REVIEWS

Flavonoids and Resveratrol as Regulators of Ah-Receptor Activity: Protection from Dioxin Toxicity

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In 2002 FAO and WHO published a joint appeal to state and public organizations and scientific community to take every effort to control the contents of dioxin and related biphenyls in the environment and food products. The toxic effects of dioxin are realized via its interaction with the Ah-receptor. Here we reviewed modern notions about the structure and functions of Ah-receptor. Particular attention was given to antagonists and agonists of the Ah-receptor, including various flavonoids and resveratrol.

Key Words: *dioxin; Ah-receptor; antagonists; agonists*

The United Nations Food and Agricultural Organization (FAO) and the World Health Organization (WHO) made a joint appeal to institute emergency measures to control the contents of dioxin and related polychlorinated biphenyls contaminating food products [36]. In European countries fish and sea products, meat and meat products, and milk and milk products contain 2-63, 6-32, and 16-39% dietary dioxins entering the human organism, respectively. FAO and WHO notify people and government about serious hazard of environmental contamination with considerable amounts of dioxin. Dioxin is a highly toxic polychlorinated cyclic (aryl) carbohydrate entering food chains in animals and humans, accumulating in the organism, and characterized by long half-life in the body (4-12 years) [12]. It should be emphasized that dioxin can enter the organism of newborns. Previous observations showed that dioxin is present in breast milk of women living in industrialized and Third World countries (Table 1) [62].

Chemical carcinogenesis and immunodeficiency often result from the influence of dioxin [12]. Dioxin *per se* is nontoxic. It is not metabolized to active electrophilic metabolites, does not form covalent bonds with DNA, RNA, and proteins, and has no mutagenic activity in the Ames test [63]. All biological effects of dioxin are mediated by its interaction with Ah-receptor (aryl-hydrocarbon receptor, AhR). Aryl carbohydrates act as ligand and interact with AhR, induce its translocation into the cell nucleus, where it activates expression of certain genes.

Competitive binding of AhR to bioactive compounds present in food products and possessing high affinity for AhR (*e.g.*, flavonoids) protects the organism and genome from aryl carbohydrate attack and decreases the risk of various diseases, including tumor growth. Leading scientists believe that these natural substances and compounds with similar physiological properties are essential for humans and should be supplied with food, medicines, and food additives [4,33, 47]. The search for new bioactive substances capable of protecting human organism and genome from ag-

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TABLE 1. Contents of TCDD and Dioxin-Like Compounds in Pooled Samples of Breast Milk from Women Living in Various Countries [62]

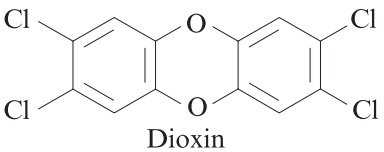
Country	Total toxic equivalent* (ng/kg milk lipids)
Vietnam (Da Nang)	34
Japan	27
Germany	27
Canada	26
USA	20
Vietnam (Ho Chi Minh)	19
South Africa, white	13
Pakistan	13
Russia	12
South Africa, black	9
Vietnam (Hanoi)	9
Thailand	3
Cambodia	3

Note. *Index of dioxin concentration multiplied by the toxic factor (ratio between toxicities of dioxin analogues and TCDD taken as 1 unit).

gressive xenobiotics (environmental contaminants) is an urgent problem of applied medical researches.

This review is a response to the appeal of FAO and WHO, which calls attention of the scientific community to this important problem and directs the way to its solution. We studied the interaction of flavonoids and other ligands with AhR.

Ah-receptor and dioxin. AhR is a cytosolic protein binding 2,3,7,8-tetrachlorodibenzo-*n*-dioxin (TCDD), other halogenated aromatic compounds, and polycyclic aromatic carbohydrates (PAC, *e.g.*, 3-methylcholanthrene and benzo(a)pyrene). Human *AhR* gene was mapped on a short arm of chromosome 7 (7p15) [46]. The receptor is present almost in all cells and tissue of the organism.



Dioxin

AhR is responsible for positive regulation (activation) of transcription in mammals (Fig. 1). It belongs to the class of transcription factors with helix—loop—helix domains (bHLP) that enter the superclass of factors with basic domains [3].

