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The Inhibitory Effect of Natural Stilbenes and Their Analogues on Catalytic Activity of Cytochromes P450 Family 1 in Comparison with Other Phenols – Structure and Activity Relationship

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1. Introduction

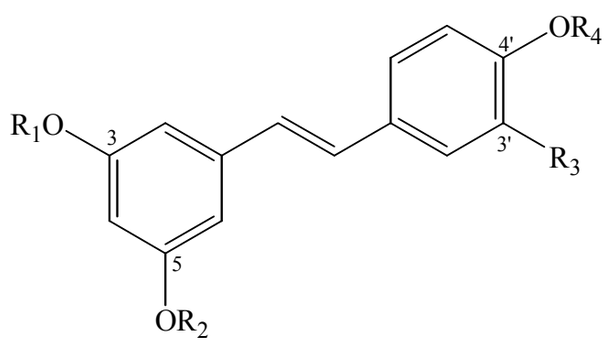
In the last decade, increasing interest in the role of nutrition in disease prevention has been observed. The World Health Organization (WHO) reported that one-third of all cancer deaths could be prevented, and that diet plays a key role in prevention (Bode & Dong, 2009). The term *chemoprevention* introduced and developed by Sporn (2005) and Wattenberg (1985) refers in general to multi-targeted pharmacological and nutritional intervention with the use of naturally occurring or chemically synthesized compounds. For this purpose, dietary phytochemicals believed to be safe for human use seem to be very promising. The importance of natural chemopreventive agents relies on their non-toxicity when given in small amounts for longer periods of time. Moreover, using a combination of phytochemicals provides synergistic or additive preventive effects.

Cancer cell growth arises through a complex multistep process by which cancer cells acquire characteristics of unlimited proliferation potential, lack of response to growth signals, and resistance to cell death. Thus, preventive/therapeutic action of phytochemicals may be directed towards numerous molecular targets that are proteins involved in procarcinogen metabolism, cell transformation and proliferation, and signaling pathways leading to apoptosis of damaged or transformed cells (William et al., 2009). Targeting enzymes of the P450 superfamily may provide one of the strategies for enhancing the efficacy of chemopreventive and therapeutic agents (Swanson et al., 2010).

Mechanistic studies of natural compounds are of great value regarding their characteristics of bioactivity, efficacy, selectivity and potential adverse side effects. Targeted inhibition of metabolic activation of carcinogens and induction of detoxifying enzymes has been considered a fundamental strategy for blocking the early stage of carcinogenesis. For example, inhibition of CYP1 enzymes was one test in the battery of assays employed in

screening of potential cancer chemopreventive agents (Gerhauser et al., 2003). Variable dietary exposure to phytochemicals may contribute to some of the inter-individual variation in the pharmacokinetics and pharmacological responses that are observed for drugs such as phenacetin, caffeine, and theophylline, which are substrates for CYP1A2 (Rendic & Di Carlo, 1997). Further research is needed to determine the extent to which the effect of dietary exposure may be modified by genetic polymorphism of xenobiotic metabolizing enzymes.

Phenolics are a diverse group of aromatic compounds broadly distributed in plants. Among this group, stilbenoids are compounds displaying multiple activities of interest with regard to cancer prevention and therapy, and their anticancer properties have been proven in various animal models (Szekeres et al., 2010). In this review, we summarize the results of studies on inhibitory activity of *trans*-resveratrol (3,4′,5-trimethoxy-*trans*-stilbene), the best recognized *trans*-stilbene (Figure 1), and its natural and synthetic analogues toward expression and activity of CYPs responsible for procarcinogen activation. We discuss the role of cytochrome family 1 inhibitors in cancer chemoprevention and chemotherapy. Additionally, we compare their effect with other natural phenols occurring in plant foods in relatively high amount and exerting significant bioactivity. Finally, we analyze the use of computational methods for biomolecular docking in structure and activity relationship studies of CYP1 inhibitors.



		R_1	R_2	R_3	R_4
1.	*trans*-Resveratrol	H	H	H	H
2.	Piceatannol	H	H	OH	H
3.	Rhapontigenin	H	H	OH	CH_3
4.	Desoxyrhapontigenin	H	H	H	CH_3
5.	Pinostilbene	H	CH_3	H	H
6.	Pterostilbene	CH_3	CH_3	H	H

Fig. 1. Structure of *trans*-resveratrol and its natural analogues

2. Potential strategies targeting CYPs for cancer therapy and prevention

One of the strategies of cancer chemoprevention is directed at drug-metabolizing enzymes such as cytochromes P450 (CYPs), a superfamily which metabolizes a wide spectrum of endogenous and exogenous substrates. Cytochrome P450 family 1 comprises three important isoforms: CYP1A1, CYP1A2 and CYP1B1 that catalyze the activation of procarcinogens such as polycyclic aromatic hydrocarbons, and aromatic and heterocyclic

amines. Additionally, CYP1B1 metabolizes 17β-estradiol (E2) to 4-hydroxyestradiol (4-OH-E2), which is further oxidized by peroxidase to estradiol-3,4-quinone to form a quinone-DNA adducts responsible for estrogen-related carcinogenesis (Liehr et al., 1996). This pathway of metabolism is extensively studied with respect to polymorphism of CYP1 enzymes and its association with carcinogenic metabolite formation (Kisselev et al., 2005).

All members of the human CYP1 family are expressed in extrahepatic tissues. However, CYP1A2 is the only constitutive form of liver enzyme, and as such takes part in metabolism of xenobiotics, including numerous drugs (caffeine, theophylline, methadone, verapamil, propranolol, warfarin, tamoxifen). On the other hand, it is worth mentioning that microbial CYPs are considered as drug targets and may be used as biocatalysts in drug biosynthesis (Lamb et al, 2007).

In humans, CYP1B1 is overexpressed in tumor cells, and this has important implications for tumor development and progression (Castro et al., 2008). It was found that CYP1B1 knockout mice were highly resistant to 7,12-dimethylbenz[a]anthracene induced tumor formation (Gonzalez, 2002). Thus, regulators of the expression and catalytic activity of family 1 cytochromes appear to play an important role in cancer chemoprevention by blocking the initial stages of tumorigenesis. With respect to cancer chemotherapy, CYP1A1 and CYP1B1 have the ability to metabolize cytostatics, diminishing their toxic effect on cancer cells (McFadyen & Murray, 2001). Considering this, the inhibition of CYP1B1, an enzyme up-regulated in many cancers, would be a strategy to prevent the loss of cytostatics effectiveness. On the other hand, the development of anticancer prodrugs specifically activated by CYP1B1 to cytotoxic compounds might be a promising novel strategy in cancer chemotherapy (Bruno & Njar, 2007).

