



"From Field to Formula"®

Caffeine-Free Energy

Presented by:
RFI Ingredients
Blauvelt, NY

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Love Affair with Caffeine? Not for everyone!

Americans love their caffeine. Whether it's from naturally-occurring sources like coffee and tea or from energy drinks or supplements, 85% of Americans use caffeine regularly. But many of us have a love/hate relationship with caffeine. We love the almost instant energy it can provide, as well as the added cognitive boost, but we hate the jitters, its addictiveness, and how it can negatively affect our sleep if taken too late in the day. We also hate that the energy profile we get from caffeine is often more a crash-and-burn energy than a long-lasting energy.

How we react to caffeine varies among individuals. Factors that may influence caffeine sensitivity include body mass, age, gender, medication use and health conditions such as anxiety disorders. Another reason for caffeine sensitivity appears to be related to genetics. The gene *CYP1A2* regulates how fast we metabolize caffeine (and other drugs) and it is estimated that 50% of the population has a gene variant (either heterozygous or homozygous for the variation) on this gene that causes them to be slow metabolizers of caffeine. Therefore, the caffeine-induced rise in blood pressure and heart rate may be more intense and last longer.¹ One population study even linked coffee consumption to increased risk of nonfatal myocardial infarction among these individuals with slow caffeine metabolism.²

Another reason people may be shying away from caffeine is the recent controversies surrounding its safety. The science behind the safety of caffeine is actually fairly thorough in respect to naturally-occurring caffeine. Naturally-occurring caffeine from tea, coffee, mate and cocoa has been shown to be well tolerated and studies have shown that the safe amount of caffeine consumed in a day from these sources is actually quite high. It is theorized that these naturally-occurring sources also contain other naturally-occurring compounds that likely help temper the negative effects of the caffeine.

What about the safety of caffeine from non-natural sources? Moderate caffeine consumption is considered safe and its use as a food ingredient has been approved, within certain limits, by numerous regulatory agencies around the world.³ The Mayo Clinic estimates moderate caffeine consumption to be 300-400 mg per day, the equivalent to about 2-4 cups of coffee a day. However, they also state that high intake – 500-600 mg per day (from any source) – can result in negative effects such as insomnia, nervousness, irritability and a fast heartbeat.

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In the last decade, caffeine has become a commonly used ingredient in “energy” drinks. The increase in popularity has brought heightened scrutiny by regulatory agencies. The level of caffeine in these drinks has also raised worries. The FDA caps the amount of caffeine in soda to 0.02%, yet there is no such limit for energy drinks. Consumption of energy drinks has been linked to a number of deaths or life-threatening injuries in recent years – enough that the FDA is investigating some of them. While the culprit might not be just the caffeine alone (the effect of the combination of synthetic caffeine with many of the other ingredients that are found in energy drinks is not well understood), the media has made the public more aware of potential dangers from caffeine consumption from “energy” products. This translates to additional consumer demand for caffeine-free energy products.

Chocamine® - longer lasting, less addictive energy

We also have a love/hate relationship with chocolate. We love its taste, its aroma and the physical and mental boost we feel after eating it. We love that there has been a lot of positive media attention on chocolate’s health benefits. However, we hate the guilt associated with eating chocolate because of the fat, sugar and dairy content. And while research reports health benefits, it also reports a conflicting health label for chocolate – increased risk of weight gain.

Chocamine® is a patented cocoa-based ingredient that delivers all that we love about chocolate – its taste, aroma and health benefits, but without the guilt, fat, calories and dairy. The beneficial effects of chocolate come from more than one component such as theobromine, amino acids, nutritional minerals, biogenic amines, anandamides and polyphenols. Chocamine® is standardized to theobromine content. Theobromine is found in many plant sources that also have caffeine, such as tea, guarana, yerba mate and kola nut, but it is found at the highest levels in cocoa.

Theobromine and caffeine are both xanthine alkaloids, and their stimulant effect results from the same mechanism – the inhibition of adenosine receptors. In humans, the adenosine receptors A1 and A2A have an effect on the heart, regulating myocardial oxygen consumption and coronary blood flow. They also play important roles in the brain, regulating the release of other neurotransmitters such as dopamine and glutamate. Xanthine alkaloids such as caffeine and theobromine act as non-selective antagonists at A1 and A2A receptors, producing a stimulant effect and rapid heart rate.

