Title

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Journal

Critical Reviews in Toxicology, 49(5)

ISSN

1040-8444

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Publication Date

2019-05-28

DOI

10.1080/10408444.2019.1635987

Peer reviewed

Critical Reviews in Toxicology

ISSN: 1040-8444 (Print) 1547-6898 (Online) Journal homepage: https://www.tandfonline.com/loi/itxc20

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To cite this article: Tian Yang, Ya-Long Feng, Lin Chen, Nosratola D. Vaziri & Ying-Yong Zhao (2019): Dietary natural flavonoids treating cancer by targeting aryl hydrocarbon receptor, Critical Reviews in Toxicology, DOI: 10.1080/10408444.2019.1635987

To link to this article: https://doi.org/10.1080/10408444.2019.1635987

Published online: 21 Aug 2019.

CRITICAL REVIEWS IN TOXICOLOGY
https://doi.org/10.1080/10408444.2019.1635987

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REVIEW ARTICLE

Dietary natural flavonoids treating cancer by targeting aryl hydrocarbon receptor

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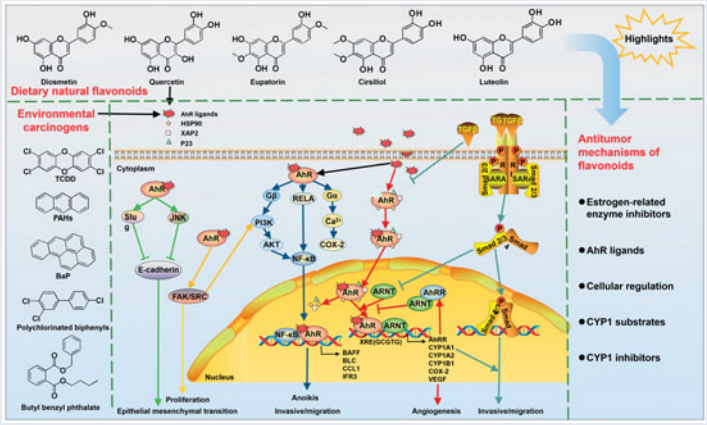
ABSTRACT

The role of aryl hydrocarbon receptor (AhR) as a ligand-activated transcription factor in the field of cancer has gradually been unveiled. A strong body of evidence indicated that AhR is implicated in cell proliferation and apoptosis, immune metabolism and other processes, which further affected tumor growth, survival, migration, and invasion. Therefore, AhR targeted therapy may become a new method for cancer treatment and provide a new direction for clinical tumor treatment. Astonishingly, the largest source of exposure of animals and humans to AhR ligands (synthetic and natural) comes from the diet. Myriad studies have described that various natural dietary chemicals can directly activate and/or inhibit the AhR signaling pathway. Of note, numerous natural products contribute to AhR active, of which dietary flavonoids are the largest class of natural AhR ligands. As interest in AhR and its ligands increases, it seems sensible to summarize current research on these ligands. In this review, we highlight the role of AhR in tumorigenesis and focus on the double effect of AhR in cancer therapy. We explored the molecular mechanism of AhR ligands on cancer through a few AhR agonists/antagonists currently in clinical practice. Ultimately, we summarize and highlight the latest progression of dietary flavonoids as AhR ligands in cancer inhibition, including the limitations and deficiencies of it in clinical research. This review will offer a comprehensive understanding of AhR and its dietary ligands which may dramatically pave the way for targeted cancer treatment.

GRAPHICAL ABSTRACT



Abbreviations: 5F 203: 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole; AhR: Aryl hydrocarbon receptor; AFP 464: Aminoflavone; $AhR^{-/-}$: AhR-deficiencies; $AhR^{+/+}$: wild-type; ARNT: AhR nuclear translocator; BaP: benzo[a] pyrene; bHLH-PAS: basic helix-loop-helix-PER-ARNT-SIM; CSCs: Cancer stem cells; CXCR4: C-X-C chemokine receptor 4; CYP1A1: cytochrome P450 1A1; DF203: 5-fluoro-2-(3,4-dimethoxyphenyl)-benzothiazole; DRE: dioxin-responsive element; EROD: ethoxyresorufin-O-deethylase; ER^{+}: estrogen receptor-positive; ER^{-}: estrogen receptor-negative; GW610: 2-(4-amino-3-methylphenyl)benzothiazole; HSP90: heat shock protein 90; KYN: kynurenine; MCDF: Methyl-1,3,8-trichlorodibenzo-furan; OM: omeprazole; PAHs: polycyclic aromatic hydrocarbons; Phortress: 2-(4-aminophenyl)benzothiazole; TCDD: Tetrachlorodibenzo-p-dioxin; TDO2: tryptophan-2,3-dioxygenase; TNBC: triple negative breast cancer; XAP2: X-associated protein

ARTICLE HISTORY
Received 4 May 2019
Revised 21 June 2019
Accepted 21 June 2019

KEYWORDS
Aryl hydrocarbon receptor; natural products; flavonoids; cancer; ligand

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1. Introduction

The ubiquitous pollutants in the environment are wantonly harming the human body. These environmental carcinogens such as tetrachlorodibenzo-p-dioxin (TCDD) and polycyclic aromatic hydrocarbons (PAHs) are derived from waste incineration, pulp manufacturing and other industrial processes (Jiang et al. 2018). Traces of environmental pollutants can be discovered throughout the world in a variety of sources, including the air, water, soil. Clinical studies have shown that these environmental carcinogens are toxic to the body by binding to AhR and cause cancer in many tissue types, especially the prostate and breast (Bianchi-Smiraglia et al. 2018; Yu et al. 2018).

The AhR is a member of the basic helix-loop-helix-PER-ARNT-SIM (bHLH-PAS) subgroup of the bHLH superfamily of transcription factors and is the only member of this family known to be activated by ligands (Figure 1). The unliganded AhR resides in the cytoplasm of a cell, forming a complex with a heat shock protein 90 (HSP90) dimer and the co-chaperone protein X-associated protein 2 (XAP2). After binding an agonist, the AhR complex translocates to the nucleus and AhR nuclear translocator (ARNT) mediates HSP90 displacement, leading to AhR-ARNT heterodimer formation. This heterodimer is capable of binding to a dioxin-responsive element (DRE) and both AhR and ARNT can recruit co-activators, leading to the transcription of a wide variety of genes. The AhR target gene cytochrome P450 1A1 (*CYP1A1*) is almost totally dependent on AhR activity for expression and is highly induced by AhR activation through multiple DREs (Murray et al. 2014). *CYP1A1* metabolizes a number of procarcinogens, such as BaP, to intermediates that can react with DNA to form adducts, resulting in mutagenesis and cancer (Zapletal et al. 2017). In view of the significant role of AhR in human physiology and pathophysiology, agonists or antagonists of AhR have the potential to become new targeted therapeutic agents for cancer.

