL-1β, and IL-6 expressions. In addition to TLR4, these inflammatory mediators were also inhibited by DC during the amelioration of acute lung injury [219,220]. An ample body of other evidence was found supporting DC’s capacity to improve liver fibrosis and acute liver injury and damage by suppressing oxidative insult and inflammation [221–226]. In these instances, DC facilitated Nrf2 nuclear translocation and enhanced the levels of HO-1, NQO1, GSH, GST, SOD1, GCL, GCLC, and Gpx. In addition, inflammatory mediators like IL-1β, IL-6, TNF-α, IκBα, NF-κB, ICAM-1, high mobility group box 1 protein (HMGB1), and COX-2 were suppressed by DC. Several signaling pathways, such as farnesoid X receptor (FXR)/AMPK, Sirt1/Nrf2, TGF-β/smads, wingless-related integration site (Wnt)/β-catenin, PI3K, AKT, and MAPK, were involved in DC-mediated liver protection. DC induced autophagy at the early stage
of DC-induced apoptosis by inhibiting the AKT/PI3K/mTOR and activating ERK1/2 and JNK signaling [227]. Figure 7 presents the mechanism of Nrf2-ARE activation by DC.

**Figure 7.** Mechanism of Nrf2-ARE activation by DC. The diagram was adapted and modified from Zhang, X. et al., 2015 [224].

### 4.10. Corosolic acid (CA)

Corosolic acid (10) is a triterpenoid and also known as 2α-hydroxyursolic acid. It is usually found in *Schisandra chinensis*, *Eriobotrya japonica*, *Lagerstroemia speciosa* L., *Orthosiphon stamineus* and *Weigela subsessilis* [49]. It has been reported to improve several cancers, including bladder, colon, liver, breast, lung cancer, etc., [228–232].

The effect of CA on cellular transformation and upregulation of Nrf2 through epigenetic regulation in TRAMP-C1 prostate cancer cells was studied [233]. Here, CA induced mRNA and protein expression of Nrf2, and its target enzymes, such as HO-1 and NQO1. Moreover, CA abrogated the expressions of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), thereby hindering the processes of DNA hypermethylation and histone modification. This suppression of DNMTs and HDACs has extensive implications in the amelioration of prostate cancer [234,235]. CA was found to be effective in abolishing tumor initiation and lung metastasis by abrogating the COX-2 and STAT3 expression in myeloid-derived suppressor cells [236]. Moreover, CA inhibited the proliferation of U373 and T98G glioblastoma cells by preventing the activation of STAT3 and NF-κB [237]. CA ameliorated cervical cancer in a dose-dependent manner by suppressing PI3K and AKT expressions [238]. A recent review on the anticancer effect of CA reported an accumulating body of evidence supporting CA’s potential effectivity against gastric, hepatocellular, colorectal, ovarian, eye, bone, and lung cancer [239]. According to the review, the anti-gastric cancer effect of CA was mediated by the regulation of AMPK/mTOR, and the inhibition of NF-κB, HER2, and EGFR/neu oncogenic signaling. In addition, CA ameliorated colorectal, ovarian and lung cancer by suppressing Wnt/β-catenin and STAT3 signaling, respectively.
Oxidative stress suppressing action of CA was reported in another study where CA-mediated Nrf2 nuclear translocation facilitated the upregulation of HO-1, NQO1 and GCLC [240]. This ameliorative action of CA was accompanied by inhibition of JNK and activation of AMPK signaling. CA also exhibited a synergistic effect with paclitaxel, cisplatin, doxorubicin, 5-FU and Adriamycin, and markedly enhanced the sensitivity to these chemotherapeutic agents [239]. It improved acute inflammation by suppressing interleukin receptor associated kinase-2 (IRAK-2) phosphorylation, which was independent of NF-κB [241].

4.11. Lycopene (LP)

Lycopene (11) is an aliphatic hydrocarbon carotenoid compound. It is found in several dietary plants including papayas, tomatoes, and watermelons [50]. LP, a master regulator of oxidative stress, has previously been shown to exhibit anti-proliferative, antioxidant and anti-inflammatory properties [50,242].

