Short communication

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An amphetamine isomer whose efficacy and safety in humans has never been studied, β-methylphenylethylamine (BMPEA), is found in multiple dietary supplements

Pieter A. Cohen,[a,d]* Clayton Bloszies,[b] Caleb Yee[c] and Roy Gerona[c]

The amphetamine isomer β-methylphenylethylamine (BMPEA) was first synthesized in the early 1930s, but its efficacy and safety in humans has not been studied. Recently, the United States Food and Drug Administration (FDA) detected BMPEA in dietary supplements labelled as containing *Acacia rigidula*. Over a year after the FDA reported its findings, we analyzed *Acacia rigidula* dietary supplements to determine if BMPEA had been removed. Supplements were analyzed using liquid chromatography-quadrupole time-of-flight mass spectrometry. Diluted methanolic extract from each supplement was run three times and each data set obtained was analyzed using Agilent MassHunter Qualitative Analysis. The presence of BMPEA was confirmed by accurate mass, retention time and mass spectra match against a reference standard. Quantification of BMPEA was determined using an eight-point calibration curve of spiked standard to a matrix blank. Twenty-one brands of *Acacia rigidula* supplements were analyzed. More than half (11/21; 52.4%) of the *Acacia rigidula* supplement brands contained BMPEA. The stimulant was present at quantities such that consumers following recommended maximum daily servings would consume a maximum of 93.7 mg of BMPEA per day. Consumers of *Acacia rigidula* supplements may be exposed to pharmacological dosages of an amphetamine isomer that lacks evidence of safety in humans. The FDA should immediately warn consumers about BMPEA and take aggressive enforcement action to eliminate BMPEA in dietary supplements.

Keywords: dietary supplements; amphetamine isomer; US Food and Drug Administration

Introduction

In the United States (USA), the US Food and Drug Administration (FDA) is tasked with identifying and removing mislabelled, adulterated, and dangerous dietary supplements from the marketplace.[1] The extent to which the FDA is enforcing the law is not known.

Some of the most dangerous supplements currently sold are those that contain synthetic stimulants lacking evidence of safety in humans.[2–5] Recently, supplements have been found to contain analogues of amphetamine, methamphetamine and 1,3-dimethylamylamine (DMAA).[6–9] The only known source of these stimulants is chemical synthesis; however, they are often sold as if they were botanical extracts. For example, an analogue of methamphetamine, *N*,α-diethylphenylethylamine (DEPEA), was labelled as if it were an extract of dendrobium orchid, and 1,3-dimethylbutylamine (DMBA) was sold as if it were an extract of Pouchung tea.[6,7]

Another stimulant recently introduced into supplements and sold as if it were a botanical extract is β-methylphenylethylamine (BMPEA, Figure 1).[8] BMPEA was synthesized in the 1930s as a potential replacement for amphetamine.[10,11] However, for unknown reasons, studies of efficacy and safety in humans were never performed, and BMPEA was never introduced as a pharmaceutical drug. BMPEA remained known only as a research chemical until early 2013 when the FDA identified BMPEA in multiple supplements labelled as containing 'Acacia rigidula', even though the stimulant has never been identified or extracted from *Acacia rigidula*, a shrub native to Texas.[8] More than two years after the FDA's discovery, the FDA has yet to warn consumers about the presence of the amphetamine isomer in supplements.

It is not known, in the wake of the FDA's published research on *Acacia rigidula* supplements, if manufacturers have removed BMPEA from *Acacia rigidula* supplements. We purchased *Acacia rigidula* supplements on sale in the USA more than one year after the FDA's discovery and analyzed the supplements for the presence and quantity of BMPEA.

Materials and methods

Materials

The reference standard for BMPEA was purchased from Sigma (St Louis, MO, USA) while the amphetamine-d5, which was used as

* Correspondence to: Pieter Cohen, MD, 236 Highland Ave, Somerville, MA 02143, USA.
E-mail: pcohen@challiance.org

a Department of Medicine, Harvard Medical School, Boston, MA, 02115, USA

b Department of Chemistry, Haverford College, Haverford, PA, 19041, USA

c Department of Laboratory Medicine, University of California, San Francisco, CA, 94143, USA

d Cambridge Health Alliance, Somerville, MA 02143, USA

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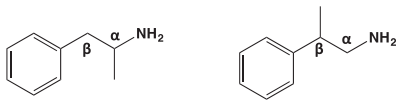

Amphetamine
α-methylphenethylamine

BMPEA
β-methylphenylethylamine

Figure 1. Structures of amphetamine and β-methylphenylethylamine (BMPEA).

an internal standard, was obtained from Cerilliant (Round Rock, TX, USA). All solvents including methanol and water were liquid chromatography-mass spectrometry (LC-MS) grade and were obtained from Honeywell Burdick and Jackson (Muskegon, MI, USA). Stock solutions of BMPEA standards were prepared at 1 mg/mL, aliquoted to 1mL portions in amber vials and stored at -80° C. All calibration standards ranging in concentration from 50 to 5000 ng/mL were prepared from the stock solution.