3. Mechanism of the expression of CYP1 genes – AHR as a target for effective chemopreventive approach

Members of the CYP1 family are under the transcriptional control of the aryl hydrocarbon receptor (AHR) localized in cytosol that is activated by polyhalogenated aromatic hydrocarbons, among them 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). AHR agonists are well known environmental pollutants. As a result of activation AHR translocates into the nucleus and forms a dimer with ARNT (aryl hydrocarbon nuclear translocator). The AHR/ARNT complex is characterized by a high affinity to specific DNA recognition sites termed DREs (dioxin response elements) or AHREs (aryl hydrocarbon response element) which upregulate a battery of target genes, including those involved in metabolism of chemical carcinogens such as CYP1A1, CYP1A2 and CYP1B1 (Fig. 2). In this way, agonists induce the expression of xenobiotic metabolizing enzymes (XMEs) that activate procarcinogens to genotoxic forms. Thus, the treatment with AHR antagonists by preventing this undesirable effect might be a chemopreventive strategy.

There are phytochemicals that possess the ability to block agonist interaction with the ligand-binding site of the AHR and agonist induction of the AHR-signaling pathways. In that respect, resveratrol is the best recognized stilbene derivative. Moreover, it is one of the best-characterized chemopreventive phytochemicals (Goswami and Das, 2009). It occurs mainly in small fruits like berries and grapes, peanuts and red wine. Its chemopreventive properties found in studies on animals *in vivo* were described for the first time by Jang and

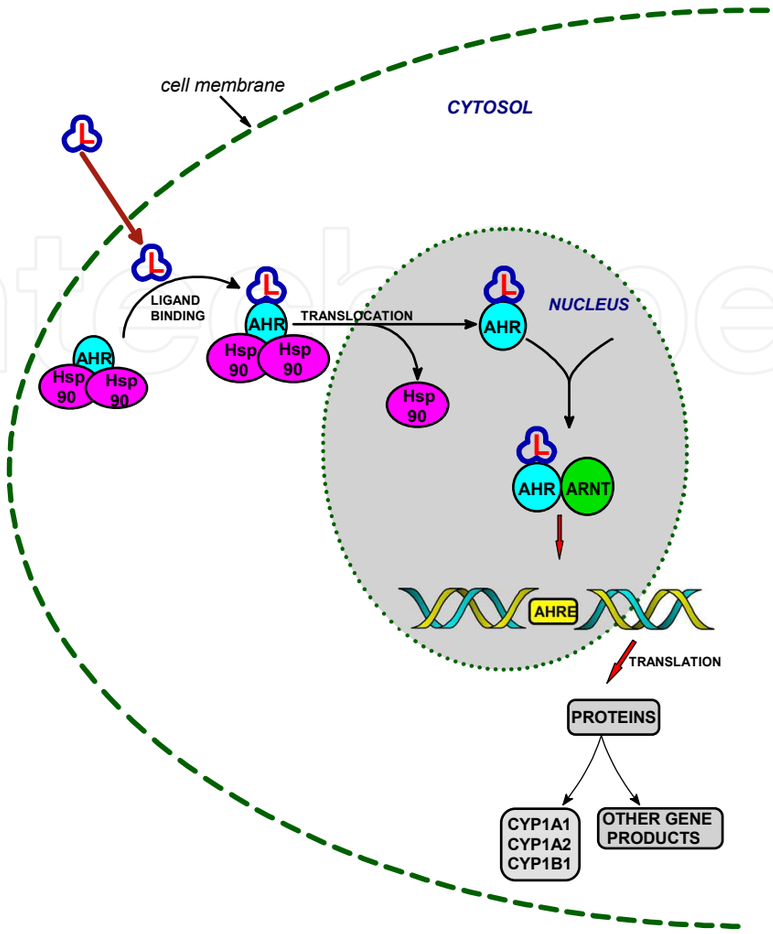


Fig. 2. AHR signaling pathway; L – ligand; Hsp90 – heat shock protein 90; ARNT – aryl hydrocarbon nuclear receptor; AHRE – aryl hydrocarbon response element. AHR/ARNT complexes bind to the DNA recognition sequence AHRE located in regulatory regions of phase I (CYP1A1, CYP1A2, CYP1B1) and phase II drug metabolizing enzymes.

coworkers (Jang et al., 1997). Chen and collaborators have reported that resveratrol strongly inhibited TCDD-induced AHR binding activity in human mammary epithelial (MCF-1-A) cells (Chen et al., 2004). The inhibition of CYP1A1 expression by resveratrol was observed in rat primary hepatocytes (Andrieux et al., 2004). In human HepG2 hepatoma cells, resveratrol inhibited the increase in CYP1A1 mRNA caused by TCDD in a concentration-dependent manner. The induction of transcription of an aryl hydrocarbon-responsive reporter vector containing the CYP1A1 promoter by TCDD was likewise inhibited by resveratrol. Resveratrol also inhibited the constitutive level of CYP1A1 mRNA and reporter vector transcription in human hepatoma HepG2 cells (Ciolino et al., 1998). Resveratrol was also effective in inhibiting CYP1A1 transcription induced by the aryl hydrocarbon dimethylbenz[a]anthracene in human mammary carcinoma MCF-7 cells and B[a]P-treated HepG2 cells (Ciolino et al., 1999). These data demonstrate that resveratrol inhibits aryl hydrocarbon-induced CYP1A activity *in vitro* by directly inhibiting CYP1A1/1A2 enzyme activity, and by inhibiting the signal transduction pathway that up-regulates the expression of carcinogen activating enzymes. The antagonistic action of resveratrol was supported by *in*

vivo experiments on phytochemicals with four different structures, where only resveratrol given topically on mouse epidermis inhibited aryl hydrocarbon hydroxylase (AHH) activity in a dose dependent manner (Table 1) (Szaefer et al., 2004). Moreover, resveratrol has been shown to prevent genotoxicity of B[a]P by inhibiting B[a]P-induced CYP1A1 expression and BPDE-DNA adduct formation in the lungs of mice (Revel et al., 2003).