Several studies using in vitro and in vivo experimental models have shown that the concentration of LP in serum and tissue can prevent the formation of human prostate cancer [243]. The amelioration of prostate cancer by LP might be both Nrf2 dependent and independent [244]. The role of Nrf2 and its antioxidant enzymes might vary in androgen-dependent and -independent prostate cancer cells. For instance, LP mediated a greater enhancement of GSH, GCL, GST-π, NQO1 and Nrf2 expressions in androgen-resistant DU145 cells than in androgen-dependent C4-2 cells [245]. Mechanistically, one study suggested the downregulation of AKT2 expression by LP in treating prostate cancer [246]. The suppression of NF-κB expression was also implicated in the management of prostate and breast cancer [247]. A recent study reported that LP enhanced the cisplatin sensitivity to cervical cancer cells by abolishing cell viability, enhancing Bax and suppressing Bcl-2 expressions [248]. Here, LP abrogated the NF-κB-induced inflammatory pathway and enhanced Nrf2 expression, recuing oxidative stress. LP downregulated the expression of MMP-7 by blocking the phosphorylation of ERK1/2, GSK-3β, and AKT/PI3K in HT-29 colorectal cancer cells in order to exert its chemotherapeutic role [249]. In MDA-MB-468 breast cancer cells, LP exhibited potential chemotherapeutic properties, whereby it provided promising ERK1/2 activation and inhibition of AKT phosphorylation and its downstream target mTOR [250]. It upregulated the Nrf2 dependent antioxidant enzymes HO-1 and GSH in endothelial cells [251]. In addition, it blocked the expression of TNF-α and NF-κB activation in the same cells. Studies on human colorectal and prostate cancers demonstrated that LP actively reduced inflammation in cancer cells by inhibiting the release of inflammatory cytokines like iNOS, COX-2, prostaglandin E2, nitric oxide, IL-1β, IL-6, and TNF-α, thereby blocking the activation of NF-κB and JNK [252,253]. LP exhibited antioxidant and anti-inflammatory activities in retinal pigment epithelium cells by abolishing ICAM-1 expression and inhibiting NF-κB activation [254]. In addition, it enhanced Nrf2 expression in nuclear extracts, facilitating the transactivity of the AREs and therefore increasing the intracellular GSH and GCL expression.

LP prevented ovarian cancer in laying hens by reducing the serum level of MDA and abrogating the expression of NF-κB [255]. Additionally, Nrf2 and HO-1 expressions were enhanced, whereas STAT3 expression was suppressed by LP. Hepatocarcinogenesis was prevented by LP as a consequence of diminished oxidative stress [256,257]. Here, Nrf2, HO-1, CAT, SOD and Gpx expressions were enhanced, inflammatory cytokines TNF-α, IL-1β and IL-12 were reduced, and NF-κB, COX-2, ERK, and AKT/mTOR activations were suppressed. LP ameliorated cutaneous tumors by stimulating the Nrf2 signaling pathway and causing p62-regulated degradation of Keap1 through a unique lysosome-mediated autophagic mechanism [258]. LP also improved DMBA/12-O-tetradecanoylphorbol-13-acetate (TPA)-mediated oxidative stress and skin carcinogenesis in a mouse model [259]. Here, it promoted nuclear translocation of Nrf2, enhanced the levels of CAT, HO-1, Gpx, SOD and GR, and thereby prevented ROS and MDA generation. A recent review on the mechanism of chemotherapeutic potential of LP reported that modulation of Nrf2/NF-κB
transcription played the key role in treating different malignancies [260]. It is known that chronic inflammation is a big driving factor in the process of tumor relapse and further carcinogenesis. Another recent review on the molecular mechanism of anticancer potentials of LP described the immunomodulatory and anti-inflammatory role of LP in preventing different cancers [261]. Chronic prostatitis/chronic pelvic pain syndrome was also ameliorated by LP, whereby it upregulated the phosphorylation of Nrf2 and enhanced the levels of CAT, Gpx, and T-SOD [262]. Additionally, it inhibited the expressions of chemokines and cytokines like monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein-1α (MIP-1α), TNF-α, IL-1β, IL-2, and IL-6, and abrogated the MAPKs phosphorylation. LP improved aflatoxin B1 and LPS-induced liver injury in mice by abolishing oxidative stress [263,264]. Here, LP pretreatment caused an increase in Nrf2, GST and GSH expressions, and reduction of TNF-α, IL-6 COX-2, NF-κB, ERK1/2 expressions. Combinatorial treatment of LP and genistein exerted protective action against hepatic inflammation and fibrosis by means of a quite similar mechanism [265].

