

# What properties of *trans*-resveratrol are so unique from its *cis*-isomer?

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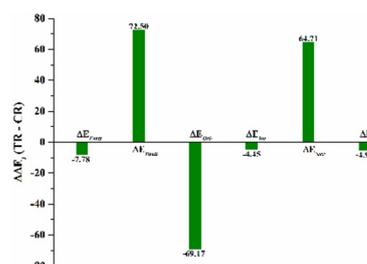
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**Synopsis:** *Trans*-resveratrol (RvL), an important red-wine/tomato molecule, is primarily associated with health benefit such as cancer chemopreventive rather than its *cis* form. The differences between the isomers i.e. properties and functionality are governed by their structures. In the present density function theory (DFT) study, through bond and through space intermolecular interactions were found to be responsible for the difference in the *trans*-RvL and *cis*-RvL, respectively. The non-planar *cis*-RvL favours a more flexible system with steric interaction in comparison to its *trans*-RvL, which is more rigid and less flexible, thus allowing little room for point mutation for *trans*-RvL and making it more viable towards health benefit.

Resveratrol (RvL), a polyphenolic compound, is a key ingredient in wine and tomatoes [1] that has been studied over years because of its important bioactivities such as anti-oxidant, anti-aging and antimicrobial properties. Out of the two geometric isomeric forms of resveratrol i.e. *trans* and *cis*, the health benefit is primarily associated with the *trans* form. The present study reveals the structural reasons behind such the phenomena.

It is discovered that the structure of *trans*-RvL, although it is C<sub>1</sub> non-planar, the backbone non-H atoms are nearly planar; whereas the *cis*-RvL is twisted with two major planes consist of two phenol rings, R1 and R2. The absence of planarity gives rise to additional H-bonds in *cis*-RvL. Rotations of the C-C single bonds between the stilbene bond and phenol rings in *trans*-RvL produces higher energy barriers as it needs to break the conjugated structure; while such rotation in *cis*-RvL produces multiple minima and maxima depending on the positions of the rings. The calculated FT-IR spectrum shows very different spectral features for *trans* and *cis*-RvL in the region 900 – 1500 cm<sup>-1</sup>, where the spectral peaks at 1138-1158 cm<sup>-1</sup> are split in *cis*-RvL compared to a single peak at 1165 cm<sup>-1</sup> in *trans*-RvL. In the Raman spectra, there is significant enhancement of *cis*-RvL in the region above 3000 cm<sup>-1</sup>. Further, the carbon chemical environment (<sup>13</sup>C NMR) of the RvL isomers exhibit a larger chemical shift for *cis*-RvL compared to *trans*-RvL ( $\Delta\delta = 8.5$  ppm) for some carbon atoms, such as C<sub>(11)</sub>, indicating that the chemical environment of the Cs in *cis*-RvL is not similar. The energy gaps between

highest occupied molecular orbital (HOMO) and the lowest occupied molecular orbital (LUMO) is 3.96 eV for *trans* and 4.37 eV for *cis*-RvL, also revealing their different electronic structures.



**Figure 1.** Excess energies of the decomposed energy of *trans*-RvL and *cis*-RvL.

A more detailed inspection using the recently developed excess orbital energy spectrum (EOES) revealed that most of the orbitals suffering large energy changes are from the outer valence shell. They are 60a (HOMO), 55a, 46a and 34a and 35a. The theoretical momentum distributions (TMDs) of the orbitals are further studied to further understand their bonding. Finally, EDA (see Figure 1) highlights the interaction energy ( $\Delta E_{int}$ ) of the phenolic compound, where *trans* is preferred over the *cis*-RvL ( $\Delta\Delta E_i = -4.45$  kcal.mol<sup>-1</sup>) isomer. Thus, these quantum mechanics results could help in unwinding the diversified beneficial activities associated with *trans*-resveratrol.

## References

1. Zhang, Y. *et al.* 2015 *Nat. Commun.* 6, 8635

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