Treatment	Dose	Activity [pmol/min/mg protein]
Acetone	0.2 ml	65.3 ± 4.6
5,6-Benzoflavone	8 μM	336 ± 17.2
Protocatechuic acid	8 μM 16 μM	75.3 ± 2.1 83.4 ± 6.4
Chlorogenic acid	8 μM 16 μM	71.7 ± 3.2 83.9 ± 2.8
trans-Resveratrol	8 μM 16 μM	18.9 ± 2.6 0.08 ± 0.01

Table 1. Effect of phenolic compounds on mouse epidermal AHH activity

Summarising, resveratrol inhibits AHR-dependent transcription by preventing AHR/ARNT binding to the AHRE. The activity of preventing the conversion of ligand-bound cytosolic AHR into its nuclear DNA-binding form and/or the interaction between the AHR and the transcription initiation complex at the CYP1A1 gene promoter may be an important part of the chemopreventive activity of resveratrol. However, the action of resveratrol is not specific because this natural stilbene as a phytoestrogen is also a potent ER (estrogen receptor) agonist. Recently, experiments on human breast cancer cells revealed that the estrogenic properties of resveratrol and its influence on the ER expression are independent of its ability to inhibit the expression of genes controlled by AHR (MacPherson & Matthews, 2010). New stilbene derivatives of resveratrol that were synthesized appeared to be selective for AHR and devoid of affinity for ER. Among the *trans*-stilbenes synthesized, all displayed a significantly higher affinity than resveratrol for AHR. Substitution of 3- and/or 5-hydroxy groups with chlorine atoms coupled with replacement of 4′-hydroxy with chlorine or a methoxy group yielded selective TCDD antagonists with high affinity for the AHR that was much higher than resveratrol. Interestingly, one of the studied compounds, 3-hydroxy-5-chloro-4′-trifluoromethyl-*trans*-stilbene, was a selective AHR agonist exerting extremely high-affinity to AHR with a K_i of 0.2 nM. None of the compounds studied showed any detectable affinity for the ER that should eliminate estrogen-related risks, such as the increased risk of ER-related cancers (de Medina et al. 2005).

In the Table 2 we summarized the studies on the effects of resveratrol and its derivatives on AHR related expression of CYP1 enzymes. However, the results of *in vivo* experiments on animals are highly dependent on the dose of a studied compound, as well as the duration and manner of its administration. Further, the effect of a studied substance may also be tissue-dependent. The expression of CYP1A1 and CYP1A2-related monooxygenases in hepatic subcellular preparations from resveratrol treated male mice did not differ from the control; while in pulmonary subcellular preparations significantly lower expression of CYP1A1/2 –dependent enzymes was observed (Canistro et al., 2009).

Effect	Compound	Experimental Model	References
AHR translocation ↑ AHRE transactivation ↓	resveratrol	47DRE reporter cell line	Casper et al., 1999
AHR DNA binding ↓, expression and activity of CYP 1A1/1B1 ↓	resveratrol	TCDD-treated MCF-10A cells	Chen et al, 2004
Expression and activity of CYP1A1/1A2 ↓	resveratrol	B[a]P-treated HepG2 cells and DMBA-treated MCF-7 cells	Ciolino et al., 1999
CYP1A1 expression ↓ Induction of transcription of AHR reporter vector containing the CYP1A1 promoter by TCDD ↓ constitutive level of CYP1A1 mRNA and reporter vector transcription ↓	resveratrol	TCDD treated human HepG2 cells	Ciolino et al., 1998
CYP1A1 expression ↓ BPDE-DNA adduct formation ↓	resveratrol	lung tissue from BP-treated mice	Revel et al., 2003
CYP1A1 expression by resveratrol ↓	resveratrol	rat primary hepatocytes	Andrieux et al., 2004
AHR binding ability of resveratrol and its derivatives ↓	resveratrol and 24 other stilbenes	47DRE reporter cell line	de Medina et al., 2005
Expression of human CYP1A1 and CYP1B1 ↓ Recruitment of the AHR complex and RNA polymerase II to the regulatory regions ↓	resveratrol	TCDD-induced human breast cancer cell line MCF-7, and human hepatocellular carcinoma cell line, HepG2	Beedanagari et al., 2009
AHR-dependent transcription of CYP1A1 and CYP1B1 ↓	resveratrol	TCDD-induced human breast cancer cells T-47D	MacPherson and Matthews, 2010
CYP1A1 and CYP1B1 expression ↓ Recruitment of AHR and ARNT to CYP1A1 and CYP1B1 enhancer regions ↓	piceatannol	TCDD-induced human breast cancer cells T-47D	MacPherson and Matthews, 2010

Table 2. AHR as a molecular target for chemopreventive action of resveratrol and its derivatives

4. Inhibitory effect of stilbene derivatives on CYP1A enzymes

4.1 *Trans*-resveratrol

The studies of the inhibitory effect of phytochemicals on cytochrome P450 dependent enzymes are mainly conducted with the use of *in vitro* techniques on cDNA-expressed enzymes. Recombinant biscistronic supersomes express particular CYP activity and cytochrome c reductase activity. It was reported that resveratrol inhibited human recombinant P450 1A1 activity in a competitive manner (Chun et al., 1999), but the IC_{50} value (the concentration that causes 50% inhibition of enzyme activity) of 23 μM was much higher than the IC_{50} value of 1.4 μM obtained for CYP1B1 inhibition (Chang et al., 2000). Interestingly, resveratrol inactivated human recombinant CYP1A2 indirectly in a mechanism-based manner (Chang et al, 2001).

