Biochemical and Biophysical Research Communications 389 (2009) 128–132

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Potent and selective inhibition of the tumor marker AKR1B10 by bisdemethoxycurcumin: Probing the active site of the enzyme with molecular modeling and site-directed mutagenesis

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ARTICLE INFO

Article history:
Received 18 August 2009
Available online 23 August 2009

Keywords:
AKR1B10
Aldose reductase-like 1
Aldose reductase
Curcumin
Bisdemethoxycurcumin
Polyphenol

ABSTRACT

A human member of the aldo–keto reductase (AKR) superfamily, AKR1B10, shares high sequence identity with aldose reductase (AR), and was recently identified as a therapeutic target in the treatment of several types of cancer. We have compared the inhibitory effects of plant components on recombinant AKR1B10 and AR. AKR1B10 was inhibited by curcuminoids, magnolol, honokiol and resveratrol, with IC_{50} values of 0.06–5 μM, which were lower than their values for AR. Among them, bisdemethoxycurcumin was the most potent competitive inhibitor (K_i = 22 nM) with the highest selectivity (85-fold versus AR), and acted as an effective inhibitor in cellular level. In contrast, demethoxycurcumin and curcumin showed >3-fold less potency and selectivity. Molecular docking studies of the curcuminoids in the AKR1B10–$NADP^+$ complex and site-directed mutagenesis of the putative binding residues suggest that Gln114, Val301 and Gln303 are important for determining the inhibitory potency and selectivity of the curcuminoids.

AKR1B10 is a human NADPH-dependent aldo–keto reductase (AKR), which was recently identified as an aldose reductase (AR)-like 1 and human small intestinal AR [1,2]. The overall amino acid sequence of AKR1B10 shows 71% identity with that of human AR, which is named AKR1B1 in the AKR superfamily (http://www.med.upenn.edu/akr/). AKR1B10 reduces a variety of aldehydes and ketones, including endogenous substrates such as methylglyoxal [1], acrolein [3], 4-hydroxynonenal [4], phospholipid aldehydes [5], retinals [6], farnesal and geranylgeranial [7], that are also the substrates of AR. Among these substrates, retinals, farnesal and geranylgeranial are excellent substrates for AKR1B10, indicating much higher catalytic efficiency compared to human AR. Thus, AKR1B10 is suggested to play roles in the metabolism of retinoids and isoprenoids.

AKR1B10 was reported to be up-regulated in lung and hepatic carcinomas (squamous cell carcinoma and adenocarcinoma) [1,8,9], as well as in esophageal and uterine cancers [10,11], suggesting its potential role as a tumor marker. In addition, AKR1B10-gene silencing results in the inhibition of colorectal cancer cell growth, suggesting that AKR1B10 regulates cell proliferation [3]. Furthermore, current studies suggest that AKR1B10 participates in the cell carcinogenesis and tumor development by detoxifying cytotoxic carbonyls [4], mediating retinoic acid homeostasis [6,12], and regulating cellular fatty acid synthesis and lipid metabolism [13]. Thus, this enzyme is a target for the prevention and treatment of the above types of cancer. However, there are three reports on the inhibitors of AKR1B10, which include some AR inhibitors, fibrate derivatives, anti-inflammatory agents and phenolphthalein [6,14,15]. Among them, an AR inhibitor tolrestat is the most potent inhibitor with an IC_{50} value in the low nM range [6,16] for both enzymes. The other inhibitors show IC_{50} values of 10–300 μM for AKR1B10 [14,15], and have not been studied for their selectivity, which is ideally required for development of drugs targeting to this enzyme.

In the present work, we have examined the inhibitory effects of dietary plant polyphenols on the tumor marker AKR1B10 and human AR. The components found to be potent and selective inhibitors of AKR1B10 were curcumin (Cur), demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC), honokiol, magnolol and resveratrol, which have been reported to show anti-cancer properties [17–20]. Among them, BDMC was the most potent and selective, showing a K_i value of 22 nM for AKR1B10 and 85-fold less inhibition against human AR. The structural base responsible for the high affinity of BDMC for AKR1B10 was investigated by com-

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doi:10.1016/j.bbrc.2009.08.107

paring the docked models of the curcuminoid–AKR1B10–$NADP^+$ ternary complexes and site-directed mutagenesis studies of the active site residues of the enzyme.