According to the classification of L. I. Patrushev [3], the bHLH class includes 9 families. Factors with the PAS domain (PER/ARNT/SIM) constitute one of these families. The PAS domain contains homologues of protein products of the Drosophila gene responsible for the maintenance of the circadian rhythm (PER, *period*) and development of the fetal nervous system (SIM, *single-minded*). This domain also contains a region for binding to ARNT (Ah-receptor nuclear translocator carrying AhR into the nucleus) [31]. The PAS family includes not only AhR, but also ARNT (HIFα, hypoxia-inducing factor α), HIFβ, AhRR, (AhR repressor) [29,37], BMAL2 (brain-muscle Arnt-like protein 2) [35] or MOP9 (member of PAS) [32], etc. [27].

By some physicochemical properties (*e.g.* Stocks radius, sedimentation coefficient, molecular weight, and friction ratio) AhR is similar to steroid hormone receptor [38]. Similarly to the receptor for steroid hormones, AhR interacts with polyanions (*e.g.*, DNA) and contains sulfhydryl groups necessary for ligand binding [17]. Spatial structure and endogenous ligands of AhR are poorly known. Only partial N-terminal sequence of mouse AhR was determined: Ala-Asp-Ser-Arg-Lys-Arg-Arg-Lys-Pro-Val-Gln-Lys-Thr-Val-Lys-Pro-Ile-Pro-Ala-Glu-Gly-Ile-Lys-Ser-Asp-Rpo-Ser-Lys [10].

Previous studies showed that affinity of TCDD for AhR in humans is similar to or lower than that in other organisms [18]. K_d for the TCDD-AhR complex in human hepatocytes varies from 0.4 to 15.0 nM. These indexes in C57BL/6J and DBA/2J mice are 1 and 16 nM, respectively.

In the absence of ligands, AhR is diffusely distributed in the cytosol and functionally inactive due to weak associations with heat shock protein HSP90, immunophilin chaperone (homologue of immunophilin binding immunodepressant FK506) XAP2/AIP/ARA9 (hepatitis B virus X-associated protein-2/aryl hydrocarbon receptor-interacting protein/aryl hydrocarbon receptor-associated protein-9), and cochaperone p23 [11]. M. S. Denison and S. R. Nagy summarized the data on AhR behavior after its interaction with agonists (Fig. 2). Binding to agonist (*e.g.*, TCDD) weakens association between HSP90 and immunophilin, the ligand-receptor complex is translocated into the nucleus, HSP90 and immunophilin are released, and free AhR forms a dimer with ARNT. This nuclear complex probably exists in a phosphorylated state [48] and interacts with canonical DNA sequence of dioxin or xenobiotic response elements (DREs/XREs) in the promoter of the *CYP1A1* gene and other Ah-sensitive

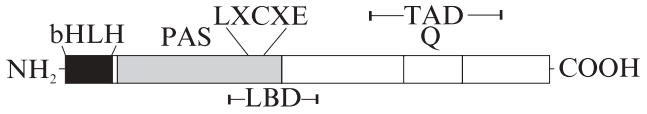


Fig. 1. Structure of functional domains in human Ah-receptor (AhR). DNA-binding and bHLH-dimerizing protein in the nuclear translocator of the aryl carbohydrate receptor (black); PAS enriched with glutathione, ligand binding (LBD) and transactivating domain (TAD); and LXCXE (residues of amino acids 331-335 in human AhR) necessary for binding of retinoblastoma inhibitor protein (pRb) [30].

