## **Therapeutic Fragrances?**

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## The intersection of perfumery and pharmacology could have implications for the treatment of Alzheimer's disease and cancer.

Many of you have probably read a recent news item about a possible new treatment for Alzheimer's disease. A study was published in Science (Cramer et al, 2012) that reports the cancer drug bexarotene rapidly clears  $\beta$ -amyloid from a strain of mice that develop Alzheimer's disease at an early age. The investigators found that bexarotene treatment cleared more than 50% of the  $\beta$ -amyloid plaque from these animals within 72 hours.

This is of course an exciting discovery. But you may well ask, what does this have to do with the subject of fragrances and perfumes? Well, there is an interesting relationship. First, let me tell you a little more about bexarotene. Bexarotene is a retinoid agonist that is selective for retinoid X receptors (RXRs). Compounds of this class are called rexinoids. Rexinoids can activate retinoid regulated genes that control cellular differentiation and proliferation. By the way, the endogenous agonist of RXR is 9-cis-retinoic acid - a metabolite of vitamin A. The activated RXRs in neurons increase production of apolipoprotein E that helps break down  $\beta$ -amyloid. Cramer et al concluded that since bexarotene is an RXR agonist, other rexinoids may be therapeutic in the treatment of Alzheimer's disease. Rexinoids also have beneficial actions in animal models of type 2 diabetes, atherosclerosis, Parkinson's disease and obesity (Friling et al, 2009; Kotani et al, 2012).



I looked at the structure of bexarotene and thought "that's interesting, it looks a little like a rose ketone." Rose ketones are fragrance compounds found in essential oil of roses, such as ionones, damascones and damascenones. These compounds are produced by the breakdown of carotenoids and are present in a variety of foods and flowers such as ginger, grapes, roses and violets. It makes sense that bexarotene would share some structural similarity to the rose ketones because they and 9-cis-retinoic acid are all derived from

carotenoids. So the question is: are any of the rose ketones possibly RXR agonists? It turns out that one very significant rose ketone may indeed be a rexinoid:  $\beta$ -ionone (Liu, et al, 2008). And like bexarotene,  $\beta$ -ionone also happens to inhibit tumor growth and induce apoptosis (programmed cell death) in cancer cells (Janakiram et al, 2008).

In addition to these actions,  $\beta$ -ionone is also an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) which is the rate-limiting enzyme responsible for production of cholesterol in the liver (Yu et al, 1994). Statin drugs such as lovastatin lower cholesterol by inhibiting this enzyme. In addition to  $\beta$ -ionone several isoprenoid fragrance compounds also modestly inhibit HMG-CoA reductase, such as d-limonene and geraniol (Elson, 1995). d-limonene is found in citrus fruits and has an intense odor of oranges. Geraniol is a major constituent of rose and ylang-ylang oil with a strong rose-like odor. Yu et al (1995) tested  $\beta$ -ionone in an animal tumor model and found it was an effective anticarcinogenic agent. These data support the idea that  $\beta$ -ionone may have a chemoprotective effect against cardiovascular disease and certain forms of cancer (Elson, 1995).

But the main point is that  $\beta$ -ionone, one of the fragrance components of violet flowers, may turn out to have pharmaceutical properties that could be therapeutic for treatment of Alzheimer's disease, not to mention cancer. Whether it fulfills this promise will depend on further investigation. In the meantime, please enjoy fresh roses, violets or add a bit of ginger to your tea.

## References

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