Materials and methods

Purification of recombinant enzymes. Recombinant AKR1B10 with the N-terminal 6-His tag, human AR and aldehyde reductase without any additional amino acid were expressed in *Escherichia coli* BL21 (DE3) pLysS cells transformed with the expression plasmids harboring their cDNAs, and purified to homogeneity as described previously [7,21] .

Site-directed mutagenesis. Mutagenesis was performed using a QuickChange site-directed mutagenesis kit (Stratagene) and the pCold I expression plasmid harboring the cDNA for AKR1B10 [7] as the template according to the protocol described by the manufacturer. The primer pair used for the mutagenesis was composed of sense and antisense oligonucleotides to alter one or two codons of AKR1B10 cDNA. The 29- to 35-mer primers were synthesized to give the Q114T, W220Y, V301L, Q303S, S304A and V301L/Q303S mutant enzymes. The coding regions of the cDNAs in the expression plasmids were sequenced in order to confirm the presence of the desired mutation and ensure that no other mutation had occurred. The mutant enzymes were expressed in the *E. coli* cells, and purified to homogeneity as described above for the wild-type enzyme [7].

Assay of enzyme activity. The reductase and dehydrogenase activities of AKRs were determined at 25 °C by measuring the rate of change in NADPH absorbance (at 340 nm) and fluorescence (at 455 nm with an excitation wavelength of 340 nm), respectively [7]. The IC_{50} values of inhibitors for AKR1B10 and AR were determined in the reaction mixture consisted of 0.1 M potassium phosphate, pH 7.4, 0.1 mM NADPH, 0.2 mM pyridine-3-aldehyde and enzyme in a total volume of 2.0 ml. In the assay for human aldehyde reductase 10 mM pyridine-3-aldehyde was used as the substrate. Kinetic studies in the presence of inhibitors were carried out in both pyridine-3-aldehyde reduction and $NADP^+$-linked geraniol oxidation over a range of five substrate concentrations (0.2–5 × K_m) at a saturating concentration of coenzyme, and vice versa. The IC_{50} and K_i values are expressed as the means ± standard errors of at least three determinations.

Molecular modeling and energy minimization. The coordinates for AKR1B10 were obtained from the RCSB Protein Data Bank (PDB code 1ZUA). The structure was prepared using the Maestro (Schrödinger, LLC) software package Version 8.5 as described previously [7]. In order to eliminate any bond length and bond angle biases from the crystal structure, the ligand, BMDC or Cur, was subjected to a full minimization prior to the docking. The docking calculations were performed using Glide 5.0 [22] on a Linux workstation under the conditions described previously [7]. Figures were generated using *PyMOL* (DeLano Scientific).

Cell culture experiments. The culture of HeLa cells, transfection of the pGW1 plasmids harboring the cDNA for AKR1B10, activity assay of the expressed enzyme and analysis of the metabolism of [1-^{14}C] *trans,trans*-farnesol in the cells were carried out as described previously [7].

Results and discussion

Inhibition of AKR1B10 by plant polyphenols

The inhibitory plant components found in this study were polyphenols (Table 1), and their structures are illustrated in Fig. 1. Among them, BDMC exhibited the lowest IC_{50} value and highest selectivity to AKR1B10 (85-fold versus AR). The inhibitory potency and selectivity were decreased in DMC and Cur that have one or two methoxy groups on the phenolic rings of BDMC. Other

Table 1
Effects of polyphenols on reductase activities of AKR1B10 and human AR.

Inhibitor	IC_{50} (μM)		Ratio AR/1B10
	AKR1B10	AR	
BDMC	0.060 ± 0.009	5.1 ± 0.2	85
DMC	0.18 ± 0.01	1.2 ± 0.1	7
Cur	0.38 ± 0.05	7.3 ± 0.2	20
Magnolol	3.6 ± 0.2	28 ± 3	8
Honokiol	3.8 ± 0.1	36 ± 3	9
Resveratrol	5.0 ± 0.6	73 ± 5	12

