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ORIGINAL PAPER

Lignin-derived oak phenolics: a theoretical examination of additional potential health benefits of red wine

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Abstract Lignin-derived phenolic compounds can be extracted from oak barrels during the aging of red wine, and it is hypothesized that these compounds may contribute to the health benefits of red wine by their antioxidant, radical-scavenging, or chemopreventive activities. Density functional calculations (B3LYP/6-311++G**) support the radical-scavenging abilities of the oak phenolics. Sinapaldehyde, syringaldehyde, syringol, and syringylacetone all have bond dissociation energies that are lower than resveratrol and comparable to the flavonoid catechin. Molecular docking studies of the oak phenolics with known resveratrol protein targets also show that these compounds dock favorably to the protein targets. Thus, lignin-derived oak phenolics, although found in small concentrations, may contribute to the beneficial antioxidant, chemopreventive, and cardioprotective effects of red wine.

Keywords Antioxidant · Radical-scavenging · Density functional theory · Molecular docking · Coniferaldehyde · Guaiacylacetone · Sinapaldehyde · Syringaldehyde · Syringol · Syringylacetone · Vanillin

Introduction

The potential health benefits of red wine have been copiously reviewed (see, for example, [1–4]). Many of the health-related benefits of red wine have been attributed to polyphenolics such as gallic acid, catechin, epicatechin, and resveratrol [5–7]. It has been suggested that these compounds exert their beneficial effects by way of their antioxidant properties, which reduce free-radical formation and prevent oxidative damage of biologically relevant targets [8–10]. Resveratrol has exhibited cancer chemopreventive [11], cardioprotective [12, 13], and anti-inflammatory [14, 15] activities. A number of biochemical targets of resveratrol have been identified [16, 17], including estrogen receptor α (ERα) [18], histone deacetylase (HDAC) [19], cyclooxygenases 1 (COX-1) and 2 (COX-2) [11, 20–22], phosphoinositide 3-kinase (PI3K) [23], ornithine decarboxylase (ODC) [24], transthyretin (TTR) [25], lipoxygenase (LOX) [26], aromatase (CYP 19) [27, 28], inducible nitric oxide synthase (iNOS) [29], ribonucleotide reductase (RNR) [30], quinone reductase 2 (QR2) [31], c-Src tyrosine kinase (CSK) [32], protein kinase C (PKC) [32], leukotriene A4 hydrolase (LTA4H) [33], F_1-ATPase [34], and human cytosolic sulfotransferases (SULT) [35].

In addition to the polyphenolic compounds from grapes, aging red wine in oak barrels leads to the extraction of additional polyphenolic compounds into the wine that enhance the flavor and aroma [36–38]. In particular, toasted oak leads to a number of extractible guaiacyl and syringyl derivatives, including syringol (2,6-dimethoxyphenol), vanillin (4-hydroxy-3-methoxybenzaldehyde), guaiacylacetone [1-(4-hydroxy-3-methoxyphenyl)-2-propanone], syringaldehyde (4-hydroxy-3,5-dimethoxybenzaldehyde), coniferaldehyde (4-hydroxy-3-methoxycinnamaldehyde), syringylacetone [1-(4-hydroxy-3,5-dimethoxyphenyl)-2-propanone], and sinapaldehyde (3,5-dimethoxy-4-hydroxycinnamaldehyde) [39–41] (see Fig. 1). These lignin-derived materials have previously shown radical-scavenging and antioxidant activities [42–46]. This work presents a theoretical examination of the potential antioxidant and health-related benefits of oak-derived phenolics found in red wine.

