Go Condition: Improved Mental Performance, Reduced Inflammation and Augmented Immunity

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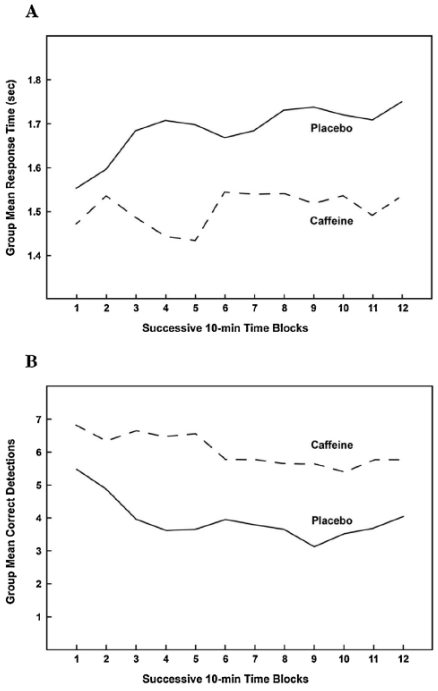
Go Condition (formerly known as "Bionuvo") is a unique blend of diverse flavonoids (quercetin, 13 different types of anthocyanins, and four different types of catechins), caffeine, fish oil, and vitamin C. These ingredients (both individually and in combination) have been linked in multiple studies to enhanced mental function, reduced inflammation, and improved immunity.

CAFFEINE AND FLAVONOIDS: MENTAL FUNCTION, VIGILANCE, LEARNING, MOOD

Intake of caffeine has an acute effect on mental performance across multiple cognitive domains (Bell et al. 2015; McLellan et al. 2016). Mental benefits with acute ingestion of caffeine include improved vigilance, attention, working memory, reaction time, and psychomotor processing speed. These cognitive improvements occur within a time frame of 0-6 hours.

Following ingestion, caffeine is rapidly absorbed, with plasma levels rising to peak levels within one hour (Blanchard & Sawers, 1983). Caffeine plasma half-lives vary from 2.7 to 9.9 h, and behavioral effects are in part due to antagonism of A_1 and A_{2a} adenosine receptors in the central nervous system (CNS) and interactions with dopamine receptors, and an increased release of a variety of neurotransmitters including dopamine and serotonin (McLellan et al., 2016).



Most studies support that ingestion of moderate caffeine doses improves vigilance, learning, and mood (Childs & de Wit, 2008; McLellan et al., 2016). **Figure 1** shows the effect of caffeine on reaction time and stimulus detection in in rested young males. In that study, ingestion of a 200 mg dose of caffeine significantly and consistently improved the number of stimulus detections and reaction times to stimuli in comparison to placebo across 12, 10-minute test blocks for a total of 2 h of testing (McLellan et al., 2016). Caffeine's effect on vigilance are very consistent from study to study.

One meta-analysis of 21 studies concluded that caffeine ingestion reduced ratings of perceived exertion (RPE) during exercise by 5.6%, with an equivalent RPE effect size of −0.47 (Doherty & Smith, 2005). This means that exercise at a certain workload feels "easier" with caffeine than without. Caffeine also improves the overall mood state (Church et al., 2015; McLellan et al., 2016).

Figure 1 *Effect of 200 mg caffeine compared to placebo on reaction time (A) and stimulus detection (B) in a visual vigilance task. Data taken from the review by McLellan et al., 2016.*

Long-term intake of green tea catechin-caffeine beverages has been linked to a small, positive effect on weight loss and weight maintenance (Hursel et al., 2011). Acute ingestion of green tea catechin-caffeine mixtures may transiently increase energy expenditure and fat oxidation by inhibiting or stimulating several enzymes including catechol O-methyltransferase (COMT), phosphodiesterase, and hormone-sensitive lipase, and activating brown adipose tissue metabolic activity. A recent randomized, double blind, placebo controlled study with Go Condition showed that 2

capsules at 8:30 am and 2 more at 1:30 pm was effective in increasing the metabolism by 46 calories per day and fat oxidation by 6.8 grams per day (Nieman et al., 2020). This would equate to about five pounds of body fat lost per year. The increase in metabolism may be one factor explaining the increase in mood people feel with caffeine.