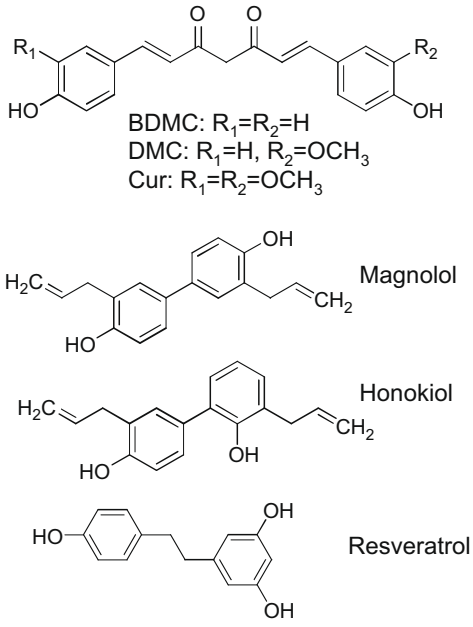

Fig. 1. Structures of plant polyphenols.

polyphenols, resveratrol, honokiol and magnolol showed less inhibition for both AKR1B10 and AR, while their selectivities were comparable to that of DMC. Human aldehyde reductase, a functionally related enzyme to human AR and AKR1B10, was not inhibited by honokiol, resveratrol (each 50 μM), BDMC, DMC, Cur and magnolol (each 20 μM).

AKR1B10 catalyzes both reduction of carbonyl compounds and oxidation of several alcohols such as geraniol and farnesol, and the inhibition patterns of tolrestat and inhibitory steroids for the reaction directions catalyzed by the enzyme are different [7]. BDMC inhibited the enzyme noncompetitively with respect to the pyridine-3-aldehyde and NADPH in the reduction direction, whereas the inhibition patterns in the oxidation direction are uncompetitive and competitive with respect to $NADP^+$ and geraniol, respectively. The inhibition patterns were the same as those reported previously for tolrestat and the inhibitory steroids [7], and the K_i value for BDMC estimated from the competitive inhibition with respect to geraniol was 22 ± 4 nM. The inhibition patterns of DMC, Cur and honokiol with respect to geraniol were also competitive, showing the K_i values of 60 ± 5 nM, 170 ± 30 nM and 1.9 ± 0.1 μM, respectively. Thus, the affinity for BDMC was the highest among the inhibitors tested, and is comparable to those for previously known potent inhibitors, tolrestat and isolithocholic acid [6,7].

Inhibitory effect on cellular metabolism by AKR1B10

The efficacies of AKR1B10 inhibition by BDMC, Cur and honokiol were examined in the cellular metabolism of farnesal using the HeLa

cells expressing the enzyme as reported previously [7]. In the control cells that are transfected with the vector alone, the added farnesol is metabolized into farnesoic acid through farnesal, which is not detected as the intermediate metabolite because of its rapid conversion into farnesoic acid. The metabolic rate of farnesol into farnesoic acid in AKR1B10-overexpressed cells is decreased, because the enzyme efficiently reduces the intermediate metabolite, farnesal, back into farnesol [7]. Compared to the rapid metabolism of farnesol into farnesoic acid in the control cells, significant decrease in this metabolism by overexpression of AKR1B10 was confirmed in the present cells (Fig. 2), in which the farnesal reductase activity of the extract from the AKR1B10-overexpressed cells was 8-fold higher than that of the control cells. If an added compound inhibits AKR1B10 (i.e., the reduction of farnesal into farnesol), the metabolic rate of farnesol will be increased, producing higher amounts of farnesoic acid, as seen in the case of the known potent inhibitor tolrestat. BDMC (from 1 μM) and Cur (from 10 μM) increased the metabolic rate of farnesol into farnesoic acid in a dose-dependent manner. It should be noted that no significant decrease in the cell viability was observed at 50 μM Cur and BDMC. The IC_{50} values for BDMC and Cur calculated from the dose-dependent curves were 11 and 61 μM, respectively. The IC_{50} value of BDMC is 10-fold higher than that of tolrestat determined with retinal reductase activity of AKR1B10 in monkey COS-1 cells [16]. This may be due to the different cells and assay conditions between the present and previous studies. In fact, the inhibition of the farnesal reduction in the present human HeLa cells by tolrestat was almost the same as that by BDMC. In addition, honokiol, a less *in vitro* inhibitor, inhibited approximately 50% of the cellular metabolism of farnesal by the enzyme at 25 μM, which was lower than the IC_{50} value of Cur. Thus, the permeability of the tested inhibitor into the cells may also affect its cellular effectiveness in the enzyme inhibition.