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However, the energy from theobromine differs from caffeine. The specific distinctions between theobromine and caffeine are why many individuals shy away from caffeinated energy. First, theobromine has a milder stimulant effect,⁴ resulting in energy without the jitters. Second, theobromine has a longer half-life in the body,^{4,5} thereby providing longer-lasting energy. Third, caffeine and theobromine show differential affinities for different adenosine receptor subtypes. Theobromine is at least 10 times less active than caffeine as an A2 receptor antagonist. One subtype of A2 receptors, the A2A receptors, play a role in the desire/addictive quality of caffeine.⁴ This may explain why theobromine is less addictive than caffeine. Lastly, theobromine has been shown to have less of an effect on sleep than caffeine. In a human clinical study comparing theobromine and caffeine and their effect on sleep, the theobromine group reported reduced sleep latency (the time it takes to fall asleep) and better sleep quality than the caffeine group.⁴

GS15-4® Fermented Panax Ginseng Extract – Adaptogenic Energy

Panax ginseng is considered to be one of the fundamental tonics in traditional Chinese medicine. In fact, it may be the world's best known herb. *Panax ginseng* has been used medicinally in Asia for more than 5000 years and has been known in Chinese ethnopharmacology for more than 3000 years. Pharmacologically speaking, ginseng is classified as an adaptogen. Ginseng is the world's most powerful adaptogenic herb which assists the body to manage stress and achieve homeostatic balance, optimizing the body's ability to resist fatigue, stress, trauma, and support healthy aging and overall wellness. Ginseng has a remarkable capacity to restore the body's natural balance.

As an adaptogen, ginseng supports nonspecific resistance to biochemical and physical stressors, thereby improving vitality and well-being. Reviews suggest that Panax ginseng has immunomodulating activity by affecting the hypothalamic-pituitary-adrenal (HPA) axis. Clinical studies have shown that ginseng extract stimulates the immune system, improves mental and physical performance, reduces fatigue, supports healthy glucose regulation, and improves overall quality of life.^{6,7 8,9}

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The unique active compounds found only in *Panax ginseng* are plant saponins called ginsenosides. Other plants that have the common term “ginseng” in their names are not true ginseng since they are from a different genus or family and do not contain these unique compounds. These include Siberian ginseng (*Eleutherococcus senticosus*), Prince ginseng (*Pseudostellaria paniculate*), Indian ginseng/Ashwagandha (*Withania somnifera*), and Brazilian ginseng/Suma (*Pfaffia paniculata*).

The quality and efficacy of *Panax ginseng* extracts may also be influenced by harvest time and processing methods. Red ginseng is ginseng root that has been peeled, heated (usually through steaming at standard boiling temperatures of 100 °C) and then dried or sun-dried. White ginseng has been processed without heat and air dried. A study comparing the ginsenoside content of the most common red Ginseng extract versus a uniquely processed white ginseng extract showed that this white ginseng extract has higher level of ginsenosides. In fact, the level of ginsenoside Rg₁, the indicator of anti-fatigue activity was found to be three or four times higher in this white ginseng than that of red ginseng.¹⁰ Growing time also impacts ginsenoside content, with roots from plants older than five years being more potent than roots from one- to two-year-old plants.⁷ In fact, a study measuring ginsenoside content of ginseng roots every year up for up to six years reported that the maximum accumulation of ginsenosides was recorded in the roots at the fifth year.¹¹ The common practice of harvesting six-year roots may have other limitations. Around the sixth year, the roots begin a downward cycle as they become more woody and fibrous, resulting in diminished levels of key compounds.

While all this science instructing manufacturers on the best way to process and harvest ginseng is important, another factor is fundamental to making an efficacious ginseng extract. It turns out the availability of intact ginsenosides is extremely low. Orally administered ginsenosides are very hard to breakdown by gastric juices or liver enzymes. They can be, however, metabolized by intestinal bacteria and then these metabolites are absorbed from intestines. Recent studies demonstrated that ginsenoside metabolites had greater biological effects than ginsenosides.¹²

The 21st Century Ginseng

Through decades of consistent scientific leadership, the Korean ginseng manufacturer Ilhwa Co. Ltd. has developed the world’s most efficacious and balancing ginseng extract, GS15-4®. Ilhwa uses a proprietary process that incorporates all the best current science to