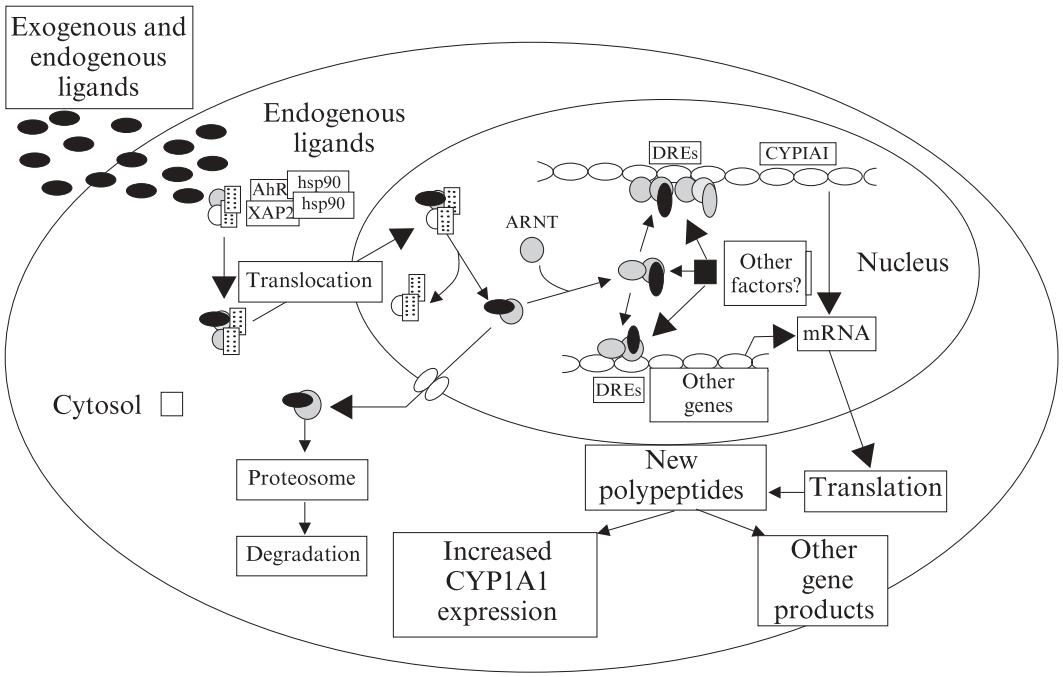


Fig. 2. Possible molecular mechanism of gene expression related to the interaction of AhR and ligand [16]. Hsp90, heat shock protein 90; XAP2, X-associated protein 2; ARNT, Ah-receptor nuclear translocator; and DREs, dioxin-response elements.

genes. The involvement of coactivators for AhR and ARNT (RIP140 and CBP/p300, respectively) [48] and common transcription factors initiates transcription (transactivation). These events were visualized and confirmed by confocal and high-resolution inversion microscopy of living mouse Hepa-1 hepatoma cells and its mutant variants deficient in AhR or ARNT [20]. This study demonstrated that unbound AhR is diffusely distributed in the cytoplasm. After introduction of the ligand (TCDD) AhR is rapidly translocated into the nucleus and accumulated in light focuses (transcription sites). The appearance of these focuses depends on the interaction between AhR and ARNT.

Ligand-activated AhR regulates transcription of various target genes, including genes for enzymes of xenobiotic biotransformation: cytochromes P450 (CYP) CYP1A1, CYP1A2, and CYP1B1, UDP-glucuronyl transferase, NAD(P)H menadione oxidoreductase, class 3 cytosolic aldehyde dehydrogenase, and glutathione-S-transferase Ya [52,56, 68]. There are data that AhR is involved in biosynthesis of phosphatidylcholine, metabolism of arachidonic acid, deacylation of lipids, and expression of phospholipase A2, γ-glutamyltranspeptidase, and protein kinase C [50-53]. These data illustrate that AhR induces a variety of effects (pleiotropism).

Extensive biochemical and genetic studies showed that AhR plays an important role in embryogenesis, functional activity of the liver and immune system, proliferation and differentiation of cells, and organogenesis [8,21,22,39,40,64,69]. Physiological role of AhR was evaluated in experiments on AhR gene knockout mice [41]. Adult homozygotes for zero AhR allele were characterized by decreased size of hepatocytes, massive portocaval bypass, and persistent embryonic signs (presence of *ductus venosus*, undeveloped sinusoidal architectonics of the liver, hyaline structure of eye arteries, and dysfunction of the renal vascular network). Experiments of P. Anderson *et al*. [7] were performed on transgenic mice carrying mutant AhR in the gene region encoding the PAS domain. This constitutive form of AhR retained functional properties, and its activation did not require the interaction with ligands. Stomach neoplasms (mainly in the pyloric portion) developed in these mice. Study of mRNA content in gastrointestinal organs revealed accumulation of constitutive mRNA for AhR and CYP1A1 exactly in the pylorus.

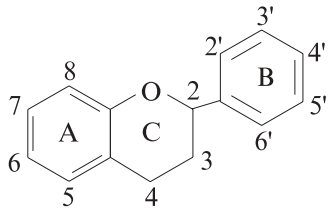
Experiments of Q. Ma and K. T. Baldwin [45] elucidated the mechanisms underlying toxicity of TCDD [45]. These investigators showed that TCDD not only acts as the ligand of AhR, but also damages the structure of this receptor. It causes degradation of AhR via the ubiquitin-dependent proteolysis system (Fig. 2). TCDD violated functional activity of the receptor. Probably, these changes lead to physiological dysfunction of AhR. Recent studies of Y. Tsuchiya *et al*. [67] showed that TCDD and other PAC induce intensive expression of AhRR in normal and cancer cells.