Possible link between curcuminoids inhibition of AKR1B10 and their anti-tumor action

BDMC, DMC and Cur are major curcuminoids included in powdered rhizome of the medicinal plant *Curcuma longa* and other *Curcuma* species [18], which are known commonly as dietary spice turmeric and have been used safely for centuries to treat indigestion, hepatitis, diabetes, atherosclerosis and bacterial infections. Curcuminoids have been reported to have several anti-cancer activities including anti-proliferation, anti-invasion and anti-angiogenesis by modulating multiple intracellular target proteins and signaling pathways [17–19]. Such target proteins include cyclooxygenase, 5-lipoxygenase [23], farnesyl protein transferase [24], glyoxalase I [25], proteasome [26] and their inhibitions by Cur have been suggested to be linked to the anti-cancer action. The IC_{50} value of Cur for AKR1B10 is lower than those for the known target enzymes. The IC_{50} values for BDMC and DMC in the inhibition of AKR1B10 are an order of magnitude lower than that for Cur, although the inhibition of BDMC and DMC has not been studied on the above known enzymes, with exception of farnesyl protein transferase (IC_{50} values of >29 μM) [24]. AKR1B10 has been recognized to be a valuable target for prevention and treatment of cancer, as well as a biomarker of several cancers [1,3,8–11]. The potent inhibition of AKR1B10 by BDMC, DMC and Cur may contribute to their anti-tumor actions against cancers, in which the enzyme is highly expressed.

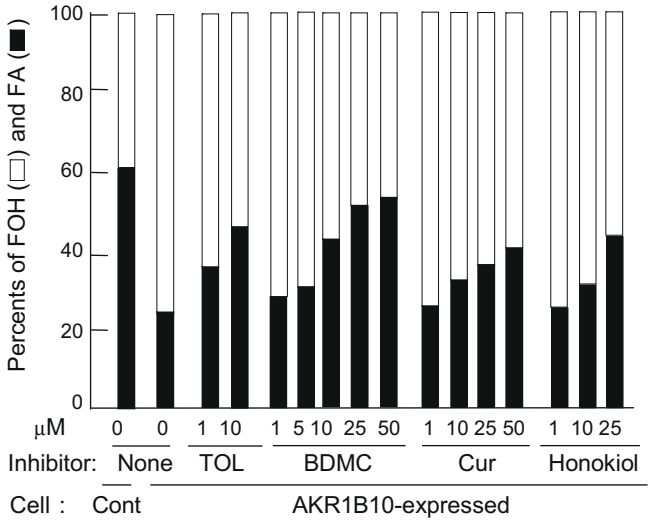

Fig. 2. Effects of AKR1B10 inhibitors on the cellular farnesal metabolism. The control (Cont) and AKR1B10-expressed cells were pre-treated with indicated concentrations of tolrestat (TOL), BDMC, Cur and honokiol for 2 h, and then incubated with 20 μM [^{14}C]farnesol for 6 h. The radioactivities of farnesol (FOH) and farnesoic acid (FA) in the media of duplicate experiments were measured, and are expressed as the mean percentages, relative to their sum.

Molecular docking and site-directed mutagenesis of inhibitor-binding residues

The underlying structural reasons for the high affinity for BDMC and its high selectivity to AKR1B10 were examined through comparison of the structural models of BDMC and less potent Cur bound to the enzyme–$NADP^+$ complex (Fig. 3A and B), which were built on the basis of the crystal structure of AKR1B10–$NADP^+$–tolrestat complex [16]. In the models, the two curcuminoids occupied in the substrate-binding site of the enzyme, and their orientations resembled that of tolrestat (Fig. 3C). Similarly to the side-chain carboxyl group of tolrestat, the hydroxyl group on one phenyl ring of BDMC was directed to the side chains of catalytically important residues (Tyr49 and His111) and the nicotinamide moiety of $NADP^+$ (Fig. 3A). The two models differ in interactions of the other parts of the two inhibitors with the enzyme: While residues within 3.5 Å from the inhibitor molecule are only three (Trp21, Phe116 and Gln303) in the tolrestat-bound structure, such residues are Trp21, Gln114, Trp220, Val301 and Ser304 in the BDMC-docked model. The side-chains of Gln114 and/or Ser304 appear to form H-bonds with the hydroxyl group on the other phenyl ring of BDMC. As evident by the superimposed structures of the models of BDMC and Cur (Fig. 3D), there were differences in the orientation of one phenyl ring near the catalytically important residues and in the interactions of the hydroxyl group on the other phenyl ring with the residues in the C-terminal loop of the enzyme, likely due to the presence of the methoxy groups on the phenyl rings of Cur. The hydroxyl group on the other phenyl ring of Cur did not interact with the side-chains of Gln114 and Ser304, but the methoxy group on the phenyl ring was close to the side-chain of Gln303 (Fig. 3B).