4.12. Astaxanthin (AX)

Astaxanthin ([I]) is a xanthophyll carotenoid compound belonging to the broad chemical class of terpenoids. It is widely found in marine species like algae, yeast, salmon, trout, krill, shrimp and crayfish [51]. AX possesses a wide range of anti-inflammatory and antioxidant activities, with 550-fold more potency than vitamin E [266,267].

AX has been reported to possess anti-inflammatory and antioxidant activities, whereby it enhanced Nrf2 activity and reduced mRNA expression of IL-6 and IL-1β by suppressing NF-κB p65 nuclear expression [268]. A recent review reported that the antioxidant capacity of AX was highly dependent on the modulation of several signaling pathway proteins, including Nrf2, PI3K/AKT, JAK/STAT-3, NF-κB, MAPKs and PPARγ [269]. This same group of signaling pathways were implicated in other reviews summarizing the protective effect of AX against various cancers [270,271]. AX upregulated the nuclear expression of Nrf2, which inhibited the proliferation and progression of K562 human leukemia cells [272]. In contrast, it reduced LPS-induced inflammation and oxidative stress by inhibiting the activation of Nrf2 in U937 human myeloid leukemia cells [273]. The previous two reports suggested that AX possessed both an activating and an inhibitory role for Nrf2 in the management of human leukemia. The Nrf2 inhibitory role of AX might be associated with the administration of high doses in test animals [274]. In LNCaP prostate cancer cells, AX epigenetically produced an ameliorative effect by mediating upregulated mRNA and protein expression of Nrf2, NQO1 and GSTP1 [275]. In hepatocellular carcinoma cells, AX induced anti-tumor action through marked suppression of NF-κB p65 and Wnt/β-catenin, and negative activation of PI3K/AKT and ERK signaling [276]. Mechanistically, the inhibition of oral cancer by AX also took place by a quite similar mechanism [277]. AX was found to be effective against human colon cancer, whereby it induced apoptosis by suppressing the phosphorylation of AKT and enhancing the phosphorylation of p38, JNK, and ERK1/2 [278]. In HUVECs, AX caused Nrf2 nuclear translocation and enhanced the mRNA levels of HO-1, NQO1 and Gpx [279,280]. Mechanistically, in this case, AX mediated ERK phosphorylation and activated ARE-driven luciferase activity to exert its antioxidant effect. In addition, activation of PTEN/AKT signaling was also reported in the Nrf2 driven antioxidant activity of AX in HUVECs. Low concentrations of AX with polyunsaturated fatty acids synergistically resulted in a marked decrease in oxidative stress by upregulating Nrf2/ARE signaling [281]. In SKOV3 ovarian cancer cells, AX in combination with human serum albumin produced a better anticancer effect and overcame drug resistance by suppressing the NF-κB and activating p53 and MAPKs signaling [282].

In myeloid-derived suppressor cells (MDSCs), AX induced Nrf2 and its antioxidant enzyme expressions, thus causing maturation of MDSCs and regulating the immunosuppressive tumor environment in mice [283]. Notably, MDSCs are immature myeloid cells that are aggregated in stress conditions like tumor. Inflammatory pathway proteins NF-κB and COX-2 were effectively downregulated by AX in ameliorating esophageal cancer [284].
AX improved cyclophosphamide-mediated oxidative stress, DNA damage and hepatocarcinogenesis in rats via induction of Nrf2 and phase-II enzymes NQO-1 and HO-1 [285]. Here, it markedly downregulated the p53 and p38 expressions. In lying hens, it ameliorated oxidative stress by upregulating Nrf2, SOD1, SOD2 and Gpx4 [286]. It showed anti-colon cancer activity in vivo by abrogating the NF-κB, COX-2 and increasing the AKT and ERK-2 expressions [287]. The chemopreventive potential of AX was found to be prominent in hamster buccal pouch carcinoma, where it suppressed JAK2/STAT3 signaling, particularly the phosphorylation and consequent nuclear translocation of STAT3 [288]. Doxorubicin- and ochratoxin-induced liver injury was improved by AX through activating Nrf2, degrading Keap1, and upregulating HO-1 and Mn-SOD expressions [289,290]. Here, ERK level was increased and NF-κB level was decreased by AX. Figure 8 represents the mechanism of Nrf2-ARE activation by AX.