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produce a “21st Century Ginseng Extract.” First, Ilhwa uses white ginseng root that has not been peeled, as peeling removes the minor rootlets and hair rootlets that carry key bioactive compounds. Second, they use a proprietary low heat vacuum extraction of the whole unpeeled root, which maintains the vitamins, amino acid profile and organic germanium lost in the high heat steaming process used in traditional processing. Third, Ilhwa harvests the roots at the optimum time between the fourth and fifth year. In comparison, red ginseng extract available from most companies uses the traditional 6-year harvested root. Finally and most importantly, Ilhwa uses a proprietary enzyme fermentation process to improve absorption. High-yield enzyme fermentation mimics the fermentation that occurs in the intestine to transform ginsenosides to an end-stage metabolite called compound K or IH-901. Compound K has been proposed to be the most bioavailable metabolite from colonic fermentation.¹³ Fermented ginseng extract containing this metabolite has been shown to have many adaptogenic qualities such as strong antioxidant,¹⁴ anti-stress,¹⁵ hepatoprotective,¹⁶ anti-allergy¹⁷ and anti-inflammatory¹⁸ activities as well as support healthy glucose and lipid regulation.¹⁹ In addition, GS15-4[®] has been clinically proven to provide 15 times increased absorption, four times faster absorption and four times more consistent absorption (Figures 1-3). In addition, the fermentation process also provides an improved taste profile compared to conventional ginseng extracts. Improved bioavailability means improved adaptogenic support for fatigue and stress.

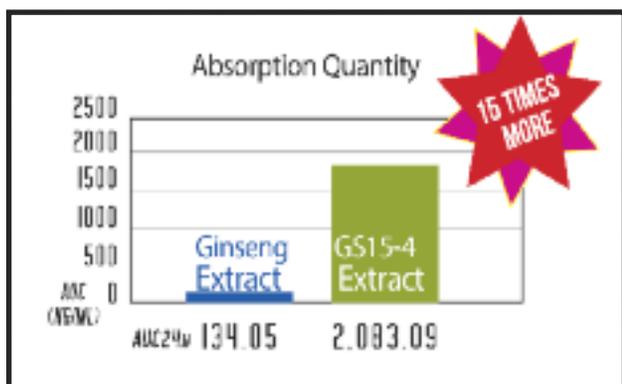


Figure 1

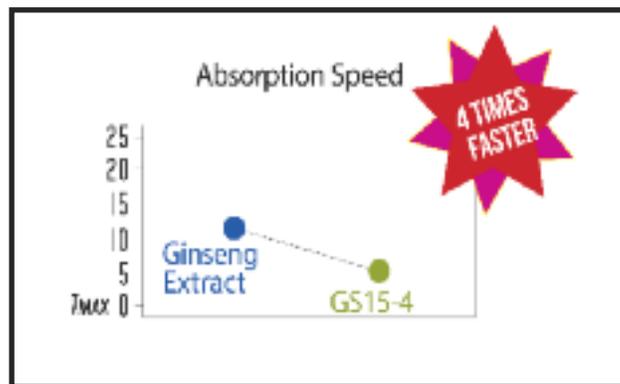


Figure 2

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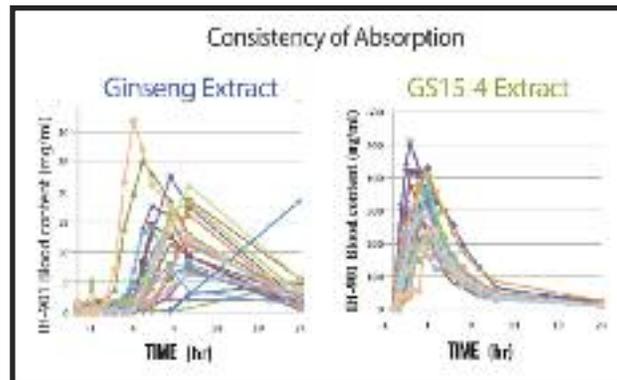


Figure 3

Conclusion

For a number of reasons, more consumers are seeking caffeine-free energy from supplements and beverages. Whether consumers have a fear-based response to the media reports on highly-caffeinated energy drinks, or are simply looking for a different type of energy than the jittery, addictive energy from caffeine, product developers are more likely to find a receptive audience for caffeine-free energy than ever before. In addition, the energy category is evolving beyond the simple "stimulant" energy we get from caffeine and is beginning to recognize that "energy" has many profiles that can be offered to fit consumers' lifestyles and interests.