As interest in the AhR and its ligands increases, it is essential to discover more high-affinity AhR ligands. In addition to environmental contaminants, two other sources of AhR ligands with pharmaceutical potential are currently considered. Firstly, various dietary phytochemicals were identified as potential ligands (Busbee et al. 2013; Naganuma et al. 2018). For many polyphenols, especially large amounts of flavonoids have been shown to be involved in immune regulation and AhR activation (Schiering et al. 2017; Bartonkova and Dvorak 2018; Kerimi and Williamson 2018). Secondly, some products of amino acid metabolism, such as tryptophan-derived ligand 6-formylindolo[3,2-b]carbazole and kynurenine, also can as potential ligands (Moura-Alves et al. 2014). But natural products are always the biggest asset in the study of novel anti-cancer agents. Flavonoids represent the largest group of natural dietary AhR ligands (Iyer et al. 2018). Some flavonoids acted as either AhR agonists or antagonists to bind AhR and alter *CYPs*. Ronnekleiv et al. found that the combination of chrysin and AhR can up-regulate pro-apoptotic cytokines tumor necrosis factor α and β genes to play a chemoprophylactic role in human colorectal cancer cells (Ronnekleiv-Kelly et al. 2016) dietary natural flavonoids

The diversity and low toxicity of these dietary natural flavonoids, combined with their various effects on the immune system through their interaction with AhR, make them interesting candidates for researchers' research. However, there is no clear epidemiological evidence to prove the link between flavonoids and human health. Some studies support the protective effects of flavonoids on cancer, other studies have shown no effect, and even some studies have shown that it may be harmful. Therefore, further research on laboratories and populations is important (George et al. 2017; Rienks

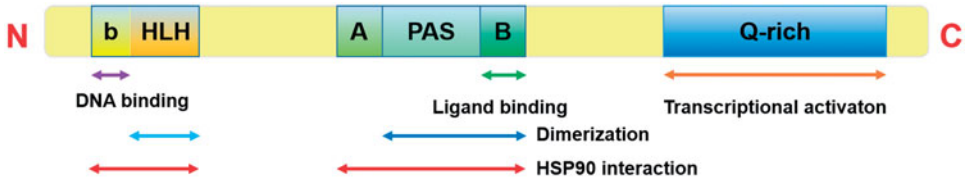

Figure 1. The functional structure of AhR protein. A bHLH (basic helix-loop-helix) domain that allows the dimerization with its partner ARNT, the binding of DNA and the interactions with chaperones such as Hsp90. And it also contains sequences important for both nuclear import and export; A PAS (PER–ARNT–SIM) domain which comprises two structural repeats A and B which are also involved in the dimerization with ARNT (PAS A) but which also allows the ligand binding (PAS B); Q-rich region (enriched with glutamine), coactivators and co-repressors interact with the AhR via this domain.

et al. 2018). We searched the PubMed database with the words "flavonoids", "cancer" and "AhR" before March 2019, and excluded duplicate and poor quality literature. In this review, we will discuss the role of AhR in tumorigenesis and progression and the potential of targeting AhR for tumor therapy. At the same time, the latest research progress on natural and dietary AhR ligands is provided by taking dietary flavonoids as an example.

2. The role of AhR in tumor

Epidemiological and experimental animal data indicate that AhR dysfunction is significantly associated with cancer. For example, Iqbal et al. showed that BaP or TCDD interact with AhR and induce osteoporosis and fracture through the activation of *CYP1A1/CYP1B1* enzymes to react osteoclast bone resorption (Iqbal et al. 2013). The classical pathway suggests that AhR promotes the expression of phase I metabolic enzymes at the initial stage of tumors and leads to the metabolic activation of carcinogens such as TCDD/BaP intermediates or end products with genetic toxicity, which leads to DNA damage and promotes tumorigenesis (Romagnolo et al. 2016). At the same time, researchers found that AhR not only plays a role in the induction stage of tumors, but also plays an important role in the proliferation, apoptosis, migration, invasion and other stages of tumors (Feng et al. 2013; Tummala et al. 2014). In addition, AhR is associated with the regulation of multiple signal transduction pathways such as FAK/Src (Tomkiewicz et al. 2013; Wei et al. 2018), PI3K/Akt (Popolo et al. 2017), TGF-β (Gagliani et al. 2015), and NF-κB (Galle-Treger et al. 2016) (Figure 2). There have been numerous excellent literature reviews on the specific roles of AhR in various stages of cancer, and we will not discuss it much here (Safe et al. 2013; Esser and Rannug 2015; Gutierrez-Vazquez and Quintana 2018).

It is worth noting that recent studies have shown that activation of AhR is associated with poor response of chemotherapy and target-therapy in cancer. For example, Ye and colleagues showed that the AhR/CYP1A1 signaling pathway mediates breast cancer stem cells (CSCs) proliferation and chemoresistance by inhibiting PTEN and activating of the β-catenin and Akt pathways (Ye et al. 2018). In addition, the expression of AhR and CYP1B1 in inflammatory breast cancer carcinoma tissues is associated with poor prognostic markers, such as lymphovascular invasion, tumor grade, cellular proliferation and the number of lymph node metastases. Furthermore, AhR can promote therapeutic resistance to CSC and inflammatory breast cancer aggressive phenotypes by stimulating the Wnt5a/β-catenin signaling pathway (Mohamed et al. 2019). It has now been demonstrated that AhR is an effective contributor in conferring resistance to apoptosis against several apoptosis-inducing treatments on different breast cancer cell lines. Based on the results of the current study a question arose: why does the AhR act in such a broad spectrum capacity? A possible explanation by Bekki et al. is that the AhR has evolved as an overall pro-survival factor against environmental stress, which is also effective for stress-induced apoptosis (Bekki et al. 2015). Therefore, it is important to further determine whether AhR activation also contributes to resistance to ROS1 TKIs, ALK TKIs and other targeted therapeutics in non-small-cell carcinoma.

More importantly, AhR is frequently overexpressed in human or animal tumor tissues even without exogenous ligands. On the one hand, researchers believe that this may