Mechanism-based inhibition was not observed in rat liver microsomes; EROD (7-ethoxyresorufin-O-deethylase) activity as an indicator of both CYP1A1 and CYP1A2 was inhibited by resveratrol and piceatannol (3,3′,4,5′-tetrahydroxy-*trans*-stilbene) with K_i value of 0.4 μM for both compounds and a mixed type of inhibition (Chang et al., 2007). It was found that resveratrol is metabolized to piceatannol in the reaction of hydroxylation catalyzed by CYP1A2 (Piver et al. 2004) and CYP1B1 (Potter et al. 2002). Poor bioavailability of resveratrol caused by its fast metabolism to glucuronides and sulphates limits the use of this stilbene as a potent chemopreventive / chemotherapeutic agent (Walle et al., 2004). To explain the bioactivity of resveratrol, its accumulation to active levels in target organs or synergistic / additive effects with other food components are taken into account.

4.2 Natural resveratrol analogues

During the last decade, other naturally occurring stilbenoid compounds with potential health benefit were found and examined. Piceatannol and pterostilbene (3,5-dimethoxy-4′-hydroxy-*trans*-stilbene) occur mainly in grapes and blueberries, with their amount depending on plant variety (Rimando et al., 2004). Pterostilbene that was shown to have cancer chemopreventive activity similar to resveratrol (Rimando et al., 2002) occurs also in some medicinal plants used in traditional medicine. Beneficial bioactivity of natural resveratrol analogues have been demonstrated in numerous *in vitro* experiments and in preclinical animal models (Rimando and Suh, 2008). Resveratrol analogues exert multiple bioactivities involved in cancer chemoprevention; for example, they are efficient inhibitors of family 1 cytochromes. The inhibitory action of natural stilbenes appears to be highly selective depending on the cytochrome isoform. Moreover, the extent of CYP inhibition changes according to the stilbene structure; the types and positioning of functional groups linked to the stilbene scaffold significantly influence inhibitory activity of stilbene derivatives. Rhapontigenin (3,5,3′-trihydroxy-4′-methoxystilbene) was found to be a very selective and potent inactivator of CYP1A1 activity with IC_{50} value 0.4 μM and K_i value of 0.09 μM (Chun et al., 2001a). Pinostilbene (3,4′-dihydroxy-5-methoxy-*trans*-stilbene), pterostilbene and desoxyrhapontigenin (3,5-dihydroxy-4′-methoxy-*trans*-stilbene) were more efficient inhibitors of CYP1A1 and CYPA2 in comparison to the parent compound, while they inhibited CYP1B1 to the same extent as resveratrol (Guengerich et al., 2003; Mikstacka et al., 2006, 2007). The data on the inhibition of CYP1 enzymes by natural stilbenes are summarized in Table 3.

4.3 Resveratrol methyl ethers and other synthetic stilbenes

In the last decade, new stilbene derivatives have been designed and synthesized in order to find more potent chemopreventive agents (Szekeres et al., 2010). The additional aim of this approach was to find resveratrol derivatives demonstrating better bioavailability in comparison to the parent compound. The bioactivity of resveratrol analogues could be altered due to the presence and positioning of methoxy groups on the basic resveratrol backbone that prevent the conjugation reaction with sulphuric and glucuronic acids. Synthesized derivatives are tested with regard to their inhibitory activity toward CYP 1 enzymes in order to find more efficient and selective inhibitors. A series of *trans*-stilbene derivatives containing a 3,5-dimethoxyphenyl moiety were prepared and evaluated on human recombinant CYP1A, CYP1A2 and CYP1B1 to find a potent and selective CYP1B1 inhibitor. It was shown that substitution at the 2-position of the stilbene skeleton plays a very important role in discriminating between CYP1A1/2 and CYP1B1. Chun and his group found 3,5,2′,4′-tetramethoxy-*trans*-stilbene as a new selective and very potent inhibitor of human CYP1B1 (Chun et al., 2001b). Among the whole series of compounds tested, 3,5,2′,4′-tetramethoxy-*trans*-stilbene exerted the most potent inhibitory activity toward CYP1B1 with an IC_{50} value of 2 nM. 2-[2-(3,5-dimethoxyphenyl)vinyl]tiophene showed comparable inhibitory activities, but its selectivity toward CYP 1B1 was lower (Kim et al. 2002).

Another series of stilbenes with 4-methylthiophenyl moiety were synthesized and their inhibitory potency toward human recombinant CYPs: CYP1A1, CYP1A2 and CYP1B1 was evaluated. Among compounds tested, 2-methoxy-4′-methylthio-*trans*-stilbene and 3-methoxy-4′-methylthio-*trans*-stilbene demonstrated the most potent and selective inhibitory effect on CYP1A1 and CYP1B1 activities (Mikstacka et al, 2008).

Compound	CYP1A1		CYP1A2		CYP1B1	
	K_i [μM]	Mode of inhibition	K_i [μM]	Mode of inhibition	K_i [μM]	Mode of inhibition
Resveratrol	1.2[a]	mixed type	15.5[a] 5.33[c]	mixed type	0.75[a]	mixed type
Piceatannol	3.01	competitive	9.67[c]	mixed type	0.27	competitive
Desoxyrhapontigenin	0.16	competitive	1.04	mixed type	2.06	competitive
Pinostilbene	0.13	mixed type	0.94	mixed type	0.90	competitive
Pterostilbene	0.57	competitive	0.39[c]	mixed type	0.91	competitive
Rhapontigenin	0.21[b] 0.4 (IC_{50})	competitive	160 (IC_{50})	n.d.	9 (IC_{50})	n.d.

[a] Chang et al., 2001; [b] Chun et al., 2001; [c] in mouse liver microsomes (Mikstacka et al., 2006); n.d. not determined

Table 3. Effect of natural *trans*-stilbenes on human recombinant CYP1A1, CYP1A2 and CYP1B1 activities

