by Roger Clemens

Raspberry Ketone Weight Loss Hype Not Substantiated

Raspberry ketone (RK) is an aromatic, phenolic compound [4-(4-hydroxyphenyl) butan-2-one] that imparts scent and flavor to raspberries and to some lesser degree in blackberries, cranberries, and kiwis. It has also been used in cosmetics, soaps, candies, and processed foods and beverages as a flavorant, and as a scenting agent in perfume (Guichard 1982).

Extraction of this compound is inefficient and expensive (Beekwilder et al. 2007), so it is more commonly synthesized in an industrial process from chemical intermediates (Tateiwa et al. 1994). The Beekwilder report has the cost of extracting 1 kilogram (~2.2 lb) of the natural compound from raspberries at $20,000. Recently, RK appears to have surged in popularity as a weight loss supplement. Internet sites are replete with advertisements and declarations of efficacy, safety, and purity.

Let's take a closer look at RK and consider a critical evaluation of the evidence: The molecular structure of RK is likened to two biosimilar compounds: synephrine, a catecholamine similar to epinephrine (the butanone-substituted phenyl group replaces the ethylamine group of synephrine), and capsaicin (which shares para-substituted phenolic and ketone functional groups) (Park 2010). These similar compounds have been studied in some detail, and there are a few frequently cited papers (i.e., Morimoto et al. 2005) that make inferences about the "anti-obese action" of RK, in part on the basis of their similarity in structure. Moreover, the same report relied upon rodent studies using small numbers of animals and exaggerated doses of industrially produced RK. The principal outcome measure was prevention of weight gain, not treatment of pre-existing obesity, which, of course, under U.S. law classifies RK as a drug.

The sole clinical study that reported weight loss in human subjects used a mixture of compounds including RK, capsaicin, synephrine, caffeine, garlic, and ginger (Lopez et al. 2013). The principal confound or threat to validity lies in the inability to attribute the observed effect to a single variable.

Another *in vitro* study by Park (2010) suggested RK, when administered via a 10 mM concentration, an arguably high dose, stimulated lipolysis in fat cells, and still another *in vitro* study by the same investigator reported increased activation of genes associated with lipolysis (Park 2015).

A single notable study looked at topical application of RK on dermal production of insulin-like growth factor-I in mice and on hair growth and skin elasticity proxies in a small number of human subjects (Harada et al. 2007). Observations suggested that RK might increase dermal IGF-I production.

Finally, two studies in the midwifery literature (Parsons et al. 1999, Parsons et al. 2000) suggest that labor is shortened by intake of raspberry leaf tea, but neither potential mechanism of action nor safety assessment is explored.

In summary, there is no strong human evidence for the purported health effects of raspberry ketone, particularly with respect to weight management. Again, the studies on rats in the adiposity research have used an apparently arbitrary and exaggerated dosage range of 0.545–2.18 g/kg, which proportionately correlates to a human estimated dose of 80–340 mg/kg. This means that doses for a 150 lb human would vary between 870–3,700 mg daily, 1,100–5,000 mg for a 200 lb human, and 1,500–6,200 mg for a 250 lb human.

If we accept the convention that the no observed adverse effect level for a human being is 100 and adjust the above doses accordingly, the doses still are wildly in excess of the estimated dietary intake for a human being. The FDA first categorized raspberry ketone as a "Generally Recognized as Safe" (GRAS) food additive in the 1960s. Recall, though, that GRAS status is given under the assumption that humans will consume less than 2.0 mg of a standard compound reliably identified as RK, per day. And, in fact, the estimated dietary intake for a human being is 0.42 mg/kg bw (Gaunt et al. 1970).

Despite the fact that there are no studies of efficacy, bioavailability, or toxicity in humans, extracted and commercially synthesized raspberry ketone is widely marketed and sold via the Internet as a "safe and effective" weight loss supplement at a typical recommended daily dose of 1,000 mg (250–500 mg per capsules). For some over-the-counter products, even doses greater than 1,200 mg daily are "recommended" and may be mixed with a multitude of other ingredients such as green tea extracts, açai fruit, and African mango (for which bioavailability and interaction effects with other ingredients, the food matrix, or drugs are not known).

The public health implications of the commercial landscape become even more disturbing when the advertising copy and labels are scrutinized: The legal disclaimer on a typical label states, "Actual product packaging and materials may contain more and different information than what is shown on our website. We recommend that you do not rely solely on the information presented." And the safety information caption reads as

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follows: "This is not a treatment, cure, or remedy for a disease"…. Contrast this phrasing with the indications caption that makes the following assertion: "Our product was developed for those looking to experience all of the incredible health benefits of a Raspberry Ketone supplement (as promoted on numerous health expert programs) without the side effects. In fact, there is limited evidence of safety from a short-term, 8-week study (Lopez et al. 2013). If you're looking to reduce your appetite, eat less, lose weight, and feel better...our powerful formula was created specifically for you." These messages are contradictory and without foundation, obfuscating, and unsupported by any well-designed clinical studies of safety or efficacy.

The Natural Medicines Comprehensive Database of the U.S. Dept. of Defense Human Performance Resource Center (http://hprc-online.org/dietary-supplements/nmcd) deems the weight loss evidence on raspberry ketone as "insufficient." Ulbricht et al. (2013) performed a systematic review of the literature and concluded that "reliable research is lacking" for any health-promoting benefit of RK in human subjects.

In conclusion, there are, at best, limited data in support either of efficacy, and more importantly, safety for RK as a nutritional supplement for humans. While the potential for health benefits may well exist, widespread marketing and distribution is unjustified until requisite data are developed and validated. Moreover, concentrating individual components that occur in foods may well take these substances out of the realm of nutrition and into that of pharmacology. And that, of course, absolutely requires a comprehensive regulatory process in support of public health. **FT**

References cited are available via hyperlinks in the digital version of this column.

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