Epidemiological studies support a strong linkage between high versus low dietary polyphenol intake and reduced risk for neurodegenerative diseases (Solanki et al., 2015). Additionally, long term studies show that higher intakes of fruits and vegetables rich in flavonoids are linked to better cognitive performance and mental health (Mao et al., 2019). Specific types of flavonoids have been shown to promote improved mental function and blood flow to the brain. Epicatechin found in green tea has a positive effect on cognitive tasks that involve memory, executive function, and processing speed, especially in older adults Haskell-Ramsay et al., 2018). The effects are especially apparent when intake is more than 50 mg epicatechin/day for 28 days or longer. For comparison, two capsules of Go Condition has 55 mg of epicatechin and epicatechin gallate (Nieman et al. 2017).

Blueberries and bilberries are rich sources of anthocyanins that are responsible for the fruit's deep purple and blue colors. Anthocyanins have been found in the brain after supplementation, especially in the hippocampus and neocortex, regions essential for cognitive performance (for review, see Travica et al., 2019). Blueberry ingestion in animal and human studies has been linked to cognitive improvement. In one study, 3 months of consuming 1 cup/d blueberries resulted in reduced repetition errors during word list recall and increased accuracy during task switching among healthy older adults (Miller et al. 2018). Rodent models have demonstrated significant improvements in working and short-term memory, and reversal of age-related cognitive decline in aged animals (for review, see Barfoot et al., 2018). Positive cognitive effects have also been observed throughout the human lifespan. The neuroprotective findings from rodent models are mirrored in older adults with a reduction of cognitive impairments and delayed onset of ageing disorders, such as Alzheimer's disease. Additionally, acute and chronic berry flavonoid interventions enhance cognition in healthy older and young adults. Recently, berry flavonoid interventions have shown significant improvements in mood for both adolescents and school-aged children, and acute ingestion of anthocyanins improved memory and attentional aspects of executive function in 7-10 year olds (Barfoot et al., 2018).

Taken together, the ingredients in Go Condition (caffeine, anthocyanins, epicatechin) have strong literature support for improving several important aspects of mental performance, both acutely and chronically.

FLAVONOIDS COUNTER INFLAMMATION, OXIDATIVE STRESS, AND RELATED DISEASES

Chronic inflammation and oxidative stress levels are elevated in middle-aged, overweight/obese adults and are characteristic of the metabolic syndrome and chronic diseases including heart disease, diabetes, and cancer. Epidemiological studies support a strong linkage between high versus low dietary polyphenol intake and reduced risk for overall mortality, cardiovascular disease, diabetes, high blood pressure, and a wide spectrum of health conditions including systemic inflammation and oxidative stress (Wang et al., 2014; Annuzzi et al., 2014). High dietary intake of flavonoids has been linked in the Framingham Heart Study Offspring Cohort with decreased systemic inflammation using a cluster of biomarkers (Cassidy et al., 2015).

There is increasing evidence that increased flavonoid intake leads to elevated levels of gut-derived phenolics that reduce post-exercise inflammation and oxidative stress at the cell level, enhancing the recovery process from physical stress (Malaguti et al. 2013; Romain et al. 2017; Cialdella-Kam et al. 2016; Jowko et al. 2015; Nieman et al. 2013; Haramizu et al. 2013; Hursel et al. 2011; Maleki et al., 2019). Recent studies have demonstrated that flavonoids can inhibit regulatory enzymes or transcription factors important for controlling mediators involved in inflammation (Maleki et al., 2019). In general, studies using biotransformed phenolics at physiologically relevant concentrations indicate that degradation of flavonoids to simpler phenolics actually increases their overall anti-inflammatory bioactivity (Kay et al., 2015, 2017).