4.4 Other natural phenols

The influence of other phenolic phytochemicals on CYP1 activities is worth presenting in the context of possible additive or synergistic effects of the micro-components of human diet. The properties of plant extracts rich in numerous bioactive substances are particularly interesting in terms of herb-drug interaction, which could be a subject of independent review. At the beginning of the last decade, Piver and collaborators (2003) discovered that non-volatile components of red wine or various Cognac beverages exert stronger inhibitory effect on CYP1A1, CYP1A2, and CYP1B1 than resveratrol and its dimer ε-viniferin. Another extract, prepared from the most widely used herbal medicine *Ginkgo biloba,* was tested for its ability to inhibit the major human cytochrome P450 enzymes (Gaudineau et al., 2004). It was demonstrated that the flavonoidic fraction of standardized extract inhibits human CYP1A2 and other cytochromes (CYP2C9, CYP2E1, and CYP3A4), wheras its terpenoidic fraction significantly inhibits only CYP2C9. *In vivo* CYP1A2 induction was observed as a result of herbal dietary supplementation (Rye et al., 2003). Effects of Cuban and Mexican herbal extracts used in traditional medicine (obtained from *Heliopsis longipes*, *Mangifera indica* L. and *Thalassia testudinum*) on CYP1A1/2 and other cytochromes involved in drug metabolism of CYP3A4 and CYP2D6 were studied with the use of human liver microsomes and compared with the pure constituents isolated from the extracts of affinin (an alkamide isolated from the *H. longipes* extract), N-*iso*-butyl-decanamide, and mangiferin. The extracts significantly inhibited CYP1A1/2 activities, which reflects the high content of flavonoids with recognized CYP1A1/2 inhibitory properties (Rodeiro et al., 2009).

Numerous natural phenols demonstrate inhibitory activity toward CYP1 enzymes. Phytochemicals that exert inhibitory effects on CYP1A enzymes comparable to natural stilbenes comprise: flavonoids, isothiocyanates, coumarin and its derivatives.

Flavonoids represent a large class of phenolic phytochemicals. They are ubiquitously present in plant-derived foods and are important microcomponents of the human diet. Humans ingest approximately 0.6-1 g of these bioactive compounds daily (Kuhnau, 1976). The effects of flavonoids on CYP1 activities have been explored since the early nineties, including the effects of flavone and five hydroxylated derivatives on the methoxyresorufin O-demethylase activity catalyzed by human recombinant CYP1A1 and CYP1A2 (Zhai et al., 1998). The authors found galangin (3,5,7-trihydroxyflavone) as the most potent inhibitor of CYP1A2 with K_i value of 8 nM. It should be mentioned that no stilbene derivative with a comparable inhibitory potency toward CYP1A2 was found. Furthermore, galangin showed almost 5-fold selectivity for CYP1A2 over CYP1A1; while, 7-hydroxyflavone exhibited 6-fold greater selectivity for CYP1A1 over CYP1A2. The other hydroxylated flavone derivatives: 3-hydroxy; 5-hydroxy; 7-hydroxy- and 3,7-dihydroxyflavone were also potent inhibitors of CYP1A1 ($IC_{50} < 0.1$ μM) and CYP1A2 ($IC_{50} < 0.3$ μM).

In experiments with the use of human recombinant CYPs, seven flavonoids (myricetin, apigenin, kaempferol, quercetin, amentoflavone, quercitrin, and rutin) occurring in St. John's Wort were tested. They were found to be slightly more selective for CYP1B1 activity compared to CYP1A1. Apigenin and amentoflavone were competitive inhibitors of CYP1B1, while quercetin showed a mixed type of inhibition. The most potent CYP1B1 inhibitor was apigenin with K_i of 60 nM. The same authors investigated CYP1 inhibition in cell system. Myricetin, apigenin, kaempferol and quercetin inhibited TCDD-induced EROD activity in

intact 22Rv1 human prostate cancer cells. Because flavonoids were added 30 minutes prior to the EROD assay, the inhibition did not reflect down regulation of CYP1 mRNA or protein level (Chaudhary et al., 2006). The influence of flavonoid constituents of St. John's Wort were also studied by Schwarz's group. They demonstrated the differentiated inhibition of CYP1A1-catalyzed estradiol 2-hydroxylation according to CYP1A1 genotype. The variant CYP1A1.2 (Ile462Val) was significantly inhibited by quercetin, hypericin and pseudohypericin (naphthodiantrones), with IC_{50} values for 2-hydroxylation being more than two times lower than the wild-type enzyme. Additionally, the wild-type enzyme was efficiently inhibited by kaempferol, myricetin and resveratrol (Schwarz et al., 2011).

The synthesis of structures differentiated by type and positions of substituents leads to a continuation of structure and activity relationship (SAR) studies. Recently, Takemura and coworkers (2010) evaluated the structure–property relationship of 18 major flavonoids on inhibiting enzymatic activity of CYP1A1, 1A2 and 1B1 by using an ethoxyresorufin O-deethylation assay. Flavones and flavonols indicated relatively strong inhibitory effects on CYP1s compared with flavanone that does not have the double bond between C-positions 2 and 3 on the C-ring. Flavonoids used in this study selectively inhibited CYP1B1 activity.

Special attention is paid to methoxy derivatives of flavone, which have inhibitory potency exceeding that of the parent compound (Walle & Walle, 2007). In particular, methoxy types of flavones and flavonols such as chrysoeriol and isorhamnetin showed strong and selective inhibition against CYP1B1 (Takemura et al., 2010). The most potent inhibitors of CYP1 catalyzed ethoxyresorufin O-deethylation were the methoxylated flavones acacetin, diosmetin, eupatorin and the dihydroxylated flavone chrysin, indicating that the 4′-OCH_3 group at the B ring and the 5,7-dihydroxy motif at the A ring play a prominent role in EROD inhibition (Androutsopoulos et al., 2011). It was observed that high metabolic turnover of methoxylated flavonoids may result in enhanced antiproliferative activity. Several flavonoid metabolites produced in reactions catalyzed by CYP1A1 or CYP1B1 have been shown to inhibit cancer cell cycle progression. The authors observed CYP1A1-catalyzed biotransformation of acacetin to luteolin, apigenin and scutellarein. The chemopreventive ability of these metabolites was previously established. Generally, it is suggested that dietary flavonoids exhibit three distinct modes of action with CYP1 enzymes: (1) inhibitors of CYP1 enzymatic activity, (2) CYP1 substrates and (3) substrates and inhibitors of CYP1 enzymes.

Coumarin (1,2-benzopyrone) and its derivatives occur naturally in several plant families. They are components of essential oils, and are often used as fragrance ingredients in human diet. Their effect on CYP1 activities have been studied since the early nineties. The naturally occurring coumarins: bergamotin, coriandrin, isoimperatorin, imperatorin, ostruthin are potent inhibitors of the metabolic activation of benzo(a)pyrene and dimethylbenzanthracene in the cell culture model system of mouse epidermis (Cai et al., 1997). In experiments *in vitro*, mechanism-based inactivation of hepatic EROD activity by natural coumarin coriandrin was observed (Cai et al., 1996). These results demonstrate that certain coumarins to which humans are exposed in their diet are bioactivated by CYP1A1 to reactive intermediates that subsequently form covalent adducts with the apoprotein, effectively destroying enzyme activity.

