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Pterostilbene Caffeine Co-Crystal: Bioavailable Caffeine Alternative Enriched with Pterostilbene

Pterostilbene is a powerful polyphenol and has beneficial properties as anti-aging ingredient through modulating the hallmarks of aging such as inflammation, oxidative damage, telomere attrition, and cell senescence.[1] It has been known to exhibit other health beneficial effects such as antiatherosclerosis, antidiabetic, anti-inflammatory, anti-obesity, antioxidant cardioprotection, cognitive support, and neuroprotection as well.[2] Another well-known and pharmacological active polyphenol is resveratrol, but in various studies, pterostilbene was reported to have better bioavailability (80% bioavailability compared to 20% for resveratrol).[1] Pterostilbene has two methoxy (–OCH3) groups which makes it more lipophilic and enhances its membrane permeability, bioavailability, and biological potency.[1,2] Caffeine is known for its positive effect on arousal and fatigue, perceptual processing, motor behavior, stress, learning and memory, and energy and performance in limited dose.[3,4]

Laurus Labs introduces a combination of pterostilbene and caffeine as pterostilbene caffeine cocrystal (CO-CRYSTAL), a unique and patented ingredient that includes benefits of pterostilbene and caffeine both. Highly caffeinated products have been coming under increased regulatory scrutiny regarding the possible risks of consuming high amount of caffeine. CO-CRYSTAL formulation of caffeine offers higher bioavailability and longer half-life and additional functional health benefits of pterostilbene that include cognitive function, antioxidant activity, and heart health. Bioavailability and half-life of CO-CRYSTAL were tested in the pharmacokinetic study at Vimta Labs, a National Accreditation Board for Testing and Calibration Laboratories accredited premier preclinical research facility in India. The objective of this study was to assess the comparative pharmacokinetic profile of pterostilbene and caffeine when administered alone as well as in a combined CO-CRYSTAL form in Sprague Dawley rats by the oral route.

In this study, rats were administered orally with pterostilbene at 15 mg/kg, caffeine at 11.29 mg/kg, or CO-CRYSTAL at a dose of 26.29 mg/kg (of which 15 mg/kg of pterostilbene and 11.29 mg/kg of caffeine) as a single dose through gavage. Following the dose administration, 250–300 µL of blood sample from each rat at 0 (predose), 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, and 24.0 h postdose was collected through retro-orbital plexus into prelabeled K_2EDTA-coated microcentrifuge tubes. The plasma from the blood samples was centrifuged and separated and was analyzed for test item levels by the liquid chromatography–mass spectrometry/mass spectrometry method. The mean plasma concentration versus time profile was used to calculate pharmacokinetic parameters using noncompartmental analysis tool WinNonlin® Software V 6.2.1 (Pharsight Corporation USA, a Certara™ company). The protocol was approved by the Institutional Animal Ethics Committee of Vimta Labs, and all the ethical practices as laid down in the CPCSEA guidelines for animal care were followed during the conduct of the study.

The results suggest that peak plasma concentration (C_{max}) of pterostilbene in CO-CRYSTAL was 26% higher than pterostilbene alone, whereas C_{max} of caffeine in CO-CRYSTAL was comparable to caffeine alone. As shown in Figures 1 and 2, the results validate that there were more pterostilbene and caffeine from CO-CRYSTAL compared to pterostilbene and caffeine alone over a 12-h period. The outcomes of the rat study ensure that CO-CRYSTAL has extended-release and sustained energy profile over pterostilbene and caffeine alone.

The area under the curve (AUC) is one of the most important parameters in pharmacokinetics as bioavailability generally refers to the fraction of compound absorbed systemically, and this is often measured by quantifying the AUC. The mean extent of absorption (AUC_{0-24}) for pterostilbene and caffeine in CO-CRYSTAL was increased by ~50% and ~142% respectively, as compared to pterostilbene and caffeine alone [Table 1]. Another factor, half-life has important implications for dosing. If the half-life is too short, it may require more frequent dosing to maintain the desired exposures. The half-life of pterostilbene and caffeine in CO-CRYSTAL was reported two times and eight times longer, respectively, in comparison of pterostilbene and caffeine alone [Table 1].

PURENERGY™ (registered trademark by ChromaDex, Inc.), a CO-CRYSTAL, was tested by scientists from Miami Research Associat to determine the relative bioavailability, pharmacokinetics, and safety of the ingredient. In a 4-week, single-blind, crossover human study (n = 12), 232 mg of PURENERGY™ (providing 99.76 mg of caffeine) was