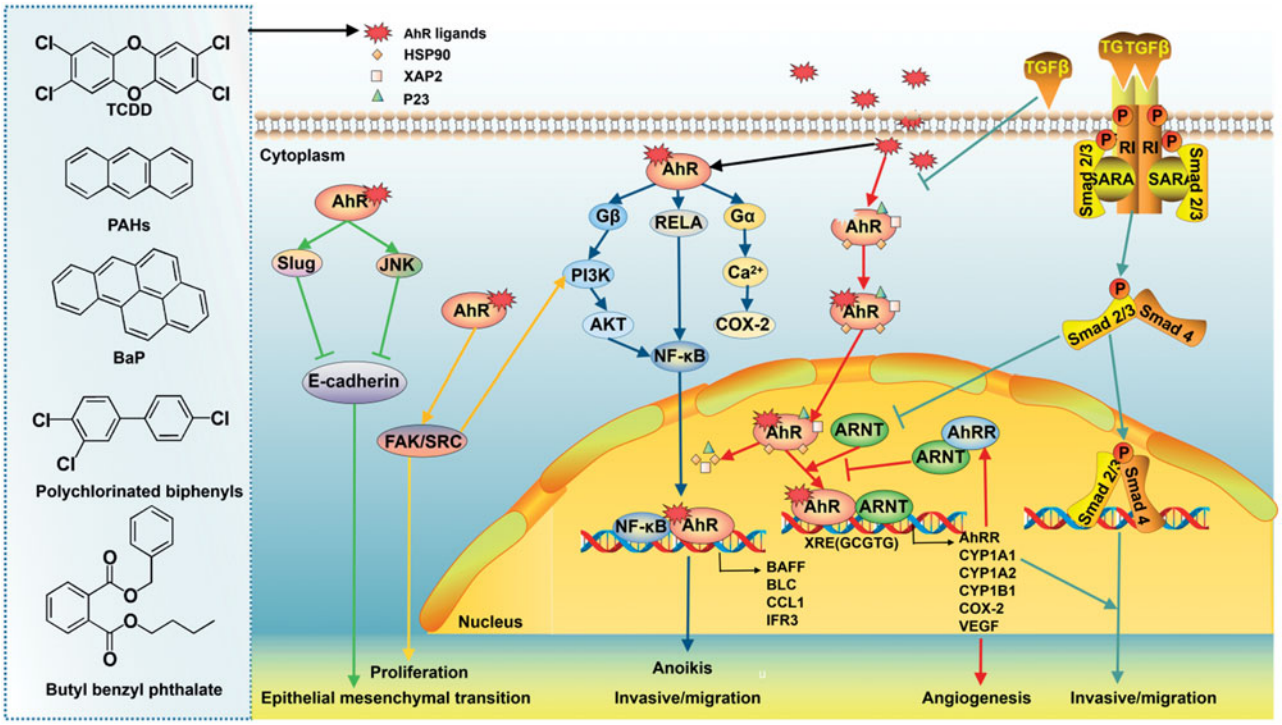

Figure 2. The signaling pathway of AhR in tumors. In the tumor microenvironment, AhR is involved in the regulation of a variety of signal transduction pathways, such as JNK/Slug, FAK/Src, PI3K/Akt, NF-κB and TGF-β. JNK: Jun amino-terminal kinases; FAK: Focal Adhesion Kinase; PI3K: phosphoinositide 3-kinase; Akt: protein kinase; NF-κB: nuclear factor-κB; P: phosphorylation.

be related to endogenous AhR ligands. Opitz et al. claimed that tryptophan-2,3-dioxygenase (TDO2)-derived kynurenine (KYN) inhibits anti-tumor immune responses and promotes tumor- cell survival and motility through the AhR in an autocrine/paracrine manner (Opitz et al. 2011). Subsequently, D'Amato et al. found that in triple-negative breast cancer cells, the TDO2-KYN-AhR signaling axis was activated in an NF-κB-dependent manner to promote anoikis resistance and metastasis (D'Amato et al. 2015). Rogers et al. further discovered that miR-200c, a gene used to target and inhibit epithelial-mesenchymal transition, can directly TDO2 resulting in reduced production of the immunosuppressive metabolite kynurenine (Rogers et al. 2019). This has developed novel therapeutic strategies for current immunotherapies. These results indicate that endogenous ligands of AhR play a role in tumor formation and progression. However, the inference still has problems. For example, do these endogenous AhR ligands originate from entire body tissues or local tissues? Are they produced in the body or by bacteria? Whether they reached sufficient concentrations to activate AhR in tumor microenvironment? These issues still need further study. On the other hand, AhR can interact with some growth factors to promote the progress of tumors, such as fibroblast growth factor 9, osteopontin. The promoters of these factors contain DNA response elements of AhR, which can be enhanced by AhR agonists. At the same time, as a strong mitogen, they are likely to further promote the proliferation of cancer cells. For example, AhR is overexpressed in lung adenocarcinoma and positively correlated with fibroblast growth factor 9, which may promote tumor growth by regulating the interaction of tumor cells with fibroblasts (Wang, Hang, et al. 2009; Ueng et al. 2010). Chuang et al. found a positive correlation between osteopontin and AhR expression in lung cancer specimens. And AhR-deficiencies ($AhR^{-/-}$) mice indicate down- or up-regulation of osteopontin expression in lung cancer cells (Chuang et al. 2012). But interestingly, Kuznetsov et al. showed that osteopontin is negatively regulated by the dioxin receptor, and that down-regulation of its expression correlates with development of stomach tumors in mice expressing a constitutively active mutant of dioxin receptor (Kuznetsov et al. 2005). These all illustrate the ability of AhR to promote tumor progression.

In contrast, some scholars have found that in some cases, AhR is clearly "silent" (*i.e.* not expressed) during the formation of some tumors, suggesting that it has anti-cancer function. In $AhR^{-/-}$ mice, the incidence of liver cancer induced by diethylnitrosamine (non-AhR ligand) was higher than that in wild-type ($AhR^{+/+}$) mice, because high levels of oxidative stress and stable expression of TGF-B promoted tumor development in $AhR^{-/-}$ male mice (Fan et al. 2010). Huang, YK et al. discovered that after experimental autoimmune uveitis induction, $AhR^{-/-}$ mice had more severe clinical and histopathological findings of uveitis than $AhR^{+/+}$ mice (Huang et al. 2018). More recently, Iu et al. found that AhR can inhibit inflammation, oxidative stress and apoptosis caused by cigarette smoke through mechanisms involved in RelB gene (NF-B member) regulation (Iu et al. 2017). These data suggest that AhR can act as a tumor suppressor gene under certain conditions, but the underlying molecular mechanisms are still unknown.

It is worth mentioning that when AhR is activated by exogenous ligands, experiments with different cell lines often result in different, even opposite results. Harrill et al. showed that rodent cancer bioassays indicate that TCDD activates AhR and causes increases in both hepatocytic and cholangiocytic tumors (Harrill et al. 2015). However, Yamaguchi et al. found that TCDD can inhibit the growth of liver cancer cells through various signaling pathways mediated by AhR and its related cofactors (Yamaguchi and Hankinson 2018). Why and how to produce contradictory results from these different work? Some scholars speculate that it may be because AhR has cell specificity for cell proliferation, and cell type is an important factor that determines whether AhR promotes or inhibits cell growth and proliferation (Narasimhan et al. 2018). To sum up, we find that AhR is a double-edged sword for tumorigenesis. There may be some balancing mechanism in organisms that will determine whether AhR promotes or suppresses cancer. Nevertheless, what is the molecular basis for determining this balancing mechanism associated with a particular cell type? How do they work? Such institutional problems are not yet clear. Therefore, it is necessary to further study the potential cellular/molecular mechanisms and finally clarify the contribution of AhR to cancer progression or prevention.

3. The mechanism of AhR ligands as anti-cancer drugs

Natural products have been widely used for treatment of CKD in clinic (Zhao 2013; Tian et al. 2014; Wang, Chen, Wang, et al. 2017; Chen, Feng, et al. 2018; Chen, Hu, et al. 2018; Chen, Yang, et al. 2018; Hu et al. 2018; Wang et al. 2018; Chen, Feng, et al. 2019). Treatment with ergone (Zhao et al. 2011, 2012; Zhao, Zhang, et al. 2013), *Rhubarb* (Zhang et al. 2015, 2016; Wang, Chen, Liu, et al. 2017; Zhang, Li, et al. 2018) and the surface layer of *Poria cocos* (Zhao, Lei, et al. 2013; Zhao, Li, et al. 2013; Chen, Cao, et al. 2019) could improve myriad diseases such as cancer, cardiovascular disease and kidney diseases. At present, targeted drugs research on AhR ligands mainly includes 2–(4-aminophenyl)benzothiazole (Phortress), Aminoflavone (AFP 464), omeprazole (OM) and NK150460, etc. Phortrees and AF have entered phase I and II clinical trials and relevant studies on OM and NK150460 are in progress (Hendriks et al. 2017) (Figure 3(A)). In this section, we will introduce these drugs in turn and explain these compounds role as cancer ligands in the treatment of cancer.