Two ingredients that have different energy profiles and may be used as "caffeine-free energy" are the cocoa-based ingredient Chocamine® and GS15-4®, the fermented Panax ginseng extract. Historically, cocoa was used as a restorative food by the Aztecs. Today, however, we consume cocoa mostly in the form of chocolate, which has a negative connotation because of the unhealthy ingredients such as fat and sugar. Chocamine® contains no fat or sugar, but contains the key phytochemicals in cocoa, like theobromine, which support the longer-lasting, less addictive energy profile that many consumers seek. Like cocoa, ginseng extract also has thousands of years of traditional use for energy and vitality. It also has a different energy profile which could be called "adaptogenic" energy. GS15-4®'s proprietary processing leads to better absorption of the active components of ginseng, providing higher accessibility for this adaptogenic energy profile.

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References

1. Sachse C. et al. Functional significance of a C-->A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. *Br J Clin Pharmacol.* 1999; 47(4):445-9.
2. Cornelis MC, et al. Coffee, CYP1A2 genotype, and risk of myocardial infarction. *JAMA.* 2006. 295(10):1135-41.
3. Heckman MA, et al. Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. *J Food Sci.* 2010;75(3):R77-87.
4. Smit HJ. Theobromine and the pharmacology of cocoa. *Handb Exp Pharmacol.* 2011;(200):201-34.
5. Mumford GK, et al. Absorption rate of methylxanthines following capsules, cola and chocolate. *Eur J Clin Pharmacol* 1996;51:319–25.
6. Lakshmi T, et al. Panax Ginseng: A universal panacea in the herbal medicine pharmacological spectrum – A review. *Asian Journal of Pharmaceutical and Clinical Research.* 2011;4(S1):14-18.
7. Thorne Research. Panax Ginseng Monograph. *Alternative Medicine Review.* 2009;14(2):172-176.
8. Reay JL, et al. Panax ginseng improves aspects of working memory performance and subjective ratings of calmness in healthy young adults. *Hum Psychopharmacol.* 2010;25(6):462-71.
9. Choi KT. Botanical characteristics, pharmacological effects and medicinal components of Korean Panax ginseng C A Meyer. *Acta Pharmacol Sin.* 2008; 29 (9): 1109–1118.
10. Ko SK, et al. Analysis of Ginsenosides of White and Red Ginseng Concentrates. *Korean Food Science and Technology.* 2003;35:536-539.
11. Xiang-guo L, et al. Ginsenoside Content in The Leaves and Roots of Panax ginseng at Different Ages. *Life Science Journal.* 2012;9(4):679-683.
12. Leung KW and Wong AST. Pharmacology of ginsenosides: a literature review. *Chinese Medicine.* 2010; 5(20):1-7.
13. Hasagawa H. Proof of mysterious efficacy of ginseng: basic and clinical trials: Metabolic activation of ginsenoside: Deglycosylation by intestinal bacteria and esterification with fatty acid. *Journal of Pharmacological Sciences.* 2004;95:153-157.
14. Ramesh T, et al. Effect of fermented Panax ginseng extract (GINST) on oxidative stress and antioxidant activities in major organs of aged rats. *Exp Gerontol.* 2012 . 47(1):77-84.
15. Kitaoka K et al. Fermented Ginseng Improves the First-Night Effect in Humans. *Sleep.* 2009;32(3):413-421.
16. Lee HU, et al. Hepatoprotective effect of ginsenoside Rb1 and compound K on tert-butyl hydroperoxide-induced liver injury. *Liver International.* 2005;25: 1069–1073.
17. Choo MK, et al. Antiallergic Activity of Ginseng and its Ginsenosides. *Planta Med.* 2003;69(6):518-522.
18. Yang CS, et al. Compound K (CK) Rich Fractions from Korean Red Ginseng Inhibit Toll-like Receptor (TLR) 4- or TLR9-mediated Mitogen-activated Protein Kinases Activation and Pro-inflammatory Responses in Murine Macrophages. *Journal of Ginseng Research.* 2007; 31(4): 181-190.
19. Yuan HD, et al. Beneficial effects of IH-901 on glucose and lipid metabolisms via activating adenosine monophosphate-activated protein kinase and phosphatidylinositol-3 kinase pathways. *Metabolism Clinical and Experimental.* 2011;60: 43–51.

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