Curcumin is a natural plant food additive obtained from turmeric used in spices and traditional Indian medicine. Its chemopreventive anticancer potential is well documented (Aggarwal et al., 2003). It belongs to hydroxycinnamic acid derivatives observed ubiquitously in plants. Earlier reports on the inhibition of rat liver microsomal CYPs by curcumin showed that curcumin is a strong inhibitor of CYP1A enzymes and CYP2B as well (Oetari et al., 1996; Thapliyal and Maru, 2001, 2003). However, these data were not confirmed in studies with human recombinant cytochrome P450s, where curcumin appeared to be a moderate inhibitor of CYP1A2 with IC_{50} value 40 μM (Appiah-Opong et al., 2007). Appiah-Opong and coworkers synthesized curcumin derivatives that exhibited about 10- to 40-fold greater potency towards inhibition of CYP1A2 than curcumin itself (Appiah-Opong et al., 2008).

Other natural phenols studied more recently with respect to CYP1 inhibition include **phytocannabinoids,** constituents of marijuana, and **chromene amides** from *Amyris plumieri*, a plant grown in the Caribbean, Central America and Venezuela used in folk medicine. Three major constituents in marijuana; Δ^9-tetrahydrocannabinol, cannabidiol and cannabinol inhibited activities of human recombinant CYP1s: CYP1A1, CYP1A2 and CYP1B1 in a competitive manner (Yamaori et al., 2010). One of the amides (chromene acetamide) tested appeared to inhibit potently CYP1A1 activity *in vitro* with IC_{50} and K_i values 1.547 μM and 0.37 μM, respectively (Badal et al., 2011).

Interestingly, in the studies on different natural phenols Schwarz and Roots demonstrated that the inhibitory effect depends not only on the structure of the inhibitor, but also the substrate of the reaction catalyzed by CYPs used in the assay. They found flavonoids like myricetin, apigenin, quercetin, and kaempferol, as well as tea polyphenol (-)epigallo catechin gallate, strongly inhibited the formation of benzo(a)pyrene diolepoxide, the ultimate carcinogenic product of benzo(a)pyrene activation. Furthermore, resveratrol, an inhibitor of CYP1A1-catalyzed ethoxyresorufin deethylation, exhibited only slightly inhibitory effect on CYP1A1-mediated epoxidation of 7,8-diol-B(a)P (Schwarz & Roots, 2003).

5. Docking studies – The new approach to CYPs-phytochemical interaction

Mechanistic studies of the inhibitory effect of stilbenes on enzyme activities are mainly conducted *in vitro* with the use of human recombinant cytochromes. However, the affinity of compounds to cytochromes may be determined by computational analysis of inhibitor/substrate docking in the enzyme active site. Molecular modeling is presumed to be helpful in predicting inhibitory potential of CYP regulators by characteristics of ligand-enzyme interactions. We review *in silico* research on elucidating the mechanism of inhibitory action of phytochemicals by analysis of structure and activity relationship. Potential phytochemical candidates can be selected by *in silico* virtual screening, based on natural compound libraries (www.bioscreening.com). When active chemicals are selected, they may be "docked" into the target protein by using available programs, enabling detailed protein-ligand interactions to be obtained and the best fit of a candidate compound to be identified. The main objective of molecular docking is to determine the binding interactions between protein and ligand.

Computational procedures of molecular modeling have been employed since the nineties. Studies of Lewis and coworkers (1997) on CYP1 family enzymes structure and ligand docking in enzyme cavities have been a great contribution to the development of this field. Lewis formulated the general characteristic of CYP1 ligands as planar and polar polycyclic molecules. Substituents linked to the polycyclic hydrocarbon core influence the ligand binding responsible for molecular interactions: hydrogen bonds; π-π stacking; and hydrophobic interactions. The effect of structural modification on the inhibitory selectivity of phytochemical derivatives on CYP1A1, CYP1A2, and CYP1B1 help to elucidate which interactions determine the inhibitory ability of the compounds. There are similarities between the active sites of CYP1A2 and CYP1A1 which are in accordance with the overlapping substrate specificities of the two enzymes. However, the CYP1A1 substrates are generally of higher lipophilicity than those of CYP1A2. The reason lies in the more hydrophobic character of the CYP1A1 active site region (including the access channel) in comparison to CYP1A2 active site (Lewis et al., 1999). The differences in the structure of enzyme binding sites may determine the metabolism pathways of a substrate. With the use of computational docking the mechanism of E2 2-hydroxylation and 4-hydroxylation catalyzed by CYP1A1/2 and CYP1B1, respectively, were elucidated. CYP1A1 and CYP1A2 produced 2-OH-E2 and 4-OH-E2 in a ratio of 10 : 1; whereas CYP1B1 produces 2-OH-E2 and 4-OH-E2 in a ratio of 1 : 3 (Lee et al., 2003). The docking study suggests that CYP1A1 and CYP1A2 generate 2-OH-E2 rather than 4-OH-E2, and that CYP1B1 generates both 2-OH-E2 and 4-OH-E2. Particular amino acids residues for each CYP were identified as playing an important role in estradiol recognition (Itoh et al., 2010).

Several groups of phytochemicals were tested for affinity to active sites of CYP1 members. The first studied compounds were rutaecarpine derivatives. An alkaloid rutaecarpine preferentially inhibited CYP1A2 activity with IC_{50} value of 22 nM. However, 1-methoxyrutaecarpine and 1,2-dimethoxyrutaecarpine were the most selective CYP1A2 inhibitors. Molecular modeling showed a good fitting of rutaecarpine and the active site of CYP1A2. Two hydrogen bonds between the keto- and N14-groups of rutaecarpine and the Thr^{208} and Thr^{473} residues of CYP1A2, respectively, were visualized with molecular modeling procedures. The C-ring moiety of rutaecarpine formed π-π stacking interaction with the aromatic ring of Phe^{205} residue (Don et al., 2003).