3.1. Phortress

Phortress is a metabolically activated pro-drug that causes the formation of DNA adducts and leads to cancer cell death (Cui and Li 2014). During early screening, the researchers found that breast cancer cells MCF-7 and ovarian cancer cells IGROV-1 were sensitive to Phortress. Subsequent studies revealed that Phortress and its derivatives

2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (5 F 203), 2-(4-amino-3-methylphenyl)benzothiazole (DF 203), 5-fluoro-2–(3,4-dimethoxyphenyl)-benzothiazole (GW 610) and the like can enter the cytoplasm through the cell membrane. They bind with AhR and translocate to the nucleus and form a heterodimer with ARNT. Then, they bind to the promoter of the *CYP1A1* gene and promote the expression of *CYP1A1* mRNA. Subsequently, the content of *CYP1A1* in the cytoplasm increased and combined with 5F203 to form a substance with biological activity, which then entered the nucleus and interacted with DNA to cause the break of single and double strands of DNA, leading to DNA damage and cell death (Wang and Guengerich 2012; Stone et al. 2015; Citossi et al. 2018). Phortress are not sensitive in some cells, such as breast cancer cells MDA-MB-435 and prostate cancer PC-3 cells, and Phortress does not cause DNA damage and trigger cell death (Rowland et al. 2019).

This indicates that Phortress has a selective tumor suppressor effect in tumor cells, and its anti-tumor activity is linked to *CYP1A1* activity. In addition, some new ideas about the role of 5 F 203 in cancer treatment have been reported recently. Luzzani et al. demonstrated that 5 F 203 can inhibit c-Met receptor phosphorylation in human renal cancer cell lines (TK-10 cells). And c-Met receptor signaling is important in the migration and metastasis of tumor cells (Luzzani et al. 2017). And McLean et al. demonstrate that 5 F 203 induces reactive oxygen species mediated DNA damage at least in part via AhR, c-Jun-N-terminal kinase, or p38 mitogen-activated protein kinase activation and modulates the expression of oxidative stress-responsive genes such as cytoglobin to confer its anticancer effect (McLean et al. 2015). In addition, Rowland et al. previously demonstrated that 5 F 203 induce the expression of tumor suppressor gene cell albumin in breast cancer cells. And they recently discovered that 5 F 203 not only induces apoptosis but also induces caspase-3 activation in triple negative breast cancer (TNBC) cells and breast cancer cells. It is suggested that 5 F 203 has the potential to restore cytoglobin expression as a novel strategy for the treatment of TNBC (Rowland et al. 2019).

3.2. AFP 464

AFP 464 is a novel anticancer drug that has entered phase II clinical trials. The mechanism of action of AFP 464 and Phortress in estrogen receptor-positive (ER^+) breast cancer cells such as MCF-7 is similar, but there are still some differences (Luzzani et al. 2017). When AFP 464 acted on estrogen receptor-negative (ER^-) alpha TNBC cells and prostate cancer cells, it was not drug-induced ethoxyresorufin-O-deethylase (EROD) activity and no increase the expression of *CYP1A1* and *CYP1B1* gene (Loaiza-Perez et al. 2004). And AFP 464 can cause DNA damage, S phase arrest and senescence in TNBC cells, but its regulation of growth inhibition does not require the expression of endogenous AhR or downstream AhR target genes CYP1A1 and CYP1B1. That is to say, whether AhR is expressed or whether AhR signaling pathway is normal, which does not affect the function of AFP 464 to inhibit cell growth (Brinkman et al. 2014).

In addition, AFP 464 has excellent applications in other fields. The emergence of drug resistance is one of the problems that plague researchers. For example, more than 40% of patients with luminal breast cancer treated with endocrine therapy agent tamoxifen demonstrate resistance. Interestingly, Rowland et al. found that elevated α6-integrin expression is associated with tamoxifen resistance and AFP 464 suppresses α6-integrin-Src-Akt signaling activation to confer activity against tamoxifen-resistant breast cancer (Rowland et al. 2019). In addition, Brantley et al.discovery that α6-integrin promotes initiating cells growth. And AhR signaling activation impedes the formation of mammospheres (clusters of cells enriched for tumor initiating Cells) (Brantley et al. 2016).

At the same time, with the emerging role of AhR in immune tolerance, Callero et al. explored the effects of AFP464 on the immune system. They concluded that AFP 464 increased splenic cytotoxic activity, diminished the number of systemic/local Treg lymphocytes and myeloid-derived suppressor cells. It is assumed that AFP464 regulates the immune response which collaborates with its anti-tumor activity (Callero et al. 2017). It is well known that one of the main challenges of cancer treatment is accurate. In order to enhance the targeting of drugs, researchers have introduced nanotechnology in anticancer drug development. A quantum-dot-based micelle conjugated with an anti-epidermal growth factor receptor nanobody and loaded with AFP 464, has been engineered for EGFR-overexpressing cancer therapeutics. Wang et al. Reported that this quantum-dot-based nanobody-conjugated micelle is more effective in the treatment of tumors and no side effects have been observed (Wang, Wang, et al. 2017).

3.3. Omeprazole

Omeprazole (OM) is an AhR agonist and a proton pump inhibitor that is used to treat people with gastric acid related diseases. For example, Dutta et al. demonstrated that OM can alleviate cough caused by acid reflux in patients with pulmonary fibrosis by randomized double-blind test, and is well tolerated and has fewer adverse reactions (Dutta et al. 2019).

OM as an AhR ligand depends not only on their structure but also on target organs and downstream reactions and genes. In the classical nuclear AhR/ARNT-mediated reaction, OM recruited AhR into the region of the c-x-c chemokine receptor 4 (CXCR4) promoter containing DRE, which was accompanied by loss of pol II on the promoter and decreased expression of CXCR4. Therefore, omeprazole inhibits its tumor invasion and regulates metabolism *in vivo* by inhibiting CXCR4 transcription (Jin et al. 2014).

In addition, the non-genomic AhR pathway was also reported, and Shimoyama et al. found that TCDD or OM caused PP2A-mediated dephosphorylation of Sp1 at Ser-59 and induced *CYP1A1* transcription. This signaling pathway did not depend on the AhR-mediated pathway. Similarly, Jin et al. suggested that in the most highly invasive subtype of

pancreatic cancer cells, OM invasion through the non-genomic AhR pathway (Jin et al. 2015).

It is worth noting that Patel et al. initially assumed that OM-mediated activation of AhR attenuated acute hyperoxia-induced lung injury in newborn mice, but the results of the trial reversed their hypothesis. The results showed that hyperoxia-induced alveolar and pulmonary vascular simplification, inflammation, oxidative stress, and vascular injury were increased in OM-treated animals. In other words, OM decreases functional activation of pulmonary AhR and potentiates hyperoxia-induced lung injury in newborn mice (Shivanna et al. 2015). This indicates that there are still toxicity and side effects of OM that cannot be ignored, which should be paid attention to in clinical treatment.

3.4. NK150460 and MCDF

In breast cancer, AhR regulates the level of estrogen in the body through the following two ways [34]. One is to induce the expression of estrogen metabolism genes in the *CYP1* family as a transcription factor, and the other is to inhibit estrogen signaling pathway and degrade estrogen receptor. Therefore, inhibition of the AhR- ER signaling pathway plays a role in anti-estrogen activity (Marques et al. 2013; Popolo et al. 2017).

As a novel AhR agonist, NK150460 has selective antitumor activity against breast cancer cell lines. Moreover, NK150460 inhibits 17β-estradiol (E2)-dependent transcription without affecting the binding of E2 to ER. The mechanism seems completely different from the existing anti-hormone drugs, indicating that NK150460 may become the fourth class of anti-hormone therapy drugs in the future (Fukasawa et al. 2015). Methyl-1,3,8-trichlorodibenzo-furan (MCDF), a relatively nontoxic selective AhR that induces *CYP1A1*-EROD activity and inhibited proliferation of ER-breast cancer cell lines (Chitrala and Yeguvapalli 2014). In short, NK150460 and MCDF have antitumor activity depending on AhR/ARNT and the target protein *CYP1A1*. However, NK150460 inhibits the growth and proliferation of tumor cells by inducing the expression of *CYP1A1* and *CYP1B1* at the mRNA level. MCDF can activate *CYP1A1*-dependent EROD activity and inhibit the proliferation of ER^- MDA-MB-231. Furthermore, MCDF inhibits cell growth and invasion by inducing expression of miR-335, which is usually accompanied by downregulation of SOX4, a miR-335 regulated (inhibited) gene (Zhang et al. 2012).

