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Further research on the biological activities and the safety of raspberry ketone is needed

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Raspberry ketone supplements have grabbed consumer attention with the possibility that they might help burn fat and aid weight loss. While raspberry ketone occurs naturally, and is found in raspberry fruit, most is synthetically produced for use in commercial products as flavorings, fragrances, or dietary supplements. Currently, the amount of raspberry ketone in dietary supplements (currently sold in the US) is well above the maximum concentration recommended for food and fragrance products, so additional toxicology work is needed to ensure that such concentrations of raspberry ketone are safe. In addition to safety data, clinical studies are also needed to validate any health benefits. Without research on the effects of consuming high concentrations of raspberry ketone, consumers should be wary of unsubstantiated claims and mindful of potential harm to their health.

1. Introduction

Until recently, raspberry ketone (also known as 4-(*p*-hydroxyphenyl)butan-2-one, 4-(*p*-hydroxyphenyl)-2-butanone, 4-(4′-hydroxyphenyl)-2-butanone, *p*-hydroxybenzyl acetone, and frambinone; Fig. 1) had mostly been an ingredient for the flavor and fragrance industry [1]. That changed in 2012 after claims of it having anti-obesity activity were made in US media [2], once again bringing the prospect of a miracle pill that will keep you slim. From North America to East Asia, popular US TV programs sway consumer purchasing with features on dietary products that suggest that consumption of their supplements offers improved health benefits [2]. Unfortunately for the widespread viewing audiences, the desire to overcome disease or just to lose weight makes it easy for them to believe in exaggerated health claims and seek out the next miracle pill/drug [2]. Dietary supplements containing raspberry ketone are one of the latest products in this optimistic spotlight.

Raspberry ketone is a volatile phenolic compound (Fig. 1) and only one component of the complex mixture of raspberry fruit volatiles (esters, aldehydes, alcohols, terpenes, terpenoids, ketones, pyrazines, etc.) that together make what we associate as natural raspberry fruit aroma [3–14]. The amount and types of raspberry volatiles found in the fruit may change between harvest and final commercial products with processing conditions, storage environment, or time. [6,7,15]. For example, one study reported raspberry volatile concentrations to have been unchanged after a one-year of frozen storage (eight compounds monitored) [6], while another [7] saw changes immediately after deep-freezing of samples (75 compounds monitored), although these two studies examined different collections of volatiles.

Raspberry ketone was discovered in 1903, and its chemical structure was first identified in 1951 from raspberries [16]. Within the raspberry plant it is biosynthesized via the phenylpropanoid pathway, like other phenolic compounds [13,17]. Pure raspberry ketone is a powder of translucent white, short needle-shaped crystals, and considered the main constituent of raspberry aroma [1]. It has a low human odor threshold of 0.001 to 0.1 mg/kg [10], and been described as having a "raspberry", "sweet", "perfume", "woody", and "hot tea" aroma and taste [8,9,15], although others report it having a slightly different smell from natural ripe raspberry fruit [18]. Raspberry fruit volatiles and their sensory perceptions were recently well reviewed previously [19].

There are numerous species of raspberries [20], but when raspberry ketone is typically mentioned in popular media (or the literature) it's in reference to red raspberry (*Rubus idaeus* L.), and for clarification, unless indicated otherwise, all raspberry mentioned in this review refers to red raspberry. The objective of this review was to summarize past scientific findings to educate researchers, medical professionals, and consumers regarding raspberry ketone.

2. Raspberry ketone concentrations and role in nature

Natural raspberry ketone has been found to range from 0.001 to 4.2 mg/kg in raspberry juices and pulps, from wild genotypes and a

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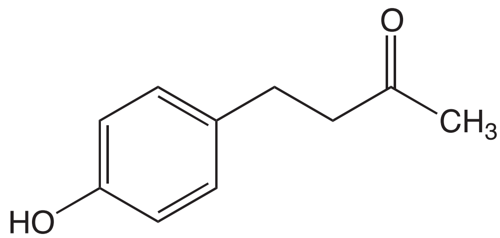

Fig. 1. Structure of raspberry ketone (volatile phenolic compound), which is also known as 4-(*p*-hydroxyphenyl)butan-2-one, 4-(*p*-hydroxyphenyl)-2-butanone, 4-(4′-hydroxyphenyl)-2-butanone, *p*-hydroxybenzyl acetone, and frambinone.

variety of cultivars (Table 1) [4,7,9,10,13]. The variations in concentrations reported have been directly attributed to fruit being wild collected versus cultivated, cultivar differences, genotypes, environments, or growing seasons, and indirectly due to sample forms, sample preparation prior to analyses, and analytical methods used [4,7,13,14,19].

Although raspberry ketone's exact role within the plant is yet to be determined, it is thought to be an insect kairomone or synomone [21,22], and has been used as an ingredient in insect baits [23,24]. General information about possible roles of plant volatiles has been well reviewed [25,26]. Raspberry ketone also has some antifungal capacity as well [1,27].

3. Raspberry ketone sources

Raspberry ketone is not unique to raspberries and has been found in baby kiwi (*Actinidia arguta* Planch. ex Miq.) [28], brewed coffee [29,30], yew (*Taxus baccata* L.) [31,32], and orchid flowers (floral lip part; *Bulbophyllum apertum*) [21] with concentrations ranging from 0.00081 to 4.2 mg/kg (Table 1). European cranberry (*Vaccinium oxycoccus* L.) and lingonberry (*V. vitis-idaea* L.; also known as cowberry) have been reported to contain raspberry ketone as well, although Honkanen et al. [7] cited unpublished work. Raspberry ketone is not as volatile as other groups of volatile compounds, and this may partially explain why some researchers have either reported low recovery, or not detected, when using a single sample preparation method for all volatiles of interest [8,11].