Toxicity of TCDD (hepatotoxicity, porphyria, immunotoxicity, embryotoxicity, reproductive toxicity, endocrine disturbances, cachexia syndrome, chloracne,

and promotion of tumor growth and carcinogenesis [60]) is related to superinduction of cytochromes P450 of the CYP1 family responsible for conversion of procarcinogens and promutagens (*e.g.*, halogenated biphenyls, PAC, and nitrose compounds) into carcinogens and mutagens, enhancement of transactivation and expression of genes involved in teratogenesis, tumor progression, immunotoxicity, and epithelial hyperplasia [15,23,42,57], structural abnormalities in AhR, and activation of AhRR.

Much attention of pharmacologists and toxicologists is now given to the search for potent and nontoxic AhR regulators competing with TCDD and its structural analogues for binding to the receptor and not affecting its physiological activity. These compounds will allow modulating the biological effects of TCDD and structurally similar compounds. Antagonists and agonists of AhR can be of high efficiency in the therapy of various diseases. The most probable candidates are plant flavonoids and resveratrol. These substances constantly enter the human organism and hold much promise for the protection from carcinogenesis.

Flavonoids. Flavonoids (FL) are plant phenol compounds. They consist of two benzyl rings (A and B) connected via cyclic pyran or pyrone (ring C).



Flavonoids nucleus

There are more than 4000 FL. They have been in existence on the Earth for more than 1 billion years [66]. FL interact with other organisms over various geologic eras. They perform a variety of functions in plants. For example, these compounds are responsible for pigmentation of plants and protect fungi from insects [1]. Depending on the nature of substituents, FL are divided into flavonols, anthocyanidins, flavones, flavanones, and chalcones (Table 2). Chemical classification of FL was presented previously [2].

Biological, preventive, and therapeutic properties of FL during various diseases were reviewed elsewhere [47]. However, the role of FL in the regulation of AhR activity was poorly understood.

Considering the regulation of AhR activity by FL, particular emphasis should be given to the concen-

TABLE 2. Main dietary sources of flavonoids*

Class of flavonoids, specimen	Dietary source
Flavan-3-ols	Apple, apricot, nectarine, peach, pear, black grape, strawberry, green beans, red wine, tea
catechins	Apple, black grape, cacao chocolate, red wine, black and green tea
proanthocyanidins	Apple, blueberry, cranberry juice, black grape, strawberry, almond, peanut, barley, corn, cacao chocolate, red and white wine, tea, beer
Anthocyanidins	Apple, blackberry, black currant, blueberry, cherry, merry, bird cherry, cranberry, elder, nectarine, peach, raspberry, black grape, red pear, strawberry, carrot, Scotch kale, red onion, red beans, red wine, cacao
Flavanones	Grapefruit, lemon, orange, tomato, honey
hesperidin	Orange and other citrus
naringenin	Grapefruit
Flavones	Grapefruit, lemon, orange, carrot, celery, parsley, red and green sweet pepper
luteolin	Red sweet pepper
apigenin	Celery
Flavonols	Orange, broccoli, Brussels cabbage, cauliflower, onion, green turnip, red wine, tea
quercetin	Apple, apricot, whortleberry, blackberry, black currant, cherry, elder, grapefruit, lemon, peach, plum, raspberry, cowberry, red and white currant, black grape, strawberry, broccoli, cabbage, chive, endive, leafy cabbage, salad, onion, pear, pepper, Brussels cabbage, leguminous bean, tomato, hop, red wine, black and green tea
kaempferol	Apple, apricot, whortleberry, blackberry, black, red, and white currant, cherry, peach, pear, plum, raspberry, cowberry, broccoli, Brussels cabbage, chive, endive, green beans, horseradish, kale, salad, leek
myricetin	Whortleberry, black, red, and white currant, grape, cowberry, red wine
rutin	Black currant