In conclusion, AhR ligands can prevent tumorigenesis in two main ways. (1) AhR ligand activation mediates the expression of downstream target genes (such as *CYP1A1*, *CYP1A2,* and *CYP1B1*) of AhR, which can promote the metabolism of exogenous toxins and protect the body from the influence of exogenous substances (Maayah et al. 2013; Minh Truong et al. 2014). (2) AhR ligands indirectly interfere the interaction between AhR and other tumor-related signaling pathways (such as AhR-ER and AhR-mitogen-activated protein kinases) to prevent the occurrence of tumors (Salisbury and Tomblin 2015). Current research results show that targeting AhR drugs are mainly focused on breast cancer research, but also involve other tumors. However, AhR ligand has the specificity of tumor and tumor cells, which makes it more difficult to screen AhR targeted drugs. Therefore, the author hopes to find out the reasons for the specificity of AhR ligands in tumors on the basis of a comprehensive understanding of the relationship between AhR and tumors, so that AhR targeting drugs can be widely used in the treatment of tumors.

4. The potential of dietary flavonoids as a cancer-targeted drug

As discussed above, AhR ligands are expected to be developed as new cancer-targeting drugs. In addition to these classical synthetic AhR ligands, scientists have begun to discover non-classical natural ligands. These natural compounds have been shown to be less toxic, but they can still trigger reactions via the AhR pathway. Most natural AhR ligands are introduced into biological systems by oral administration of food and herbal medicines, the most notable of which are flavonoids. Flavonoids are the most common plant polyphenols that provide a great deal of flavor and color to fruits and vegetables. More than 8000 different flavonoids have been identified. The seven main subclasses of flavonoids include the chalcones, flavonols, isoflavones, anthocyanidins, flavanonols, flavanones and flavanols (Dong et al. 2016). Many reports indicate a link between flavonoid consumption and health benefits (or risk) due to its antioxidant, antiproliferative, estrogenic or anti-estrogenic properties (Mozaffarian and Wu 2018; Scarmeas et al. 2018). The low toxicity of these dietary flavonoids, combined with their various effects on tumorigenesis via the interaction with the AhR, makes them interesting candidates for researchers to investigate.

4.1. The role of dietary flavonoids as AhR ligands in cancer

From independent screening of phytochemicals, certain flavonoids exhibit AhR agonist or antagonist activity in a cell line-specific manner. Numerous flavonoids were found to activate the AhR, including apigenin, baicalein, chrysin, diosmetin, daidzein, galangin, genistein and quercetin (Jin et al. 2018) (Figure 3(B)). Apart from this, Androutsopoulos et al. reported earlier that both *CYP1A1* and *CYP1B1* mRNA levels and *CYP1* enzyme activity marker EROD were increased in a dose-dependent manner upon treatment with eupatorin-5-methyl ether and luteolin (Androutsopoulos and Tsatsakis 2014). In addition, Choi et al. claimed that β-naphthoflavone, as a non-toxic flavonoid, can induce the detoxification potential of the representative detoxification enzyme cytochrome P4501A1 (Chuang et al. 2012). Subsequently, Bolton et al. reported that a potent AhR agonist 6-Prenylnarigenin in hops, resulting in a selective up-regulation of the P450 1A1-mediated estrogen detoxification pathway (Bolton et al. 2019). Of note, some flavonoids that bind to AhR elicit antagonism rather than increase *CYP1* activity. Regarding the antagonistic activity of flavonoids, kaempferol, galangin, quercetin, apigenin, and naringenin inhibited the activation of AhR induced by TCDD (Wang et al. 2012). Tan et al. found that hesperetin, a

flavonoid widely present in citrus fruits, inhibits TCDD-induced nuclear translocation of AhR. And further reporter-gene assay indicated that the effect of hesperetin attenuated the induced XRE activation (Tan et al. 2018). And Froyen et al. found that genistein significantly decreased basal hepatic microsomal *Cyp1A1* protein expression and activity but did not alter the expression of AhR protein. Furthermore, genistein-treated cells exhibited inhibition ARNT and ER-α bindings to the *Cyp1A1* promoter region (Froyen and Steinberg 2016). Interestingly, despite the structural similarity between quercetin and kaempferol, they combined with AhR produced different effects. After the active site of AhR occupied by kaempferol, it could prevent TCDD from binding with AhR, which leads to a decrease in TCDD-induced *CYP1A1* expression. And their differential effect may be due to the absence of additional hydroxyl groups on kaempferol, preventing it from achieving the best fit to the binding site on AhR to produce transcriptional activation (Androutsopoulos and Tsatsakis 2014). In a cell-free system using rat hepatic cytosol, it was also found that their antagonistic effects were dependent on their subclasses. And the order of the antagonistic activity was flavones = flavonols > flavanones > catechins ≫ isoflavones (Nishiumi et al. 2011).

After the above comparative analysis, the author found that the effect of flavonoid-mediated *CYP1* induction on physiological functions is very complicated. On the one hand, enhanced *CYP1* activity may lead to metabolic activation of pro-carcinogens, production of genotoxic metabolites, and then covalent binding of DNA and causing carcinogenesis. On the other hand, the induction of *CYP1s* and some other metabolic enzymes such as glutathione S-transferase and UDP-glucuronyltransferase may accelerate the rate of detoxification of xenobiotics (Kalthoff et al. 2017). Perhaps the contribution of dietary flavonoids to the initiation or prevention of cancer depends on the balance between pro-carcinogen activation and detoxification (Bock 2014). In order to further explore more potential natural AhR ligands, researchers tried to reveal why flavonoids are the largest source of AhR ligands. Generally, substrates for AhR are planar aromatic compounds with few bulky substituent groups. That might partly explain the activity of flavonoids, which have similar planar structures as AhR ligands. In addition, some researchers further analyzed the characteristics of dietary flavones as AhR ligands. Jin et al. indicated that a major structural determinant for AhR activation was the number of hydroxyl groups where pentahydroxyflavonoids (with the exception of morin) > hexahydroxyflavonoids > tetra-/trihydroxyflavonoids (Jin et al. 2018). And Wang et al. proposed that the prenylated naringenin derivative exhibited unique activity compared to the parent naringenin. They found that the significant *CYP1A1/1B1* induction by 6-prenylnarigenin compared to 8- prenylnarigenin may suggest that the positioning of the prenyl group is important for AhR activation (Wang et al. 2016). But Calvo et al. suggested that the oral bioavailability of 8-prenylnaringenin in healthy women and men was significantly higher than 6-prenylnaringin in a randomized crossover trial (Calvo-Castro, Burkard, et al. 2018). Obviously there are still mysteries still to be discovered.