Figure 8. Mechanism of Nrf2-ARE activation by AX. The diagram was adapted and modified from Wu, H. et al., 2015 [291].
4.13. Fucoxanthin (FX)

Fucoxanthin (13) is the most abundant marine carotenoid extracted from seaweeds and microalgae [52].

FX exhibited anti-inflammatory and antioxidant effects in RAW 264.7 cells by activating the Nrf2, which was induced by activated PI3K/AKT signaling [292]. In addition, expressions of inflammatory markers including IL-6, IL-1β, and TNF-α were suppressed by FX. It demonstrated chemoresistant activity in HepG2-C8 human hepatocarcinoma cells by upregulating the mRNA and protein levels of Nrf2, ARE luciferase activity, NQO1, HO-1, and SOD [293]. The same study demonstrated another potential mechanism of FX in preventing oxidative stress and cancer, whereby epigenetic changes to Nrf2 DNA methylation occurred, altering the gene expressions without changing the DNA composition. In contrast, a study reported that the Nrf2/ARE-mediated antioxidant action of FX was partially mediated by its pro-oxidant activity [294]. Here, FX-treated mouse hepatic BNL CL.2 cells demonstrated a marked rise in cellular ROS generation. In the same study, FX enhanced the binding of Nrf2 with ARE, upregulated the mRNA and protein expression of HO-1, NQO1 and phosphorylation of ERK and p38. However, in HepG2 liver cancer cells, FX caused suppression of antioxidant enzymes SOD1, SOD2, CAT and downregulation of AKT1, ERK1/2, and JNK signaling in order to mediate its anticancer effect [295]. Here, generation of ROS by FX increased oxidative stress, which helped to destroy the liver cancer cells by means of an apoptotic mechanism. It exerted cytoprotective activity against H2O2-mediated oxidative insult in L02 hepatic cells by PI3K-regulated increases in Nrf2, HO-1 and NQO1 expressions [296]. The effects of a combined therapy of FX and rosmarinic acid were evaluated on cell viability, apoptosis induction, inflammasome regulation, and anti-oxidative response activation in UVB-irradiated HaCaT keratinocytes [297]. This combination (1:1) demonstrated improved antioxidant and anti-inflammatory profiles, with FX facilitating Nrf2 nuclear translocation and ARE-mediated activation of its detoxifying enzymes [297]. Furthermore, this combination suppressed the inflammatory response by downregulating the NLR family pyrin domain containing 3 (NLRP3), apoptosis-associated speck-like Protein (ASC), and IL-1β expression. Again, in human keratinocytes, FX substantially facilitated Nrf2 activation and its binding to AREs, which in turn increased the mRNA and protein levels of GSH, GCLC and glutathione synthetase (GSS) [298]. The upregulated Nrf2 activity was accompanied by increased PI3K/AKT signaling. FX enhanced the sensitivity of cisplatin to HepG2 hepatoma cells by downregulating the NF-κB expression [299]. Here, the phosphorylation of ERK, p38 and PI3K/AKT signaling was attenuated by FX.

The oxidative stress suppressing effect of FX was also evident in a study in which FX treatment in experimental rats enhanced the mRNA expression of Nrf2 and NQO1 [300]. Moreover, expressions of CAT and Gpx were also increased in FX-treated rats. Alcohol-mediated oxidative injury and inflammation were ameliorated by FX through activation of Nrf2 and suppression of TLR4-induced NF-κB signaling [301]. Promotion of Nrf2 and SOD and suppression of TNF-α action were implicated in ameliorating pathogen-associated molecular pattern-induced inflammation by FX [302]. A recent review reported that signaling pathways like PI3K/AKT/Nrf2, ERK, AMPK/AKT/cAMP response element binding protein (CREB)/peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α), and Nrf2-autophagy were involved in FX-induced anti-inflammatory response [303]. Figure 9 presents the mechanism of Nrf2-ARE activation by FX.
5. Conclusions and Future Perspective