Instrumentation

All analyses were done using liquid chromatography-quadrupole time-of-flight/mass spectrometry (LC-QTOF/MS). The Agilent LC 1260 Infinity Binary LC System equipped with a binary pump that can deliver 600 bar was used to run elution gradient chromatography. The Agilent 6550 iFunnel QTOF/MS was used to detect BMPEA employing an electrospray ionization source with a dual nebulizer that allows constant introduction of reference mass during runs.

Sample acquisition and preparation

Dietary supplements met our inclusion criteria if they were: (1) labelled as containing *Acacia rigidula* and (2) available for sale online in the USA between January and April 2014. All supplements were purchased online.

Two capsules, pills, or scoops of each dietary supplement were analyzed using LC-QTOF/MS (Agilent LC 1260- QTOF 6550). The total content of each sample was weighed using an analytical balance (Sartorius CP124S). Each sample replicate was dissolved in enough methanol to make a solution that represents soluble components in 50 mg of the supplement per mL of the extracting solvent. From this stock solution 1mg/mL, 100ug/mL, 10ug/mL, 1ug/mL, and 100ng/mL dilutions were prepared in 10% methanol. The last three dilutions were used in the LC-QTOF/MS analysis.

Chemical analysis

A 2.5 uL diluted sample was injected in an Agilent Poroshell 120 C-18 column (2.1X 100 mm, 2.7 um) maintained at 55°C in each LC-QTOF/MS run. Chromatographic separation was achieved by gradient elution using LC-MS grade water with 0.05% formic acid and 5 mM ammonium formate as mobile phase A and methanol with 0.05% formic acid as mobile phase B. The elution gradient employed was- 0–0.5 min= 5% B; 1.5 min= 30% B; 4.5 min= 70% B; 7.5 min= 100% B; 7.5–10 min= 100% B; and 10.01–12 min= 5% B.

Eluates from the chromatographic column were ionized in the QTOF/MS using an electrospray ionization source operated in the following conditions: gas temperature at 225°C; sheath gas temperature at 350°C; drying gas flow at 14 L/min; sheath gas flow at 11 L/min; nebulizer pressure at 14 psi; voltage cap at 3000V; and, nozzle voltage at 500V. Data acquisition was run at 2GHz in extended dynamic range mode. TOF-MS and MS/MS spectra were collected in automated MS/MS mode using 500 arbitrary units as threshold for inducing MS/MS data collection. Each sample was run in positive polarity and injected three separate times.

Data analysis

The total ion chromatogram (TIC) obtained from the LC-QTOF/MS run was analyzed using Agilent MassHunter Qualitative Analysis software. All sample TIC were analyzed to confirm the presence of BMPEA using the following criteria: mass error $\leq$ 10 ppm; retention time $\leq$ 0.15 min; target score $\leq$ 70 (indication of isotopic pattern match) for peaks that did not exhibit detector saturation; and, the presence of at least one fragment ion peak in its MS/MS spectra. Quantification of BMPEA was done by isotope dilution method using an eight-point calibration curve and amphetamine-d5 as internal standard. Each sample replicate was run three times to obtain the mean content values. The average of all six runs was used to report the mean and the %CV of measurements for the BMPEA content of each dietary supplement. The limit of quantification (LOQ) established for the quantitative analysis of BMPEA is 50 ng/mL in a concentration dynamic range of over three orders of magnitude. Intra- and inter-assay precision at LOQ are 2.5% and 8% CV, respectively.

Results and discussion

Twenty-one brands of dietary supplements met our inclusion criteria. These 21 brands of *Acacia rigidula* supplements were marketed to lose weight (16/21; 76.2%), improve athletic performance (3/21; 14.3%) and enhance cognitive function (1/21; 4.8%). In addition to listing *Acacia rigidula* on the label, 3 supplements (3/21; 14.3%) also listed a synonym for the chemical BMPEA on the label. These 3 supplements all implied that BMPEA had been extracted from *Acacia rigidula* (Table 1).