In addition, the author noticed two important points when sorting out the literature. (1) Generally, at lower concentrations, these ligands functioned more often as AhR antagonists. However, this antagonistic effect may be reversed at higher concentrations (Puppala et al. 2007). (2) Interestingly, some flavonoids exert their effect on AhR in a species-dependent manner. For example, 3′- Methoxy-4′-nitroflavone, a synthetic flavonoid, has an agonistic effect on guinea pig AhR activity, while it shows antagonistic effects on mouse AhR (Stejskalova et al. 2011). These are of great significance for the further development of flavonoids. There is growing evidence that dietary compounds in fruits and vegetables can reduce the incidence of cancer. As a highly conserved transcription factor, AhR is positively regulated by environmental toxins, while dietary antagonists are negatively regulated. However, more research is needed to confirm the species and tissue-specific effects of AhR and dietary compounds that interact with receptors in cancer initiation and progression (Figure 4).

4.2. Epidemiological evidences on the role of dietary flavonoids on carcinogenesis

In recent decades, the proportion of scientific studies based on non-nutritive components of the diet has increased. These natural ingredients are present in diet and have the ability to protect the body from the harmful effects of degenerative diseases, tumor, cancer and cardiovascular ailments (Dhouafli et al. 2018; Carrera and Cacabelos 2019). Although it is still unknown which of the complex plant components is responsible for the protection of the body. At present, the most studied phytochemicals with anti-cancer potential are flavonoids, which play an important role in cancer prevention (Table 1). After absorption with or without metabolic conjugation, flavonoids are transported to target organs where they exert their anticarcinogenic activity. The molecular mechanisms of the anticarcinogenic effects of flavonoids include their antagonistic effect on the AhR, and regulation of phase I and II drug metabolizing enzymes and phase III transporters (Kawai 2018; Wang et al. 2019). In addition, these anticancer effects may be partly due to the antioxidant properties of the flavonoids, and recent studies suggest that interactions with essential signal transduction pathways may be more important (Alaklabi et al. 2018; Ojelabi et al. 2018). As well, flavonoids may also interact with chemotherapeutic drugs used in cancer treatment through the induction or inhibition of their metabolism (Budisan et al. 2019).

However, the data from epidemiological studies regarding flavonoids in human health are far from convincing. Currently, there are many prospective studies to investigate the association between flavonoid intake and cancer development. Quercetin and kaempferol are two of the most common flavonoids in the human diet. For endometrial cancer, a 35% a reduction in the risk of developing tumors was found among American women consuming high amounts of quercetin indicating beneficial effects for this type of cancer (Rezvan et al. 2017). Although Paller et al. found a negative correlation between high intake of quercetin and prostate

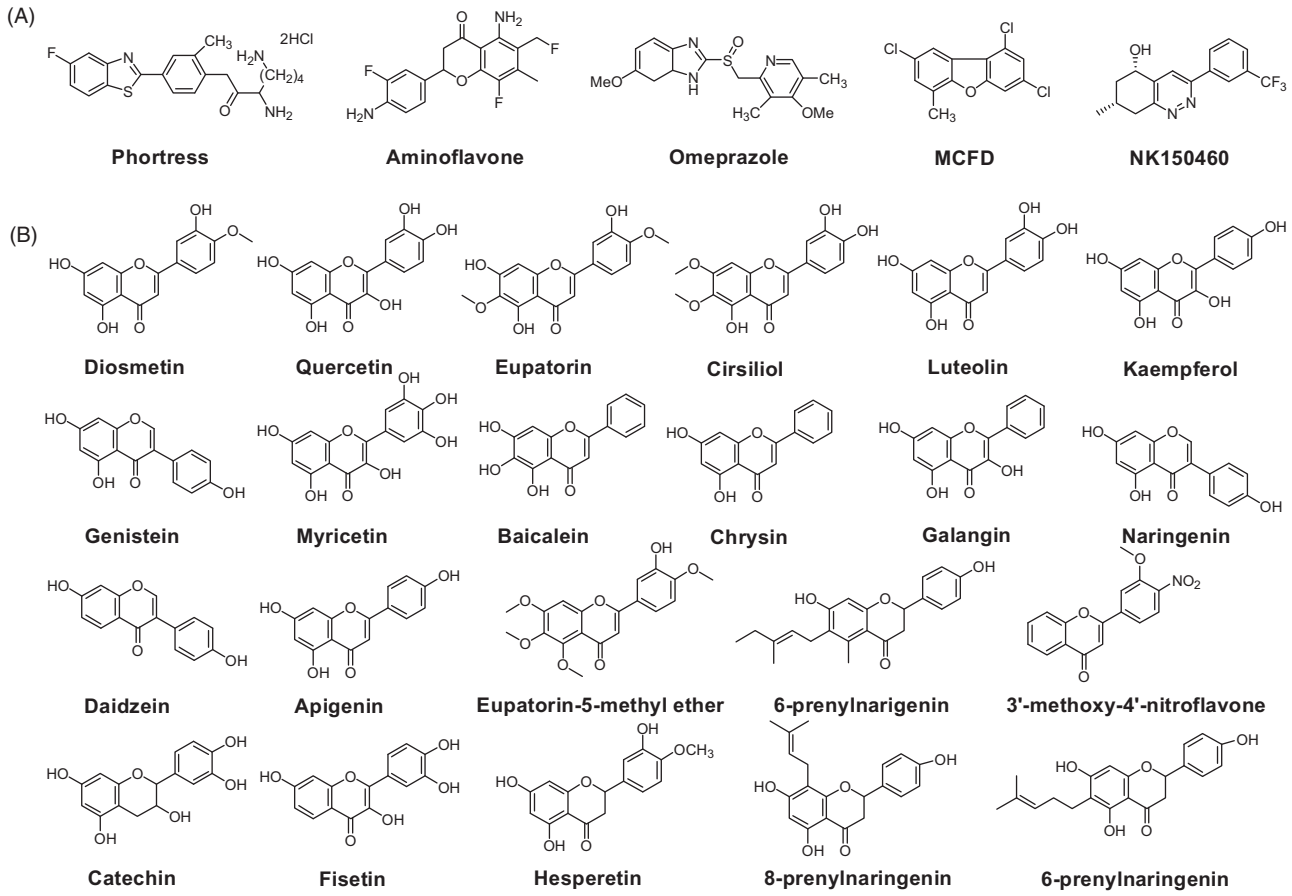

Figure 3. structure of AhR ligands compounds. (A) Structure of AhR ligands entering clinical studies; (B) Structures of flavones as AhR ligands.

cancer risk is described, this effect is not statistically significant (Paller et al. 2015). Moreover, these were not reproduced by other effects about the role of quercetin in prostate carcinogenesis (Geybels et al. 2013; Sen et al. 2019). Similarly, a case-control study conducted with Italian women and a prospective investigation among American women revealed a 37–43% reduction in ovarian cancer incidence, including serous tumors (Gates et al. 2007). On the contrary, three other studies conducted in the US reported no significant relationships between consumption of diets rich in kaempferol and incidence of ovarian cancer (Gates et al. 2009; Wang, Lee, et al. 2009; Cassidy et al. 2014). In addition, Gates et al. studied the relationship between the intake of five common dietary flavonoids and the incidence of ovarian cancer in an earlier prospective study review. These five flavonoids include myricetin, kaempferol, quercetin, luteolin, and apigenin (Gates et al. 2007; Koper et al. 2019). Unfortunately, there was no clear correlation between the total intake of the five flavonoids examined and the incidence of ovarian cancer (Kawai 2018). Cassidy et al. further analyzed the associations between flavonoid subclasses and risk of ovarian cancer, suggesting that higher intake of flavonols and flavanones and consumption of black tea may be associated with lower risk of ovarian cancer (Cassidy et al. 2014).