Coumarin was shown to be a substrate of human CYPs, specifically: CYP1A1 and CYP1A2. Molecular modeling led to recognition and localization of the amino acid residues which interact with coumarin molecules resulting in the orientation of coumarin with 3,4 bond directly above the heme moiety. Coumarin 3,4-epoxide is produced and then rearranged to hydroxyphenylacetaldehyde, which can be further metabolized to toxic products. In the CYP1A1 active site, Ser^{113} forms a hydrogen bond with coumarin, while Phe^{205} and Phe^{358} are responsible for aromatic π-π stacking. In CYP1A2, Thr^{113} forms hydrogen bonds with coumarin, and Phe^{205} is responsible for π-π stacking (Lewis et al., 2006). However the different key residues take part in the interactions with coumarin, they determine the same site of metabolism, and in consequence, the pathway of coumarin metabolism is the same for both CYP1A1 and CYP1A2 .

7,8-benzoflavone (α-naphthoflavone) is a prototype flavonoid which has been used to examine the mechanism of action on P450 enzymes. Molecular modeling studies revealed that 7,8-naphthoflavone is positioned in a hydrophobic cavity of CYP1A2 next to the

active site where it may cause a direct effect on substrate binding (Cho et al., 2003). Further studies with the use of molecular docking were aimed at methoxyflavonoids with a 2–3 double bond, which exerted strong inhibitory effect on CYP1 activities, particularly CYP1B1 (Takemura et al., 2010). The authors observed that the binding specificity of methoxyflavonoids is based on the interactions between the methoxy groups and specific CYP1s residues. For example, chrysoeriol and isorhamnetin fit well into the active site of CYP1B1, but do not fit into the active site of CYP1A2 and 1A1 because of steric collisions between the methoxy substituent of these methoxyflavonoids and Ser^{122} in CYP1A1 and Thr^{124} in CYP1A2. Androutsopoulos's group described molecular docking of several flavonoids with regard to their metabolism and inhibitory activity. The simulated binding orientation of the compounds tested was in accordance with the study of Takemura and coworkers (2010). Diosmetin and eupatorin are predicted to be oriented with ring-B over the prosthetic group so that 4'-methoxy group is at ~4.5 Å from the heme iron. The less substituted chrysin and acacetin also were shown to bind CYP1A1 with ring-B over the iron-heme group. However, a lower number of interactions were found within the active site of CYP1A1 (Androutsopoulos et al., 2011).

To better characterize stilbenes as ligands of CYPs, we performed molecular docking by simulation of resveratrol and pterostilbene binding in active sites of CYP1A2 and CYP1B. Resveratrol and pterostilbene molecules were docked into the cavities of CYP1A2 (PDB code: 2hi4) and CYP1B1 (PDB code: 3pm0) with the use of the CDOCKER procedure implemented in Accelrys Discovery Studio 2.5.5. CDOCKER uses a CHARMm-based molecular dynamics (MD) scheme to dock ligands into a receptor binding site. For assigning receptor and ligand atom partial charges, we applied the charging rules used in the MMFF94 forcefield. Docked poses were scored by the negative value of CDOCKER energy for the –CDOCKER_ENERGY function, which include interaction energy and internal ligand energy: the higher positive value of –CDOCKER_ENERGY, the stronger affinity of a ligand to the binding site.

Our docking experiment showed that in the CYP1A2 active site, all possible poses of resveratrol can be grouped into two sets. This observation indicated that two binding modes are possible for resveratrol molecule. In mode A, represented by the pose with highest score, a resveratrol molecule is directed with 4'-OH group toward a heme (Fig. 3a). In mode B, the second ring with 3-OH and 5-OH substituents is situated in the vicinity of a prosthetic group (Fig. 3b). In both orientations, resveratrol binding is stabilized by π–π stacking interactions, with phenyl ring of Phe^{226} (mode A), and with Phe^{226} and Phe^{260} (mode B). Contrary to resveratrol, a pterostilbene molecule was docked in the CYP1A2 active site only in one orientation with 4'-OH group directed toward a heme (Fig. 3c). Pterostilbene binding was stabilized by π–π interaction with an aromatic ring of Phe^{226} . For a resveratrol molecule docked in the active site of CYP1B1, we also distinguished two binding modes. In contrast to CYP1A2, the highest scored pose corresponded to binding mode B. In both orientations (A and B), resveratrol was stabilized by two π–π interactions between both of its rings and a phenyl ring of Phe^{231}, and additionally by two hydrogen bonds with Asn^{265} and Asp^{333} in mode B, or Asn^{265} and Asn^{228} in mode A (Fig. 3d and 3e).

Similar to interaction with CYP1A2, a pterostilbene molecule represented only one type of orientation in the CYP1B1 cavity (Fig. 2f). The binding conformation with 4'-OH group close to a heme was stabilized by two π–π stacking interactions with Phe^{231}. In the case of