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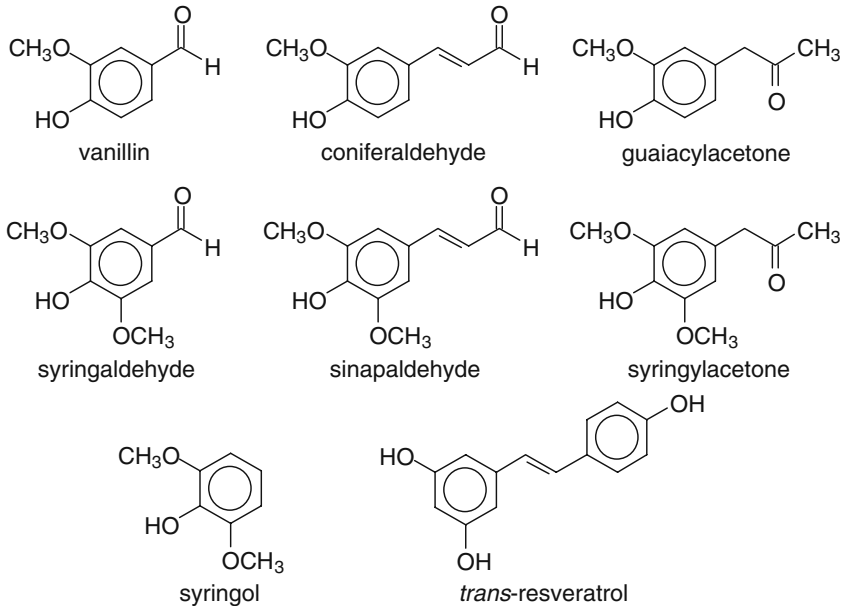

Fig. 1 Phenolic compounds discussed in this work

Computational methods

Bond dissociation enthalpies

All calculations were performed using the Spartan '08 program package [47]. In this study, bond dissociation energies for ArOH→ArO•+H• were calculated using the hybrid B3LPY functional [48, 49]. The 6-31+G* basis set [50] was used for geometry optimization. Single-point energy calculations and computation of harmonic vibrational frequencies using the 6-31+G* optimized geometries were performed with the 6-311++G** basis set for both parent molecules and their corresponding radicals in order to characterize all of their conformations as minima or saddle points and to evaluate the zero-point energy (ZPE) corrections. The total enthalpy at 298 K consisted of the thermal correction to the enthalpy and the B3LYP-calculated ZPE values.

Molecular docking analyses

Protein–ligand docking studies were carried out based on the crystal structures of estrogen receptor α (PDB: 1G50 [51], 3ERT [52], 2QSE [53]), histone deacetylase (PDB: 1T64 [54], 3MZ7 [55], 1W22 [56]), cyclooxygenase-1 (PDB: 1EQG and 1 EQH [57]), cyclooxygenase-2 (PDB: 3PGH and 4COX [58]), class 1A phosphoinositide 3-kinase (PDB: 2WXH, 2WXO, and 2WXR [59]), ornithine decarboxylase (PDB: 1D7K [60], 2ON3 [61]), transthyretin (PDB: 3KGU [62], 3IMT [63], 1DVS [64]), lipoxygenase-3 (PDB: 1JNQ [65]), aromatase (PDB: 3EQM [66]), inducible nitric oxide synthase (PDB: 3E67 and 3E7G [67], 3NQS [Rosenfeld RJ et al., to be published]), ribonucleotide reductase (PDB: 2WGH [Welin M et al., to be published]), quinone reductase 2 (PDB: 3G5M [68], 2QWX [69], 1SG0 [31]), c-Src tyrosine kinase (PDB: 3EN5 [70], 1BYG [71], 3F6X [72]), protein kinase Cα (PDB: 3IW4 [73]), leukotriene A4 hydrolase (PDB: 3FTS and 3FTU [33]), F_1-ATPase (PDB: 2JIZ and 2JJ1 [34]), and sulfotransferase SULT1B1 (PDB: 3CKL [Pan PW et al., to be published]). All solvent molecules and the co-crystallized ligands were removed from the structures. Molecular docking calculations for all compounds with each of the proteins were undertaken using Molegro Virtual Docker v.4.0 [74, 75], with a sphere large enough to accommodate the cavity centered on the binding sites of each protein structure in order to allow each ligand to search. Different orientations of the ligands were searched and ranked based on their energy scores. The RMSD threshold for multiple cluster poses was set at <1.00 Å. The docking algorithm was set at a maximum of 1500 iterations, a simplex evolution population size of 50, and a minimum of 30 runs for each ligand.