Several epidemiological findings have demonstrated that specific flavonoids can be responsible for reduction of the risk of certain cancer types. However, these results are still rather limited, inconclusive and controversial. The contradictory results of *in vitro* and *in vivo* data may be related to a variety of factors. For example, in plant-derived dietary products, phytochemicals are present in various different combinations in the context of food matrix and mutual interactions of dietary ingredients cannot be excluded leading probably to additive, synergistic or antagonistic biological effects, which are difficult to model in experimental *in vitro* studies. In addition, longer follow-up times, different populations, various doses and exposure timing, as well as diverse well-controlled confounders, also make it difficult to define the effects of flavonoids on cancer. Although it is currently difficult to determine whether dietary flavonoids are beneficial to our health by preventing carcinogenic effects, according to epidemiological studies, the possible adverse effects of flavonoids on human health are rare, so it may be present as a dietary supplement (Andres et al. 2018).

4.3. The limitations of dietary flavonoids in clinical application

Besides the innumerable number of evidences supporting the candidate role of dietary flavonoids as a potent therapeutic agent, there are also some facts that might limit the widespread acceptance of dietary flavonoids in cancer treatment. These include: (a) low bioavailability, (b) no conclusive

Table 1. Epidemiological findings on intake of dietary flavones and risk of different cancers.

Flavonoids	Cohort	Dose	Results	Classification	Reference
Fisetin	Colorectal cancer patients	100 mg/day	Reduced plasma levels of IL-8 and hs-CRP and inhibition the value of MMP-7 levels.	Probable relation (medium/ high evidence)	(Farsad-Naeimi et al. 2018)
Xanthohumol	Healthy human	12 mg /d	Reduction of B(a)P induced DNA damage after consumption of the beverage;		(Pichler et al. 2017)
Quercetin	Polycystic ovary syndrome patients	1 g /d	Improve adiponectin-mediated insulin resistance and hormone levels		(Rezvan et al. 2017)
	Obese women with polycystic ovary syndrome	1000 mg/d	Decreased resistin plasma levels and gene expression, and testosterone and LH concentration		(Khorshidi et al. 2018)
Silymarin	Hand-foot syndrome patients	silymarin gel 1%	Reduce the severity of capecitabine-induced hand-foot syndrome and delay its occurrence in patients with gastrointestinal cancer.	Possible relation (low evidence)	(Elyasi et al. 2016)
	Head and neck cancer patients	420 mg/d	Delay the development and progress of mucositis		(Elyasi et al. 2017)
Red clover extract	Women with postmenopausal osteopenic	Red clover extract (60 mg isoflavone aglycones)/d	Reduce bone mineral density loss, improve bone turnover, and promote equol production		(Lambert et al. 2017)
Genistein	Patients before prostatectomy	30 mg/d	Reduce MYC activity and increase PTEN activity		(Bilir et al. 2017)
Soy isoflavones	Women with polycystic ovary syndrome	50 mg/d	Improved markers of insulin resistance, hormonal status, triglycerides, and biomarkers of oxidative stress.		(Jamilian and Asemi 2016)
Silybin-phosphatidylcholine	breast cancer patients	2.8 g/d	Deliver high blood concentrations and selectively accumulates in breast tumor tissue		(Lazzeroni et al. 2016)
AXP107-11	patients with inoperable pancreatic carcinoma.	400–1600 mg/d	Improved physiochemical properties and oral bioavailability increased the effect and reduce chemoresistance		(Lohr et al. 2016)
Green tea extract (GTE)	Healthy postmenopausal women	4 Green tea extract capsules	No significant effect on mammography density measures in all women	Suggestive no association	(Samavat et al. 2017)
Polyphenon E	Patients prior to bladder cancer surgery	Polyphenon E capsule	No obvious strong difference in EGCG tissue levels between Polyphenon E dosage groups combined versus placebo.		(Gee et al. 2017)
Dietary flavones	male smokers aged 50–69 years	Dietary intake	Dietary flavones may not play a large role in the etiology of renal cell carcinoma in male smokers		(Bertoia et al. 2010)
Green tea extract	Healthy women	Green tea extract capsule	5.1% women in GTE developed moderate or more severe abnormalities in any liver function measure	Suggested side effects	(Yu ZM et al. 2017)

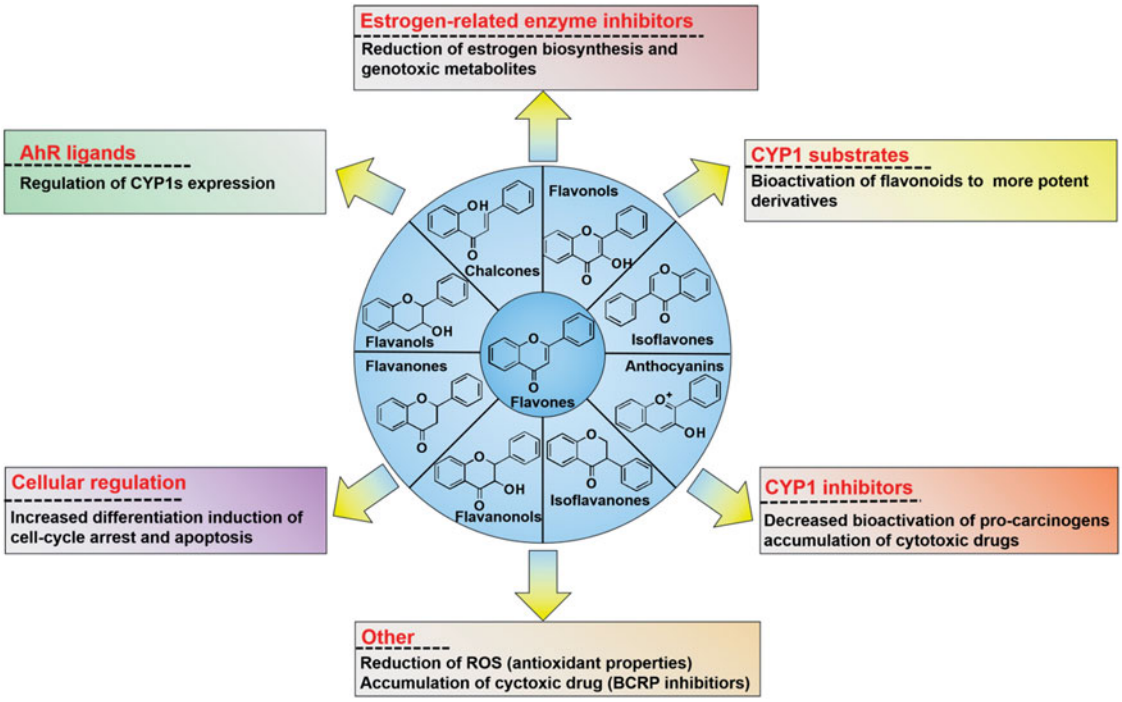

Figure 4. Several major subclasses of flavonoids and antitumor mechanisms of flavonoids. Complicated mechanisms implicated in the anticancer effect of flavonoids generally include modulation of the metabolism and disposition of foreign compounds.