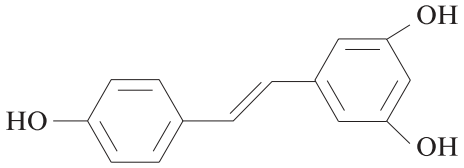
tration dependence for their binding and influence on AhR. In low concentrations various FL act as AhR antagonists [9,26,44,70]. They bind to the receptor and compete with TCDD, but do not transform AhR into active transcription factor. By contrast, FL in high concentrations play a role of AhR agonists and potentiate the effects of TCDD, including transactivation of *CYP1A1* genes [9,26,44,70]. Study of the effects induced by 2 major polyphenol components of food products (quercetin and kempferol) on expression of the *CYP1A1* gene and functions of AhR in human breast cancer MCF-7 cells showed that kempferol inhibits TCDD- and AhR-dependent induction of *CYP1A1* by competing with AhR [13]. FL galangin is found in various plant products. This compound inhibits 9,10-dimethyl-1,2-benzanthracene metabolism, cytochrome P4501A1 activity, and *CYP1A1* expression in human breast cancer MCF-7 cells. These investigators hypothesized that the effect of galangin is related to its interaction with AhR. Therefore, this FL can be used as a potent antidote to TCDD-induced toxicity and carcinogenicity [14]. FL act as agonists of AhR only in high concentration surpassing the physiological dose and not comparable with that of TCDD. Y. Amakura *et al*. [6] studied 95 plant compounds and their metabolites. They found that flavanones (naringenin and hesperidin) and flavones (baicalein, baicalin, and chrysene) act as agonists. Published data show that quercetin possesses agonistic activity, which depends on FL concentration and time [12]. The discrepancy between these data can be due to different schemes and methods for recording of the results. Some doubts are cast upon the concept of R. F. Casper *et al*. [12]. These investigators hypothesized that FL cannot be considered as potential antidioxin compounds since in high concentrations they cause side effects. Y.-F. Lu *et al*. [44] studied the effects of synthetic 3',4'-substituted flavones on binding and transactivation of AhR. Four situations were observed in the absence of TCDD: weak binding to the receptor and intensive transformation of AhR, high affinity for the receptor and weak transformation of AhR, weak binding to the receptor and weak transformation of AhR, and high affinity for the receptor and intensive transformation of AhR. Study of the effects produced by flavones in various concentrations on TCDD-induced transformation of the receptor revealed agonistic and antagonistic activity in relation to AhR. These authors concluded that the ligand causes complex conformational changes in AhR. Probably, AhR exists more than in one form. AhR is characterized by more pronounced polymorphism compared to other nuclear receptors [63]. It cannot be excluded that there are many forms of AhR with wide substrate specificity (similarly to cytochrome P450-dependent monooxygenase). J. Schmidt and C. Bradfield reported that adaptive and toxic reactions realized via AhR are mediated by similar pathways [63].

For evaluation of the regulatory effect of FL on AhR 7-ethoxyresorufin O-deethylase concentration in test cells can be measured during primary screening [59]. Systems for screening of FL with reporter genes were extensively used in recent years [5,6].

The question arises: whether anticancer activity of FL (*e.g.*, cytostatic effect on cultured tumor cells) is related to their interaction with AhR. Five cytostatic FL (flavone, α-naphthoflavone, apigenin, 3'-methoxy-4'-aminoflavone, and 2'-amino-3'-methoxyflavone) were tested as AhR ligands in mouse hepatoma 5L cells and AhR-deficient BP8 cells obtained from 5L cells. The cytostatic effect of these FL was not associated with AhR [58].

The AhR ligand competing with TCDD for binding to the receptor and not affecting relationships between the transformed receptor and promoters of important genes (*e.g.*, genes for enzymes of phase II xenobiotic metabolism involved in elimination of toxic, carcinogenic, and mutagenic metabolites from the organism) will be an ideal antidioxin compound. Resveratrol holds much promise in this respect.

Resveratrol. Resveratrol (3,5,4'-trihydroxy-stilbene) is structurally similar to synthetic estrogen diethylstilbestrol and belongs to phytoalexins.



Reservatrol

Resveratrol was first found in *Polygonum cuspidatum* roots (genus *Polygonum*, buckwheat order) in 1963. The preparation from these plants (Koiokon) is used in traditional Chinese and Japanese medicine [54]. Resveratrol was found in grapes in 1976 [43]. This substance was shown to be a component of wine in 1992 [65]. Resveratrol content in red wine markedly surpasses that in white wine [24].