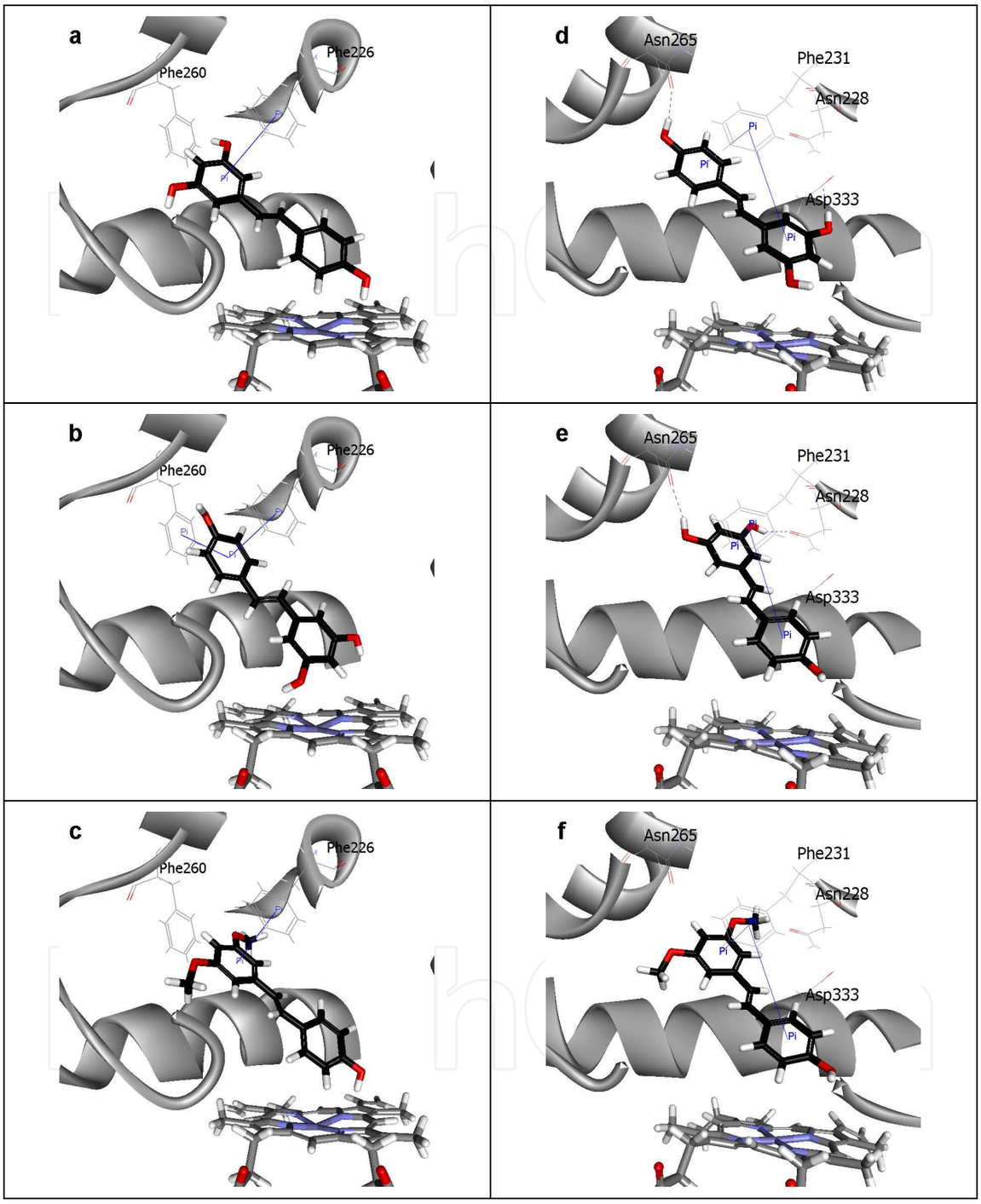


Fig. 3. Putative binding modes of resveratrol and pterostilbene in active sites of CYP1A2 (a – c) and CYP1B1 (d – f) with key residues involved in π–π stacking interactions and hydrogen bonds represented by solid blue lines and dashed blue lines, respectively. Heme molecule is at the bottom. CYP1A2 active site in complex with: (a) resveratrol in binding mode A, (b) resveratrol in mode B, (c) pterostilbene. CYP1B1 active site in complex with: (d) resveratrol in binding mode B, (e) resveratrol in mode A, (f) pterostilbene.

pterostilbene, which is a dimethoxy analogue of resveratrol, it is suggested that hydrophobic interactions might play a key role determining and stabilizing its docking orientation.

In studies of *trans*-resveratrol metabolism by human microsomal CYP1B1 enzyme (Potter et al., 2002), the authors observed formation of two metabolites, M1 and M2. The major metabolite M2 has been identified as piceatannol (3,4,3',5'-tetrahydroxystilbene), while 3,4,5,4'-tetrahydroxystilbene was proposed as the M1 product. More recent work (Piver et al., 2004) provided evidence that CYP1A2 is also engaged in the metabolism of *trans*-resveratrol to piceatannol and tetrahydroxystilbene M1. Our studies confirmed the possibility of two pathways of metabolism on the grounds of molecular docking analysis.

6. Conclusion

The finding of high affinity ligands among natural compounds for each of the CYP1 family enzymes will help to reveal more about enzyme specificity, providing a starting point for more extensive studies and improved predictive capabilities. Particularly, a selective inhibition against CYP1B1 that influences the chemopreventive properties of phytochemicals for E2 related breast cancer seems to be promising. There is a need for better characterization of potential chemopreventive/therapeutic agents in order to understand their abilities and limits to influencing numerous pathways leading to cancer development. Novel classes of anti-cancer drugs including those of plant origin are being developed that can target both drug-metabolizing enzymes and disease modifying pathways. Recently, interest in the combinatory effect of different phytochemicals is growing, with respect to the multi-targeted action of numerous components of a food matrix. Wenzel and co-workers found that metabolism of resveratrol present in beverages such as wine or grape juice is inhibited by other polyphenols due to competitive reactions with Phase -II enzymes, resulting in an increased concentration of the free form (Wenzel et al., 2005). It is suggested that an efficient chemoprevention strategy lies in the use of combinations of several chemopreventive and/or therapeutic agents which may exert multi-targeted action. In conclusion, the search for potent and selective CYP1A inhibitors appears to hold promise and should be continued with the use of novel computational techniques.

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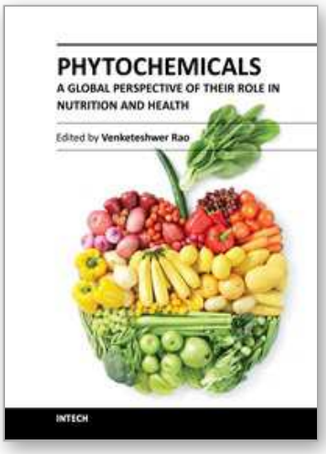

Phytochemicals - A Global Perspective of Their Role in Nutrition and Health

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Phytochemicals are biologically active compounds present in plants used for food and medicine. A great deal of interest has been generated recently in the isolation, characterization and biological activity of these phytochemicals. This book is in response to the need for more current and global scope of phytochemicals. It contains chapters written by internationally recognized authors. The topics covered in the book range from their occurrence, chemical and physical characteristics, analytical procedures, biological activity, safety and industrial applications. The book has been planned to meet the needs of the researchers, health professionals, government regulatory agencies and industries. This book will serve as a standard reference book in this important and fast growing area of phytochemicals, human nutrition and health.

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