evidence from animal or human studies, (c) no effect on spontaneous neoplasia formation (Bae et al. 2017), (d) poor water solubility and oral bioavailability. These factors have limited the use of dietary flavonoids in the pharmaceutical field. The half-life of flavonoids in the human body is relatively short and dietary exposure to these compounds should be regular so that plasma concentrations are maintained at levels sufficient to express certain biological activities (Zabela et al. 2016). In addition, flavonoids undergo extensive metabolic biotransformation in the intestine and liver, which mean that different conjugates circulate in the body with probably substantially altered biological activities and only traces of the parent flavonoids can enter the bloodstream (Bo et al. 2016). In addition, considering that flavonoids are mainly present in food in the form of glycosides (Popova and Hincha 2016), the absorption of flavonoids from the diet was believed negligible. However, recent studies have demonstrated that the bioavailability of specific flavonoids is much higher than previously thought. Several human studies have investigated the absorption and bioavailability of flavonoids. In a clinical study of healthy people, Martínez et al. found that processing tomatoes into sauces improve the bioavailability of flavanones, flavanols, and some hydroxycinnamic acids, as reflected by the increase in the area under the plasma concentration versus time curve (Martinez-Huelamo et al. 2016). It has likewise been observed that their plasma half-life was increased, especially after ingesting refined olive oil, indicating that the processing experienced by raw tomatoes improves their absorption. Analogously, Diosmin is a flavonoid that is primarily used as adjuvant treatment for circulatory disorders. μSminPlus is a micronized diosmin flavonoid complex standardized in diosmin. Russo et al. compared this with an unformulated micronized diosmin in 16 healthy volunteers. Their data indicate that μSminPlus was rapidly and well absorbed into systemic circulation (Russo et al. 2018).

At the same time, metabolic conversion must be considered when estimating the bioavailability and efficacy of flavonoids for pharmacological use. The combination of xenobiotics attenuates their reactivity, however, some conjugated metabolites of flavonoids possess biological activity and active aglycone may be generated by the site-specific activation of hydrolytic enzymes (Guillermo Gormaz et al. 2015). A number of molecular targets have been proposed to explain the chemopreventive effects of flavonoids aglycones. For example, quercetin aglycone has been demonstrated to interact with some receptors, particularly an AhR, which is involved in the development of cancers induced by certain chemicals (Kawabata et al. 2015; Andres et al. 2018).

Structurally different flavonoids have different bioavailabilities, so that the most abundant compounds in food may not be compounds that enter circulation and reach target tissues. For instance, bioavailabilities of tea flavonoids (0.2–0.9%) are significantly lower than those of quercetin (20%) or isoflavones (Mohammadi-Bardbori et al. 2012; Annunziata et al. 2018; Oyagbemi et al. 2018). In addition, the bioavailability of flavonoids is also affected by the food matrix, background diet, frequency of ingestion and certain food sources suggesting that the preventive action of specific flavonoids from diverse dietary sources may be different. In summary, the chemical structure, absorption, metabolism, bioavailability and biological properties of different flavonoids are different. Therefore, it may be more informative and relevant to evaluate the effect by intake of individual flavonoid rather than total flavonoids or flavonoid subclasses (Woo et al. 2014; Xu et al. 2016).

In order to enhance the solubility and bioavailability of flavonoids inside a human body, various scientific approaches have been taken into consideration, including the application of novel drug delivery systems such as nanoparticles and liposomes (Kulbacka et al. 2016; Zhang, Wang, et al. 2018; Oskouie et al. 2019). These and additional approaches may enable us to understand the full potential of flavonoids in cancer prevention and therapy. Calvo et al. improved oral bioavailability of resveratrol from vineatrol by micelle solubilization. The study found that the oral bioavailability of trans-resveratrol from the grapevine-shoot extract Vineatrol30 was significantly increased using a liquid micellar formulation, without any treatment-related side effects, making it a suitable system for improved trans-resveratrol supplementation (Calvo-Castro, Schiborr, et al. 2018). However, several key points must be considered when considering the potential therapeutic use of the molecule: (a) pharmacological versus nutraceutical doses applied, (b) specificity of its mechanism of action compared to other phytochemicals, and (c) identify "direct" cellular targets. We consider that these methods can help us understand the full potential of dietary flavonoids in cancer prevention and treatment.

5. Conclusion

The occurrence and development of tumors are related to various factors such as genetic factors, external environment, dietary habits, etc. In order to achieve personalized treatment of tumors, it is necessary to fully understand the mechanism of tumors in cell and molecular biology and to use targeted compounds for targeted therapy. Multiple studies have shown that AhR is a potential novel drug target for tumor treatment. The original discovery of this ancient AhR chemical sensing circuit has barely attracted interest outside the circle of environmental toxicologists. However, it is now clear that AhR plays a major role in the development and prevention of cancer. AhR has dual regulatory effects on tumor development, which means that AhR can both promote and inhibit tumor. These compounds, as AhR agonist or antagonist, can't all play an effective tumor inhibition role. Therefore, in different pathological stages of different tumors, an in-depth study of the molecular mechanism of AhR will be a new challenge.

Many antineoplastic as exogenous ligands with high affinity to AhR, participate in the classical AhR pathway for cancer treatment. They can also function through the interaction of AhR-ER signaling pathways, and reduce drug toxicity and side effects through *CYP1* family metabolic enzymes regulated by AhR (Hyzd'alova et al. 2018). Natural products are always the largest asset in the research of new anti-cancer agents. In order to design an efficacious cancer treatment strategy, it is necessary to understand the interactions of natural molecules with their corresponding cellular targets. And some studies have shown that in addition to flavonoids, other phytochemicals, such as curcumin and resveratrol, exhibit anti-inflammatory, cytoprotective, and DNA-protective effects (Banerjee et al. 2016; Sinha et al. 2016). The low toxicity of these naturally occurring compounds, combined with their various effects on the immune system through the interaction with AhR, makes them intriguing candidates for researchers to investigate.

The epidemiologic data concerning the health benefits of flavonoids in the development of cancer are not convincing. Whereas the case-control studies may suggest some positive benefit, the lack of an inverse association observed in the large cohort studies diminishes confidence in interpretation. Given that clear associations have been observed between fruit and vegetable intake and numerous types of cancer, and that fruit and vegetable intake is likely strongly correlated with flavonoid intake, the results of these epidemiologic studies are somewhat surprising. Whereas the lack of an association may be real, other explanations could include a lack of an adequate measure to assess flavonoid intake (most food frequency questionnaires employed in epidemiologic studies have not been designed to assess phytochemical intake specifically) and the multitude of factors affecting flavonoid content in foods and bioavailability. At the same time, when flavonoid supplements are used to prevent cancer, potential side effects should be considered to determine the safe level of flavonoid intake.

Many compounds (such as Phrotress, AF, etc.) have been targeted to AhR for the treatment of breast cancer, but the effects of the same compound are different for different cancer cells. In order to achieve multiple tumor therapies with AhR as a drug target, it is necessary to further study the mechanism of AhR in tumors. On the basis of previous studies, researchers need to further optimize the drug structure and explore new targeted drugs so that different types of AhR ligands can be utilized for specific treatment.

Acknowledgments

The authors are grateful for the financial support provided by the National Natural Science Foundation of China (Nos. 81872985, 81673578). The authors also gratefully acknowledge Dr Roger O. McClellan and the anonymous reviewers for the valuable feedback received, which helped the authors to improve the quality of the final manuscript.

Declaration of interest

The current employment affiliation of the authors is as shown on the cover page. This work was funded by the National Natural Science Foundation of China. All authors participated in preparation of the paper as part of their normal employment and did not receive any special compensation from any source for preparation of the paper. Yang conducted literature collation and edited the manuscript; Feng and Chen drafted parts of the manuscript and provided valuable input and suggestions; Vazirib and Zhao critically revised the paper and made amendments and corrections to the manuscript. The authors have sole responsibility for the writing and content of the paper. The authors declare that they have no potential conflict of interest. None of the authors during the past 5 years have participated in any legal or regulatory proceedings related to the contents of this review.

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