Results and discussion

In the radical scavenging mechanism for phenolic compounds, a hydrogen atom is abstracted from the phenolic hydroxyl group to the free radical [76–78]. The thermodynamic favorability of this hydrogen abstraction depends on the phenolic bond dissociation energy. That is, a weak O–H bond would lead to a higher antioxidant activity. The bond dissociation enthalpies for the lignin-derived wood phenolic compounds coniferaldehyde, guaiacylacetone, sinapaldehyde, syringaldehyde, syringol, syringylacetone, and vanil-

Table 1 DFT bond dissociation enthalpies (kcal mol^{-1}) at the B3LYP/6-311++G**//6-31+G* level

Compound	BDE (kcal/mol)	Reference
Coniferaldehyde	79.2	This work
Guaiacylacetone	80.5	This work
Sinapaldehyde	75.5	This work
Syringaldehyde	76.8	This work
Syringol	75.4	This work
Syringylacetone	75.5	This work
Vanillin	83.0	This work
Phenol	83.9	[76]
Daidzein (isoflavonoid)	81.2	[78]
Genistein (isoflavonoid)	81.1	[78]
Biochanin A (isoflavonoid)	87.8	[78]
Formononetin (isoflavonoid)	85.5	[78]
Maritimetin (aurone)	75.0	[79]
Catechin (flavonoid)	74.2	[77]
Trans-resveratrol	78.7	[80]

lin (Fig. 1) have been calculated using density functional theory at the B3LYP/6-311++G**//6-31+G* level in order to provide insight into the potential radical scavenging antioxidant activities of these materials. Analogous calculations at this level have shown good correlation between experimental antioxidant activities and calculated bond dissociation enthalpies for polyphenolic compounds [79], including flavonoids [80, 81], aurones [82], and resveratrol [83]. Bond dissociation enthalpies for guaiacyl (4-hydroxy-3-methoxyphenyl) derivatives are found to be higher by 4–6 kcal mol^{-1} than their syringyl (4-hydroxy-3,5-dimethoxyphenyl) analogs. Thavasi and coworkers [79] had noted a similar result upon comparing 1,2,3-trihydroxyphenyl and 1,2-dihydroxyphenyl compounds; more ortho –OH groups decreased the BDEs. A comparison of calculated bond dissociation enthalpies with those calculated for other phenolic compounds (Table 1) reveals that sinapaldehyde, syringol, and syringylacetone are comparable in their radical scavenging abilities to the flavonoid catechin and the aurone maritemetin, and slightly better than *trans*-resveratrol or the isoflavonoids daidzein and genistein. The experimental antioxidant activities of some lignin-derived phenolics have been examined previously [42–46]. The experimental results are consistent with the computational results in this present work. That is, syringyl derivatives generally show better antiradical and antioxidant activities than guaiacyl derivatives.

In addition to radical scavenging abilities, the wood phenolics were also examined for potential binding to the resveratrol biochemical targets estrogen receptor α (ERα), histone deacetylase (HDAC), cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), phosphoinositide 3-kinase (PI3K), ornithine decarboxylase (ODC), transthyretin (TTR), lipoxygenase (LOX), aromatase (CYP 19), inducible nitric oxide synthase (iNOS), ribonucleotide reductase (RNR), quinone reductase 2 (QR2), c-Src tyrosine kinase (CSK), protein kinase C (PKC), leukotriene A4 hydrolase (LTA4H), F_1-ATPase, and human cytosolic sulfotransferases (SULT), using a molecular docking (Molegro) approach. The average docking energies for the oak phenolics, along with resveratrol, to each of the protein targets are compiled in Table 2.