Recent human studies support that mixed flavonoid-nutrient supplementation reduces inflammation and oxidative stress. In a randomized clinical trial of 48 overweight/obese women conducted by our research group, 10 weeks' supplementation with a mixture of quercetin, green tea catechins, and fish oil was associated with gene

expression alterations consistent with reduced immune cell trafficking and phagocytosis, a component of the inflammatory response (Cialdella-Kam Nieman et al., 2016). Other studies have shown that flavonoid-nutrient mixtures lower inflammation biomarkers such as C-reactive protein in overweight individuals with systemic inflammation (Bakker et al., 2010).

Flavonoid-nutrient mixtures also decrease exercise-induced inflammation and oxidative stress. In a study conducted by Nieman et al. (2009), 2-weeks ingestion of a flavonoid-based supplement similar to Go Condition containing quercetin, catechins from green tea extract, fish oil, and vitamin C attenuated post-exercise inflammation (Figure 2). Flavonoids also function as antioxidants with the potential to attenuate tissue damage or fibrosis. A recent study with Go Condition showed that 2-weeks supplementation lowered post-exercise levels of 4-hydroxynonenal (4-HNE) and protein carbonyls, key markers of oxidative stress (Nieman et al., 2020) (Figure 3). 4-HNE is involved in many disease processes.

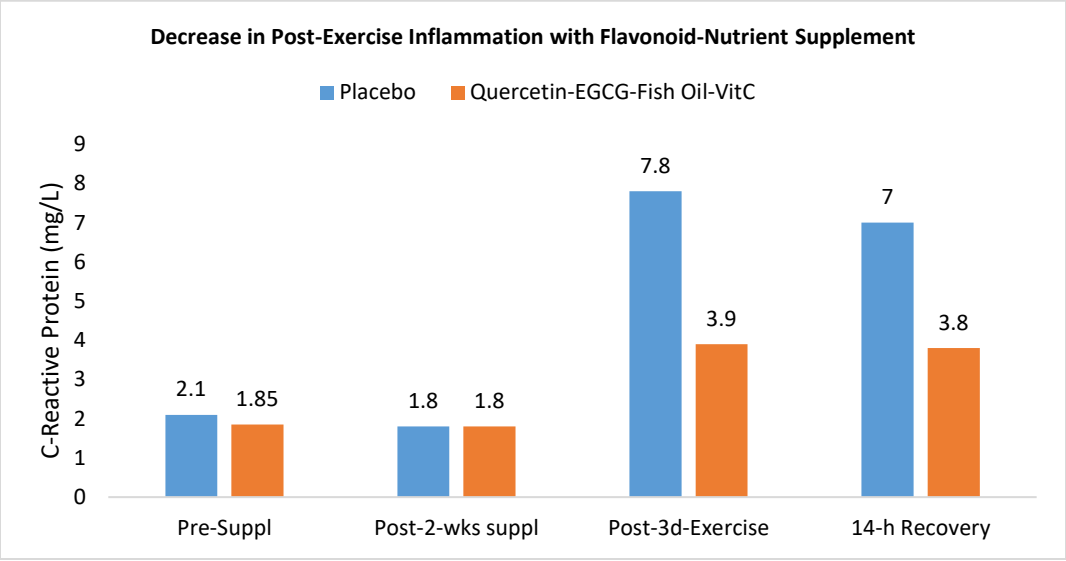


Figure 2: *Two-weeks ingestion of a flavonoid-nutrient supplement containing quercetin, EGCG from green tea, fish oil, and vitamin C decreased post-exercise CRP, a key biomarker of inflammation. Data from Nieman et al., 2009.*