A typical chromatogram for BMPEA along with amphetamine-d5 (internal standard) is shown in Figure 2. BMPEA was found in 52.4% (11/21) of the *Acacia rigidula* supplement brands (Table 1). The quantity of BMPEA in individual servings ranged from 0 mg to 31.2 mg. The coefficient of variation (%CV) measured for supplements containing BMPEA ranged from 8.4 to 31.8%. Based on recommended dosing on the label, maximum daily dosages ranged from 0 to 93.7 mg.

Research completed in the 1930s and 1940s demonstrated that BMPEA has pressor effects including increase in blood pressure and heart rate in dogs and cats.[10–15] For example, a 20 mg intravenous dose of BMPEA in a dog led to a 50 mm Hg rise in blood pressure.[12] Studies in rats found that BMPEA crosses the blood–brain barrier,[16] but, to our knowledge only one animal study investigated BMPEA's potential central nervous system stimulatory effects.[17]

In vitro studies have found a receptor in human neurons, trace amine-associated receptor 1, which can be activated by BMPEA.[18] But to our knowledge, there have been no studies of BMPEA's efficacy or safety in humans. We are aware of only one study of BMPEA involving humans: published in 1942, researchers studied the excretion of 15 mg of BMPEA in 8 human subjects.[19] However, the physiologic effects of BMPEA were not documented; therefore, BMPEA's effects on human health are entirely unknown.

Physicians should remain vigilant for patients presenting with toxicity from sports and weight loss supplements as they might contain undisclosed stimulants, such as BMPEA. All such cases in the USA should be reported to the FDA at https://www.safetyreporting.hhs.gov

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Table 1. Quantity of β-methylphenylethylamine (BMPEA) found in dietary supplements labelled as containing Acacia rigidula. Highlighted ingredients represent those labels that declared BMPEA on the label.

Supplement name (manufacturer)	Description of *Acacia rigidula* on supplement label	Maximum recommended daily dosage on label (pills/capsules/scoops)	Measured average weight of BMPEA per capsule/pill/scoop (mg)	SD (mg)	%CV	Quantity of BMPEA in maximum recommended dosage on label (mg)	Claim on label or web site
Aro Black Series Burn (Vitacost)	Blackbrush Acacia Extract (leaf)(Acacia rigidula)(yielding 200mg phenylethylamine alkaloids)	2	9.09	0.76	8.39	18.18	Weight loss
Attention Link (Hi-Tech Pharmaceuticals Inc.)	Acacia Rigidula 95% Extract (leaves)	2	0.00	N/A	N/A	0.00	Cognitive function
Benzadrine (Hi-Tech Pharmaceuticals Inc.)	Acacia Rigidula 98% Extract (leaves)	3	0.00	N/A	N/A	0.00	Weight loss
Beta-Stim (Ronnie Coleman)	Acacia Rigidula	3	0.00	N/A	N/A	0.00	Weight loss
Black Widow (Hi-Tech Pharmaceuticals Inc.)	Acacia Rigidula Extract (leaves)	3	18.71	2.16	11.54	56.12	Weight loss
Dexaprine XR (iForce Nutrition, Tribravus Enterprises LLC.)	Acacia Rigidula Extract (98%)	2	5.74	1.15	20.02	11.48	Weight loss
Fastin-XR (Hi-Tech Pharmaceuticals Inc.)	Acacia Rigidula Extract (leaves) [Yielding 200mg Phenylethylamine alkaloids including: R-Beta-Methylphenylethylamine, Methylsynephrine, N-Methyl-B-Phenylethylamine, Phenylethylamine]	3	27.35	5.87	21.48	82.04	Weight loss
Fat Free (Applied Nutriceuticals)	Acacia Rigidula (As 98% Catechins and Biogenic Alkaloids)	3	0.00	N/A	N/A	0.00	Weight loss
Green Coffee Bean Extract (Rightway Nutrition LLC)	Acacia Rigidula (leaf, flower) Powder	3	0.00	N/A	N/A	0.00	None
Jet Fuel Superburn (GAT)	Microparticulate sustained-release Acacia rigidula extract (leaf)	6	3.22	0.67	20.70	19.31	Sports supplement
Jet Fuel T-300 (GAT)	Acacia rigidula leaf extract (NLT 85% phenylethylamine alkaloids)	3	31.23	5.72	18.30	93.69	Sports supplement
Lipodrene Hardcore (Hi-Tech Pharmaceuticals Inc.)	Acacia Rigidula Extract (leaves) [Yielding 200mg Phenylethylamine alkaloids including: R-Beta-Methylphenylethylamine, Methylsynephrine, B-Phenylethylamine, and N-Methyl-B-Phenylethylamine]	3	9.89	1.26	12.69	29.67	Weight loss
Lipodrene Xtreme (Hi-Tech Pharmaceuticals Inc.)	Acacia Rigidula Extract 95% (leaves)(yielding 175 mg Phenylethylamine Alkaloids)	3	3.35	0.74	22.20	10.05	Weight loss
Lipodrene-SR (Hi-Tech Pharmaceuticals Inc.)	Acacia Rigidula Extract (leaves)	3	0.00	N/A	N/A	0.00	Weight loss
MX-LS7 (iSatori)	Blackbrush Acacia Extract (Acacia Rigidula) (leaf) (Thermo-RX) (standardized to 98% phenylethylamine alkaloids)	2	3.26	0.55	16.96	6.52	Weight loss
Myo-Blitz (Ronnie Coleman)	Acacia Rigidula	1	0.00	N/A	N/A	0.00	Sports supplement
Reps Fat Burner (Powermill Labs)	Acacia Rigidula	4	0.00	N/A	N/A	0.00	Weight loss
Ripped Cocktail (Lecheek Nutrition)	Acacia Rigidula	2	0.00	N/A	N/A	0.00	Weight loss