To investigate the participation of the residues predicted by the docked models in the inhibitor binding, we replaced Gln114, Val301 and Gln303 with the corresponding residues, Thr, Leu and Ser, respectively, of human AR, which showed low sensitivity to BDMC and Cur. Although Ser304 corresponds to Cys in human AR, it was replaced by Ala to remove its possible interaction with the hydroxyl group of BDMC. In addition, Trp220 was replaced by a smaller aromatic residue, Phe. The effects of the mutations on the K_i values for BDMC, DMC and Cur are summarized in Table 2. With exception of the S304A mutation, other mutations decreased the affinity for any of the three curcuminoids by more than 3-fold compared to the wild-type enzyme. The affinity for BDMC was greatly impaired by the mutation of W220Y, which gave much lower effect on those for DMC and Cur. The mutation of Q114T decreased only the affinity for BDMC by 3-fold. The results supported

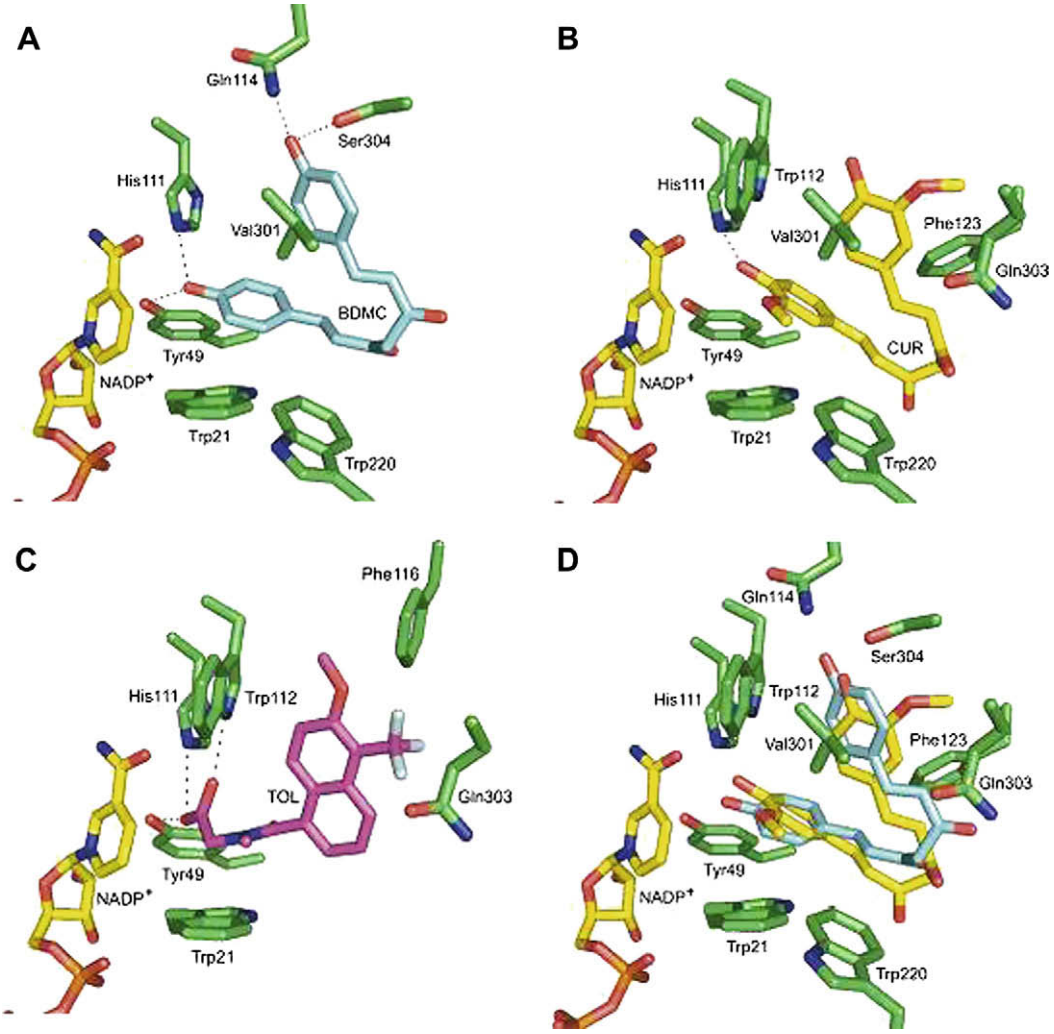

Fig. 3. The binding site of the AKR1B10 model with docked BDMC (A) and Cur (B) and that of tolrestat (TOL) in the crystal structure of its ternary complex (C). The structures of BDMC (sky-blue) and Cur (yellow) are superimposed (D). The nicotinamide nucleotide portion of $NADP^+$ and residues within 3.5 Å from the curcuminoids and tolrestat are depicted with possible H-bonds.

the different orientations of BDMC and Cur in the enzyme shown in Fig. 3D, and indicate that the H-bond interaction with Gln114 and hydrophobic contacts with Trp220 are important for the high inhibitory potency of BDMC. Although the side-chain of Gln114 forms a H-bond with that of Ser304 in the crystal structure of AKR1B10–$NADP^+$–tolrestat complex [16], the alteration in the affinity for BDMC resulted from the mutation of Q114T, but not from that of S304A, being further supportive of the important H-bond interaction of the phenolic ring of BDMC with Gln114. In the binding of less potent Cur and DMC to the enzyme, the methoxy group on the phenyl ring of the two curcuminoids may cause their orientations to differ from BDMC, leading to the prevention of the H-bond interaction with the side-chain of Gln114 and alteration of the hydrophobic contacts with Trp220.

The mutation of V301L similarly increased the K_i values for BDMC, DMC and Cur, supporting the hydrophobic interaction of the side-chain of Val301 with the phenolic rings of the curcuminoids (Fig. 3D). In contrast, the mutation of Q303S influenced only