Table 2 Average docking energies (kcal/mol) of oak phenolic compounds to resveratrol protein targets

Protein target	Coniferaldehyde	Guaiacylacetone	Sinapaldehyde	Syringaldehyde	Syringol	Syringylacetone	Vanillin	Resveratrol
ERα	−16.3	−15.4	−16.8	−14.7	−13.3	−16.5	−14.0	−19.2
HDAC	−19.0	−18.5	−20.2	−17.6	−14.9	−20.1	−15.8	−23.0
COX-1	−18.4	−17.7	−18.0	−17.2	−14.8	−18.1	−15.6	−20.1
COX-2	−18.2	−18.4	−19.4	−18.2	−15.4	−18.9	−15.9	−21.6
1A PI3K	−17.9	−15.9	−18.3	−15.6	−13.7	−17.3	−13.4	−20.3
ODC	−18.8	−17.7	−20.5	−18.1	−15.0	−19.6	−16.0	−21.3
TTR	−13.3	−12.9	−13.4	−13.0	−12.1	−12.6	−12.2	−13.8
LOX-3	−18.4	−17.5	−19.0	−16.6	−16.1	−18.6	−15.7	−21.5
CYP 19	−18.7	−17.7	−18.0	no dock	−12.3	−16.8	−14.8	−21.7
iNOS	−19.1	−19.3	−18.8	−15.0	−16.0	−17.4	−16.9	−23.4
RNR	−19.6	−19.8	−21.4	−19.3	−16.1	−21.8	−17.1	−22.7
QR2	−19.2	−19.0	−20.3	−18.2	−16.1	−20.4	−16.7	−24.9
CSK	−16.4	−15.3	−17.7	−15.8	−13.9	−16.4	−14.4	−19.2
PKCa	−17.1	−16.0	−18.1	−14.9	−12.5	−16.4	−13.6	−19.7
LTA4H	−21.3	−20.1	−21.7	−19.2	−16.4	−21.7	−17.3	−25.3
F1-ATPase	−19.9	−18.6	−20.9	−17.7	−15.3	−19.6	−16.7	−23.1
SULT1B1	−19.2	−18.8	−18.4	−16.7	−14.6	−18.7	−16.2	−20.9

The Molegro docking analysis reveals that none of the oak phenolic compounds bind to any of the protein targets as well as resveratrol. Nevertheless, all of the oak phenolics examined do bind to the protein targets, with the exception of syringaldehyde with aromatase, which had a positive docking energy. Additionally, sinapaldehyde binds to ornithine decarboxylase and transthyretin with only slightly higher docking energies (0.8 and 0.4 kcal mol^{-1}, respectively) than resveratrol, and syringylacetone had a docking energy that was 0.9 kcal mol^{-1} higher than resveratrol with ribonucleotide reductase. Interestingly, except for coniferaldehyde, all of the compounds examined, including resveratrol, had stronger binding energies to COX-2 than to COX-1. Syringaldehyde has been shown to be a moderate COX-2 inhibitor [84]. The protein target most strongly docked by the oak phenolics was LTA4H.

Summary and conclusions

DFT calculations (B3LYP/6-311++G**) calculations suggest that oak-derived phenolic compounds have radical-scavenging abilities. Sinapaldehyde, syringaldehyde, syringol, and syringylacetone all have bond dissociation energies that are lower than resveratrol and comparable to the flavonoid catechin. Molecular docking studies of the oak phenolics with known resveratrol protein targets also show that these compounds dock favorably to the protein targets. The inhibition of enzymes such as COX, LOX, ODC, PKC, PI3K, iNOS, HDACs, RNR, LTA4H, or aromatase could serve to inhibit the development/progression of tumor cells [30, 85–89]. Additionally, inhibition of COX-1, COX-2, LOX, or iNOS could lead to enhanced anti-inflammatory effects [90, 91], while the inhibition of ATPase or HDACs may play a role in cardioprotective benefits [34, 92]. Based on the theoretical studies in this work, lignin-derived oak phenolics in red wine, although found in small concentrations, are expected to contribute to the beneficial radical scavenging and antioxidant activity as well as contribute to chemopreventive and cardioprotective effects through interaction with protein targets comparable to resveratrol.

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