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Table 1. *(Continued)*

Supplement name (manufacturer)	Description of *Acacia rigidula* on supplement label	Maximum recommended daily dosage on label (pills/capsules/scoops)	Measured average weight of BMPEA per capsule/pill/scoop (mg)	SD (mg)	%CV	Quantity of BMPEA in maximum recommended dosage on label (mg)	Claim on label or web site
Stimerex (Hi-Tech Pharmaceuticals Inc.)	Acacia Rigidula 70% extract (leaves)	3	0.00	N/A	N/A	0.00	Weight loss
Stimerex-ES (Hi-Tech Pharmaceuticals Inc.)	Acacia Rigidula Extract (leaves) [Yielding Phenethylamine Alkaloids: B-Phenylethylamine, Methylsynephrine, N-Methyl-B-Phenylethylamine, R-Beta-Methylphenylethylamine]	3	0.97	0.31	31.82	2.90	Weight loss
Yellow Scorpion (Hi-Tech Pharmaceuticals Inc.)	Acacia Rigidula (leaves)	3	23.05	2.79	12.08	69.14	Weight loss

%CV, coefficient of variation
SD, standard deviation
N/A, not applicable

as the FDA relies on MedWatch reports to identify dangerous supplements.[20]

Although the health effects of BMPEA are not yet known, consumption of BMPEA could have significant consequences for athletes and other consumers who are subject to urine drug testing as BMPEA is banned by the World Anti-Doping Agency.[21] Since 2010, several athletes have tested positive for BMPEA in urine toxicology studies including an Olympic canoeist who claimed he had inadvertently consumed BMPEA in a supplement.[21,22]

In addition to the current study, several other investigators have found BMPEA in dietary supplements.[8,9,22] FDA scientists analyzed 21 supplements labelled as containing *Acacia rigidula* purchased in 2012 and found that 9 of 21 (42.9%) contained BMPEA.[8] The calculated daily dose of BMPEA in the FDA's study ranged from 0 to 146 mg compared to the range of 0 to 94 mg found in the current study.[8] Five of the supplements tested in the current study were also analyzed in the FDA's study. However, the FDA investigators are not at liberty to disclose which ones. We are, therefore, unable to compare our results for individual supplements directly with the FDA's findings. Health Canada, however, has recently identified BMPEA in JetFuel Superburn which concurs with our analysis of the same brand.[23] A European team has also detected BMPEA in two sports supplements, NO-Shotgun and NOXPUMP.[9,22] (NO-Shotgun and NOXPUMP were not analyzed in the current study because they did not meet our inclusion criteria.)

In Europe, the Food Standards Agency has clarified that *Acacia rigidula* has not been previously consumed as a food and is not permitted to be sold until there is additional evidence of safety.[24] Despite the marketing of BMPEA as an extract of *Acacia rigidula*, there is no scientific evidence that BMPEA has ever been extracted from *Acacia rigidula* or any other plant.[8] Instead, the dosages of BMPEA in supplements strongly suggest that the amphetamine isomer is synthetically produced and placed in the supplement to lead to physiologic effects.

