Many drugs have mirror image chemical structures: While one may be helpful, the other may be harmful

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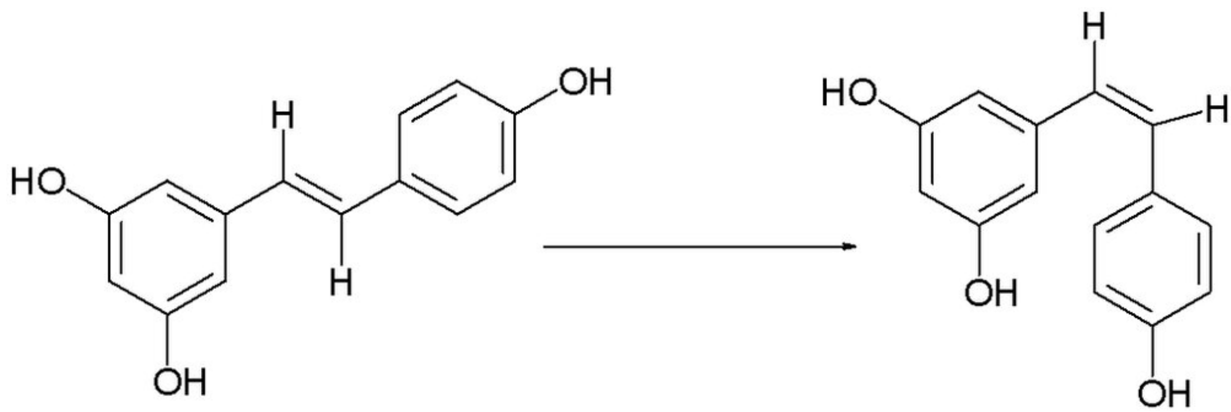

At low concentrations, the trans form of resveratrol, left, can switch to the cis form, right. Credit: V8rik/Wikimedia Commons, CC BY-SA

The effects a drug or chemical compound have on the body depend on how its atoms are arranged in space. Some compounds have a dark twin with the same molecular formula but different 3D structure—and this can have consequences for what they do or don't do in the body.

Consider the tragic story of thalidomide, a morning sickness drug that caused thousands of birth defects and miscarriages. While one form, or isomer, of thalidomide has a sedative effect, the other is thought to cause abnormal physiological development. Because the two versions can convert back and forth in the body, it's dangerous to take either form of thalidomide while pregnant.

My research has focused on one such compound found in red grapes and peanuts, resveratrol. It has been a scientific mystery why clinical trials on using resveratrol to treat Alzheimer's disease have had inconsistent results. Turns out, it may be because two different forms were used —while one may help with cognition and memory, the other may be toxic to the nervous system.

Isomers and amino acids

Many drugs have the same atoms and bonds but are arranged differently in space. These drugs are called chiral compounds—meaning they exist as two nonsuperimposable mirror images. For example, your hands are also nonsuperimposable mirror images of each other. Although they look the same, they don't overlap when you put one on top of the other.

Usually these mirror-image versions have very similar properties because they share the same elements and bonds. But the way they are arranged in space can drastically change the effects they have in the body. Just as you wouldn't be able to fit a left-handed glove on your right hand, a left-handed version of a drug wouldn't be able to fit into a target in the body shaped to fit a right-handed molecule.

Chiral molecules come in two versions, or isomers, defined by their optical activity. This means that if you shine polarized light on a chiral molecule, one will rotate the light to the left (indicated by the prefix L-, or levorotatory) while the other will rotate it to the right (indicated by the prefix D, or dextrorotatory).

Amino acids, the building blocks of proteins, are chiral molecules. Living organisms primarily make proteins from amino acids with L configurations. The D configuration, however, has many other functions in nature. Bacteria, for example, use D configuration amino acids to make their cell walls. Mammals use D configuration amino acids as messengers in their nervous and endocrine systems.

The amino acid tyrosine is one important exception to the L configuration rule. Unlike other amino acids, both the L and D configurations of tyrosine can be activated for protein synthesis by an enzyme called tyrosyl-tRNA synthetase (TyrRS).

The presence of D-tyrosine can make it difficult for cells to synthesize proteins that only use L-tyrosine. However, cells have evolved enzymes that can discriminate between both versions and ensure that only L-tyrosine is used. When tyrosine-consuming enzymes are absent, the resulting increased levels of tyrosine in the body can have toxic effects, including damage to the nervous system.

Recently published work from my lab suggests a potential reason why too much tyrosine can be neurotoxic. When we added increasing amounts of L-tyrosine to rat brain cells in a petri dish, we found that it decreased levels of TyrRS, the enzyme that activates tyrosine to make proteins without causing damage to the body. Surprisingly, adding D-tyrosine not only caused TyrRS levels to drop, but also killed the neurons.

When we looked at the brains of Alzheimer's patients who show increased tyrosine levels, we also found that TyrRS enzyme levels are depleted. Our hypothesis is that as tyrosine levels in the brain increase, TyrRS enzyme levels drop and cause damaging effects on the brains of those with Alzheimer's. These findings indicate the potentially important role TyrRS may play in the synthesis of proteins essential for cognition and memory.

Grapes, peanuts and Alzheimer's

These findings have implications for studies on resveratrol, a compound found in red wine that researchers have been examining for potential health benefits. While some clinical trials found that resveratrol can improve cognitive function in people with Alzheimer's disease, others found it had the opposite effect and made the disease more severe. Why resveratrol can have such varying effects has remained a scientific enigma.

Resveratrol comes in two forms, cis-resveratrol and trans-resveratrol. The "cis-" and "trans-" prefixes, much like L- and D-, describe how the same atoms in two isomers are arranged differently in space.

My colleagues and I found that because the two forms of resveratrol bind to TyrRS in different ways, they can result in opposite effects in neurons. While cis-resveratrol was able to increase TyrRS levels in rat neurons in a petri dish, high concentrations of trans-resveratrol depleted TyrRS and caused neural damage. However, low concentrations of trans-resveratrol can convert into cis-resveratrol in the body. This result leads to an increase in TyrRS levels and its associated benefits.

We hypothesize that many clinical trials on resveratrol failed because none tested cis-resveratrol alone. We believe that this may also explain why trials that used high doses of trans-resveratrol saw harmful effects, while trials that used low doses of trans-resveratrol that were then converted into cis-resveratrol in the body saw beneficial effects.

Beyond the individual atoms and bonds of molecules, the body also cares about how they're arranged in space. Paying attention to the different forms a drug takes could help lead to more effective treatments.