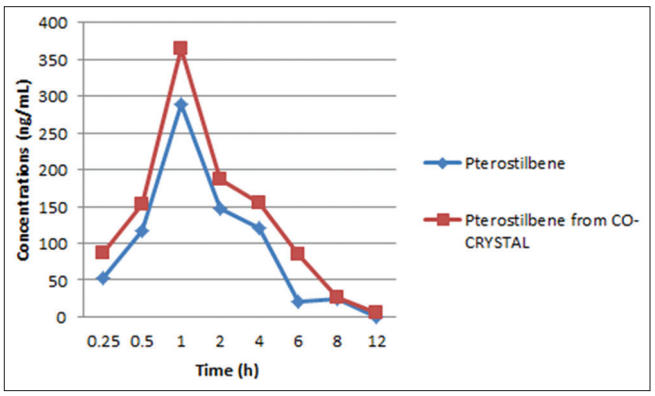

Figure 1: Peak plasma concentration of pterostilbene

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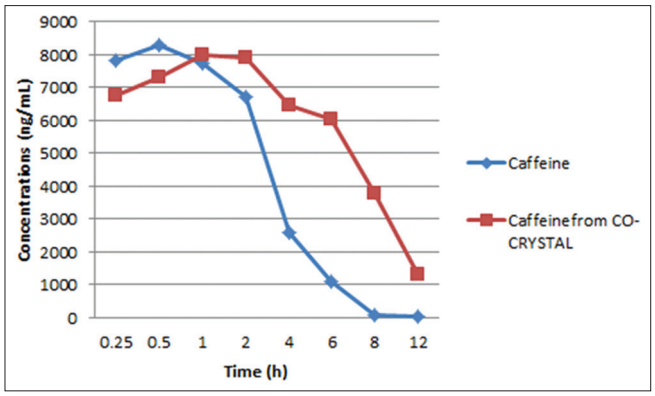

Figure 2: Peak plasma concentration of caffeine

compared to 100 mg of ordinary caffeine, and the following effects were demonstrated:[5,6]

- CO-CRYSTAL delivered almost 30% more caffeine into the blood than ordinary caffeine
- The absorption rate of the caffeine from CO-CRYSTAL was considerably slower by approximately 30% compared to ordinary caffeine
- The half-life of caffeine from CO-CRYSTAL was extended significantly by about 25% compared to ordinary caffeine
- At 4 h, result showed 45% more caffeine from COCRYSTAL
- At 6 h, result showed 51% more caffeine from COCRYSTAL
- At 6 h, individuals taking CO-CRYSTAL showed significantly less fatigue and greater concentration compared to the baseline, whereas ordinary caffeine did not
- At 6 h, individuals taking CO-CRYSTAL showed improved energy, alertness, and focus compared to the baseline, whereas ordinary caffeine did not
- CO-CRYSTAL showed no adverse events.

The results suggest that formulators have a choice to reduce the amount of caffeine needed in a formulation to produce tangible results with sustained energy boost. In the above-mentioned study, CO-CRYSTAL also delivered approximately 50% more total pterostilbene into the blood than pterostilbene alone.[7] This difference is also significant as pterostilbene acts as an antioxidant and known to support heart health, cognitive function, healthy cellular ageing and metabolism.

Another study in twenty one resistance-trained subjects concluded that supplementation with a combination of CO-CRYSTAL (PURENERGY™), B vitamins, ancient peat, and apple extracts may enhance resistance training-induced skeletal muscle hypertrophy without adversely affecting blood chemistry. The combination was safe in a 12-week study and showed no adverse events.[8] Twelve male golfers participated in a double-blind, placebo-controlled, crossover design to determine the effect of a caffeine-containing supplement on golf-specific performance and fatigue. They were randomly assigned to consume 155 mg caffeine-containing supplement (raw caffeine and PURENERGY™ in a multi-ingredient proprietary blend) or placebo. Golfers played an 18-hole round of golf on 2 consecutive days (36-hole tournament) and supplement/placebo was consumed before and after nine holes during each 18-hole round. The results advised that a moderate dose (1.9 ± 0.3 mg/kg (−1)) of caffeine consumed before and during a round of golf improves golf-specific measures of performance and reduces fatigue in skilled golfers.[9]

Table 1: Comparative pharmacokinetic profile in Sprague Dawley male rats

Groups	$AUC_{(0-24)}$ (h*ng/mL)	t1/2 (h)	Highlights
Pterostilbene in CO-CRYSTAL	1204.38	4	50% higher $AUC_{(0-24)}$ 2 times longer half-life
Pterostilbene alone	804.72	2	
Caffeine in CO-CRYSTAL	69,137.71	8	142% higher $AUC_{(0-24)}$
Caffeine alone	28,567.52	1	8 times longer half-life

hr*ng/mL: Nanograms per milliliter multiplied by hour. AUC: Area under the curve

The effect of cocrystalizing pterostilbene and caffeine on their respective bioavailability was evaluated in various studies. Cocrystalizing pterostilbene and caffeine modulates the bioavailability of the two components and provides a choice for a reduction in the amount of caffeine in different products without noticeably impacting the consumer experience. Nowadays, consumers are interested in reduced caffeine energy beverages and powders that deliver the same benefits and feel without the adverse events and avoid the associated hangover and crash from the ordinary caffeine. The results of various studies of CO-CRYSTAL validate its suitability as an alternative to ordinary caffeine in energy drinks and other energy products and add to product efficacy with additional benefits of pterostilbene.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Quick Response Code:

Website: www.matrixscimed.org

DOI: 10.4103/MTSM.MTSM_27_19

How to cite this article: Jain R. Pterostilbene caffeine Co-Crystal: Bioavailable caffeine alternative enriched with pterostilbene. Matrix Sci Med 2020;4:24-6.

Received: 07-12-2019, **Accepted:** 16-12-2019, **Published:** 09-03-2020

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