The so-called "French paradox" gave impetus to extensive research of resveratrol. Long-term epidemiological observations revealed a negative correlation between consumption of red wine and high-fat foods and incidence of cardiovascular diseases [28, 34]. Resveratrol possesses a variety of therapeutic properties [28]. It has antibacterial, antifungal, antioxidant, vasorelaxing, antiallergic, estrogenic, antiestrogenic, and antitumor activities. Resveratrol inhibits the synthesis of eicosanoids and monoamine oxidase in rat brain, decreases activities of H^+,K^+-ATPase in cells of the gastric mucosa, inactivates protein tyrosine kinase and protein kinase C, suppresses platelet

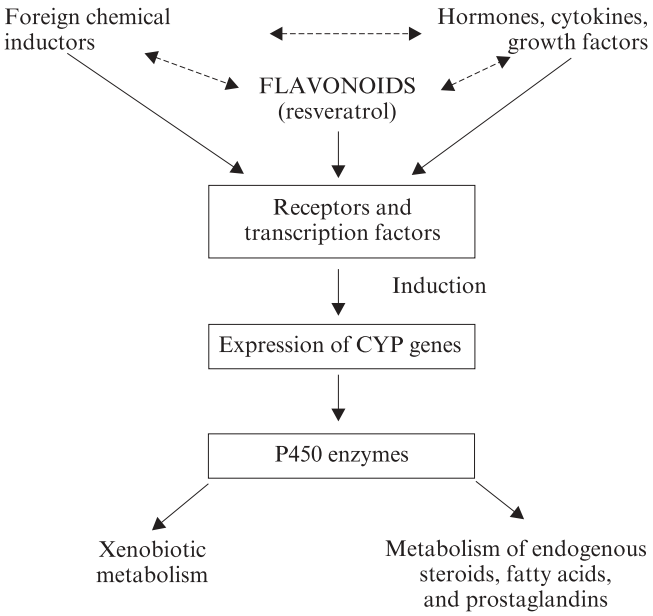


Fig. 3. Induction of CYP genes: cross-interaction between exogenous and endogenous regulators of gene expression [68]. Shaded arrow: possible reciprocal cross-reactivity of inductors.

aggregation, chelates copper, has antiinflammatory properties, and affects metabolism of lipids and lipoproteins. The mechanisms underlying therapeutic activity of resveratrol were reviewed previously [28,34].

R. F. Casper *et al*. [12] studied in details the mechanisms of interaction between resveratrol and AhR. They investigated human breast cancer T-47D cells that were stably transfixed with a construction carrying the DRE element linked to the thymidine kinase promoter and chloramphenicol acetyltransferase reporter gene. Resveratrol in micromolar concentrations completely blocked TCDD-induced transactivation and, therefore, acted antagonistically to AhR in the presence of dioxin. Study of competitive binding to AhR was performed with the cytosol of rabbit hepatocytes (source of AhR). Resveratrol efficiently replaced labeled TCDD from the receptor binding site. To understand the mechanisms underlying therapeutic activity of resveratrol, its action on other AhR-dependent genes in T-47D cells was studied in the presence of TCDD. Under these conditions resveratrol did not suppress the gene for NAD(P)H-quinone oxidoreductase involved in phase I xenobiotic metabolism, but abolished TCDD-induced transactivation of the LTR protein promoter for human immunodeficiency virus (HIV-1) and inhibited superexpression of the gene for interleukin-1 (inflammatory mediator).

Conclusion

In the present work we analyzed the effects of only one cytosolic AhR that regulates expression of at least 3 genes belonging to the CYP1 family of cytochromes P450 (*CYP1A1*, *CYP1A2*, and *CYP1B1*) and 1 gene of the CYP2 family (*CYP2S1*) [60]. There are a lot of receptors that regulate expression of at least 17 families of cytochrome P450 genes [68]. Nuclear receptors are involved in the expression of cytochrome P450 genes interacting with endogenous substrates (Fig. 3). Published data show that tumor necrosis factor-α and transforming growth factor-β inhibit induction of enzymes of the CYP1A subfamily by PAC [25,49]. This is an example of reciprocal cross-reactivity of inductors. We believe that this scheme should be amplified by dietary FL and resveratrol entering human organism. These compounds are involved in competitive inhibition of CYP gene expression and act as gene protectors. They protect a small part of the genome from reactive toxic metabolites generated during metabolism of foreign compounds with cytochromes P450 of families 1-4. It should be emphasized that exogenous and endogenous regulators of gene expression can cross-react with the corresponding receptors.

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