Confusingly to some consumers, perhaps due to its common chemical name including the term raspberry, this compound might be perceived as being of a natural purified origin. Though, for the quantity of raspberry flavorings needed for commercial production of food, fragrances, and cosmetics, volatiles like raspberry ketone have to be manufactured [18,33]. As very little raspberry ketone can be isolated from natural sources due to its low concentration concentrations (Table 1), for its use in the majority of products it is synthesized, either chemically [34], by tissue culture [18,35,51], or by biotransformation/bioconversion (chemically or enzymatically) [17,34,36,37]. The history of how raspberry ketone became synthetically produced in sufficient amounts to supply the baking, cosmetic, and beverage industries was well summarized previously [18,33,34].

Raspberry ketone has held GRAS (Generally Recognized as Safe; 21CFR172.515) status since 1965 [1] as an ingredient for use in a food, drug, or cosmetic and is listed under synthetic flavoring substances with the instruction to use minimum quantity that produces intended effect. According to Code of Federal Regulations (21CFR101.22) definitions, "natural flavor/flavoring" compounds have to be extracted from a plant or substance listed in 21CFR172.510. So, by that definition most (or all) commercially available raspberry ketone would not be considered natural, but rather a synthetic flavoring (21CFR172.515) [38]. The European legal definition for "natural" flavoring is even stricter than that of the US [39] regarding manufacturing process to obtain flavoring compounds. A stable isotope ratio comparison technique for identifying the authenticity of (natural versus synthesized) raspberry aromas like α-ionone, β-ionone, and α-ionol has been demonstrated, but its ability to distinguish natural raspberry ketone from synthetic has not been shown yet [39].

Table 1
Raspberry ketone concentration ranges in mg/kg of natural source material reported in the literature.

Source	Concentration (mg/kg) n = sample size	References
Raspberry fruit (*Rubus idaeus* L.)	0.001–4.2 n = 359	Borejsza-Wysocki et al., 1992; Honkanen et al., 1980; Larsen & Poll, 1990; Larsen et al., 1991; Paterson et al., 2013
Baby kiwi (*Actinidia arguta* Planch. ex Miq.)	0.00081 n = 1	Garcia et al., 2011
Orchid flower lip (*Bulbophyllum apertum*)	0.7 n = 1	Keng-Hong & Nishida, 2005
Freshly brewed coffee (*Coffea arabica* L.)	0.00119–0.00163 n = 9	Akiyama et al., 2008

4. Possible health benefits versus harmfulness

Scientific research of any health benefit from consuming raspberry ketone is in its infancy. Morimoto et al. [40] evaluated raspberry ketone effects on mice fed a high fat diet for 5 weeks, then subsequently a high fat diet with a control or with the addition of 0.5, 1.0, or 2.0% raspberry ketone (500, 1,000, or 2,000 mg/kg) for an additional 5 weeks. Mice fed 1.0 and 2.0% raspberry ketone did not show weight gain when measured for indication of anti-obesity activity. Liver protective effects from raspberry ketone in rats fed a high fat diet [41], and potential antiandrogenic activities on human breast cancer cells [42] have also been shown. While Outlaw et al. [43] demonstrated increased resting energy expenditure in eight human subjects after raspberry ketone ingestion (unknown/unreported amount), though their tested product was a mixture also containing yerba mate, green tea, and ginseng, so their results can't be attributed to raspberry ketone alone. Unfortunately, even showing that positive effects occur in mice, rats, or human cell models does not establish a potential benefit to humans. It is clear that additional work is needed to understand if raspberry ketone is likely to offer any health advantages. The importance of evidence based health claim research has been well summarized [44].

Raspberry ketone LD50 (lethal dose, 50%), taken orally, was 1.3 g/kg for male rats and 1.4 g/kg for female rats [1,45]. There were no effects on body weight changes when rats were fed <0.4% for 13 weeks [45]. Gaunt et al. [45] estimated the safe intake of raspberry ketone for humans to be 0.42 mg/kg/day, but saw no toxicity up to 100 mg/person/day, and calculated human daily intake of it from food to be less than 25 mg/person/day.

For this review, random examples of raspberry ketone supplements were purchased. The information printed on bottle labels suggested consuming much more than what has been studied in humans. One manufacturer recommended taking 300 mg twice a day (total 600 mg), while the other proposed one 500 mg capsule daily, with neither label describing such dosage in relation to the GRAS advised minimum level of raspberry ketone that achieves raspberry flavor and aroma. As pointed out in European Union by Bredsdorff et al. [46], there is real toxicological concern with the amount of raspberry ketone that (US) dietary supplements advertise will aid weight loss. Additionally, the intake of raspberry ketone at supplement levels also means consumers experience elevated exposure to manufacturing by-products from the synthesis or extraction of target compounds (residual processing chemicals, etc.), and this has not been studied either.

Since dietary supplements sold in the US are not regulated like food or drugs, they are labeled with the warning that the Food and Drug Administration (FDA) have not evaluated manufacturer's claims. In 2009