The health benefits of dietary supplements containing terpenoids are well established. Reportedly, terpenes are strong candidates for the prevention of inflammation and carcinoma, as evidenced by a large number of in vitro cell line and in vivo animal-based studies. Usually, these dietary constituents do not destroy the ROS in vivo by directly reacting with them. Instead, they directly or indirectly boost body’s defense mechanism by modulating the Keap1-Nrf2-ARE signaling system, which is able to regulate the expressions antioxidant genes, phase I and II detoxification enzymes, chaperones, growth factors and their receptors, transport proteins, proteasome subunits, and some other transcription factors (Table 3) [64]. As the incidence of different types of cancers is on the rise, dietary supplements containing terpenoids may lead to more promising preventive therapies for the prevention of cancer occurrence. This review would like to add that there are still a lot of existing areas of investigation for terpenoids with respect to cancer prevention. Researchers and nutritionists should pay more attention to the study of dietary terpenoid compounds and their possible use in the prevention of cancers. Considering these thirteen compounds, there the evidence of chemopreventive activity in animal mod-
els and especially in humans is still insufficient. It can be suggested that further animal- and human-based studies are indeed necessary to reconfirm and clinically establish the chemopreventive nature of the terpenoids. Focus can also be given towards using dietary terpenoids in patients who are already suffering from cancer with a view to restricting the further progression of cancer. This kind of epidemiological approach could be critical for assessing the practical chemopreventive nature of the terpenoids on a case-by-case basis. Because of the widespread abundance of antioxidative properties in dietary terpenoids, the inclusion of these in regular food diets might help a great deal in alleviating the incidence of diseases like cancer and inflammation.

Table 3. Cellular signaling and targeted downstream proteins of dietary terpenoids.

| Compound Number | Compound Name   | Proteins Modulated Keap1-Nrf2-ARE System | Proteins Modulated after Nrf2 Activation/Inhibition | References |
|-----------------|----------------|------------------------------------------|-----------------------------------------------------|------------|
| 1               | Zerumbone      | p38 MAPK, AKT/PI3K, ERK, JNK, PKC, AMPK | HO-1, γ-GCLC, and Gpx                                | [78, 86, 90]|
| 2               | Khayandirobilide A | p38 MAPK                         | HO-1                                               | [40]        |
| 3               | Brusatol        | HER2/AKT/ERK1/2, PI3K/AKT/mTOR,       | HO-1, NQO1, GSTm2, and GCLC                         | [102, 122]  |
| 4               | Withaferin A    | ERK1/2, JNK, p38 MAPK, AKT/mTOR, JAK/STAT, AMPK/ AKT/GSK-3β, MAPK, AhR | HO-1, NQO1, GSR, CAT, SOD1, and TXN                | [131, 132, 137]|
| 5               | Betulin         |                                        | NADPH, NQO1, HO-1, GCLC, GCLM, Gpx, CAT and SOD    | [145, 148]  |
| 6               | Ganodermanondiol| ERK, JNK, p38 MAPK, AMPK p62, NF-κB, ERK, PI3K/ AKT, MAPKs | GSH, GCL, HO-1                                      | [45, 151, 158]|
| 7               | Oleanolic acid  | p62, NF-κB, ERK, PI3K/ AKT, MAPKs     | SOD-1, NQO1, GCL, GCLC, HO-1                        | [170, 171, 180, 184]|
| 8               | Ursolic acid    | NF-κB, AKT, JNK                     | UDP-glucuronosyltransferase 1A1, GST               | [192, 194, 198, 202, 205]|
| 9               | Dioscin         | Sirt1/FOXO1/NF-κB, IkBα, FXR/AMPK, TGF-β/Smad, p38 MAPK | HO-1, GST, NQO1, GCLC, GCLM                         | [217, 218, 222, 224]|
| 10              | Corosolic acid  | JNK, AMPK                           | HO-1, NQO1, GCLC                                   | [233, 240]  |
| 11              | Lycopene        | NF-κB, JNK, STAT3, AKT/mTOR, p62     | HO-1, NQO1, GSH, CAT, SOD, GCL, GST-π, Gpx         | [245, 252, 255–258]|
| 12              | Astaxanthin     | NF-κB p65, Wnt/β-catenin, PI3K/ AKT, ERK, JAK2/STAT3, p53, p38 | NQO1, HO-1, SOD1, SOD2, Gpx4                     | [276, 285, 286, 288]|
| 13              | Fucoxanthin     | AKT1, ERK1/2, JNK, NF-κB, p38, PI3K/ AKT | NQO1, HO-1, SOD1, SOD2, CAT                    | [293, 295, 299]|

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