Table 2
Effects of mutations of AKR1B10 on K_i values for curcuminoids.

Enzyme	BDMC		DMC		Cur	
	K_i (nM)	Mu/Wt[a]	K_i (nM)	Mu/Wt[a]	K_i (nM)	Mu/Wt[a]
Wild type	22		65		170	
Q114T	65 ± 2	3.0	87 ± 9	1.4	290 ± 12	1.7
W220Y	440 ± 20	20	390 ± 30	6.0	500 ± 10	2.9
V301L	110 ± 9	5.0	270 ± 11	4.2	1300 ± 100	7.6
Q303S	70 ± 28	3.2	90 ± 8	1.4	670 ± 30	3.9
S304A	29 ± 2	1.3	54 ± 4	0.8	210 ± 10	1.2
V301L/Q303S	150 ± 22	6.8	470 ± 21	7.2	1500 ± 100	8.8

[a] Ratio of the mutant enzyme to wild-type enzyme.

the K_i values for BDMC and Cur. This suggests that the orientation of DMC in the enzyme is slightly distinct from those of BDMC and Cur, and is related to its low selectivity to AKR1B10.

The above results suggest that at least the differences in the residues at positions 114, 301 and 303 between AKR1B10 and human AR are responsible for the high selective inhibition of AKR1B10 by BDMC. Since any of the above single mutations did not result in large decreases in inhibitory potencies of the three curcuminoids, we further examined the effect of a double mutation of V301L/Q303S on the inhibitory potencies of the curcuminoids (Table 2). The double mutation altered the K_i values for the curcuminoids more largely than the respective single mutations. The result, together with the changes by the single mutations, suggests that Gln114, Val301 and Gln303 have a combined role in inhibitor binding and selectivity.

In conclusion, the present search for tumor-marker AKR1B10 inhibitors targeting safety plant-derived compounds reveals that this enzyme is potently and selectively inhibited by several plant polyphenols with anti-tumor actions. Our data raise the intriguing possibility that the enzyme's inhibition by the polyphenols is due to a novel mechanism of their anti-tumor actions. BDMC, the most potent and selective inhibitor, represents a promising lead for the development of more potent and specific agents targeting AKR1B10. In addition, molecular modeling and site-directed mutagenesis analyses on the binding of BDMC and related curcuminoids to the enzyme provide novel structural futures that would facilitate the design of anti-cancer agents.

Acknowledgement

This work is supported in part by a Grang-in-Aid for Young Scientists (B) from the Japan Society for the Promotion of Science.

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