While the European Food Standards Agency has cautioned against the consumption of *Acacia rigidula* products, the FDA has been silent. The FDA's research detecting BMPEA in *Acacia rigidula* supplements garnered recognition within the FDA as one of the FDA's noteworthy accomplishments of 2013,[25] but, more than two years later, the FDA has not yet warned consumers about BMPEA nor moved to eliminate BMPEA from supplements.

Since the FDA discovered BMPEA in supplements, the percentage of brands of *Acacia rigidula* supplements that contain BMPEA has appeared to increase from 42.9% in 2012 to 52.4% in 2014. Whether this represents a true increase in the prevalence of BMPEA or is due to differences in sampling methods or other factors is not known. Regardless, the continued presence of BMPEA in mainstream supplements continues to expose consumers to potential risks.

Our study has several limitations. We only determined the quantity of BMPEA in *Acacia rigidula* supplements. It is possible that caffeine and other stimulants might be present in these supplements, potentially increasing the risks these supplements pose to consumers.[26] In fact, European investigators have found an analogue of methamphetamine, N,N-dimethyl-2-phenylpropan-1-amine (DMPPA) combined with in BMPEA in the same dietary supplement (i.e., NOXPUMP).[9] Furthermore, our study only tested supplements labelled as containing *Acacia rigidula*; therefore, it is possible that other brands of supplements on sale in the USA may also contain BMPEA but might not list *Acacia rigidula* on the label.

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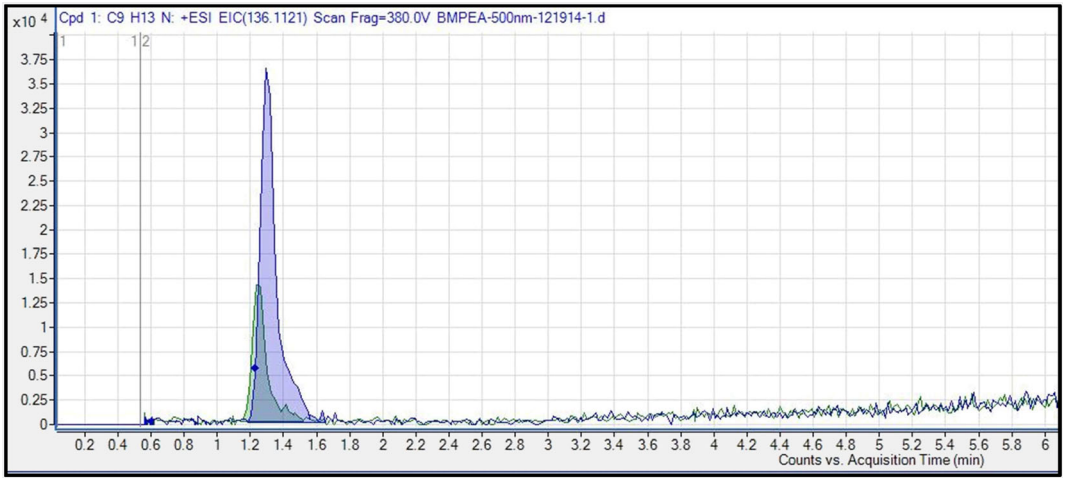

Figure 2. Extracted ion chromatograms of BMPEA (500 ng/mL, lighter) and amphetamine-d5 (100 ng/mL, darker).

Conclusion

We found the amphetamine isomer BMPEA in more than half of all brands of supplements labelled as containing *Acacia rigidula* sold in the USA. The efficacy and safety of BMPEA has never been studied in humans; therefore, BMPEA's effect on human health is entirely unknown. BMPEA has not before been sold as a food or supplement and, therefore, is not a legitimate supplement ingredient.[27] The FDA discovered BMPEA in supplements purchased as early as 2012[28] but has yet to inform the public or take enforcement action to remove BMPEA from dietary supplements. We recommend that supplement manufacturers immediately recall all supplements containing BMPEA, and that the FDA use all its enforcement powers to eliminate BMPEA as an ingredient in dietary supplements. Consumers should be advised to avoid all supplements labelled as containing *Acacia rigidula*. Physicians should remain alert to the possibility that patients may be inadvertently exposed to synthetic stimulants when consuming weight loss and sports supplements.

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