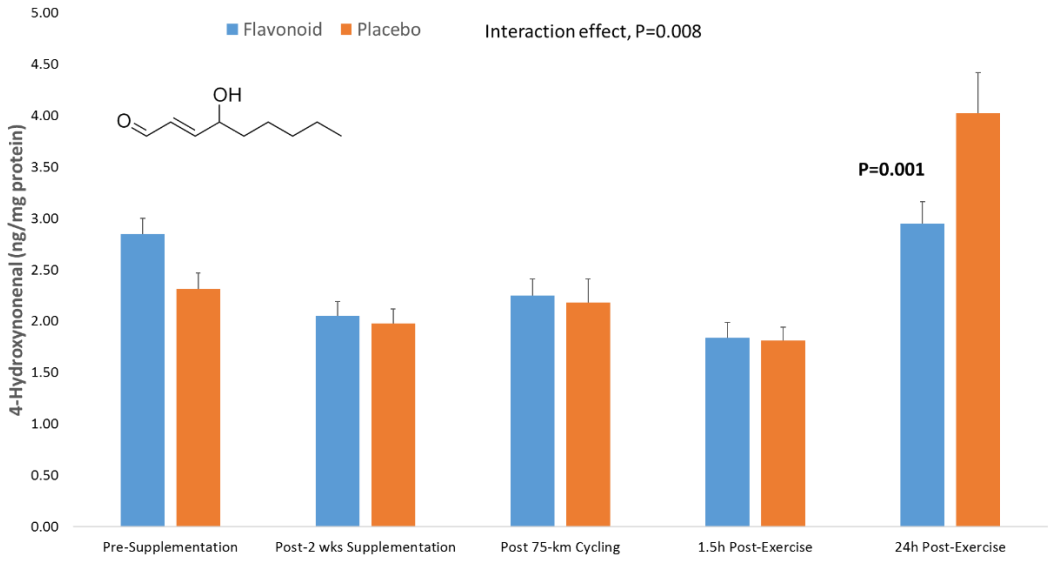


Figure 3: *The long duration (nearly 3 h), high intensity, 75-km cycling bout induced significant post-exercise changes in oxidative stress in the cyclists (n=22), with lower 21h post-exercise levels for 4-HNE when comparing flavonoid and placebo intake. Data from Nieman et al., 2020.*

FLAVONOIDS AUGMENT IMMUNITY AND REDUCE ILLNESS RATES

Flavonoid ingestion reduces illness rates in the general population. A systematic review and meta-analysis showed that flavonoid supplementation (range of 0.2 to 1.2 g/day in 14 selected studies) decreased URTI incidence by 33% compared with control ((Somerville et al. 2016). Quercetin supplementation was also linked to a reduction in the severity and number of sick days associated with upper respiratory tract infections (URTI) in older, physically active adults (Heinz et al., 2010).

Flavonoids also decrease illness rates among athletes. A study conducted by Nieman et al. (2007) and funded through DARPA showed that illness rates in cyclists after a 3-day period of overtraining were significantly reduced in those using quercetin compared to placebo.

Flavonoids modulate immunosurveillance outcomes in response to exercise training including natural killer (NK) cell activities, regulatory T (Treg) cell properties, macrophage inflammatory responses, and serum anti-viral effects (Ahmed et al. 2014; Kim et al. 2015; Nieman & Mitmesser 2018; Nieman et al. 2007).

In a study conducted at the NCRC, ingestion of a polyphenol supplement from blueberries and green tea compared to placebo during a 3-day period of intense exercise training was associated with increased post-exercise translocation of gut-derived phenolics (e.g., hippurate, 2-, 3-, and 4-hydroxyhippurate) into the blood compartment where virus replication was countered. These data support the role of gut-derived phenolics derived from blueberries and green tea in protecting athletes from virus infections when they are most susceptible (Ahmed, Nieman, et al. 2014) (Figure 4). The mechanism by which quercetin, green tea catechins, and other flavonoids provide protection from virus infections remains to be determined, but flavonoids may interfere with viral penetration into cells by damaging the virus particle.

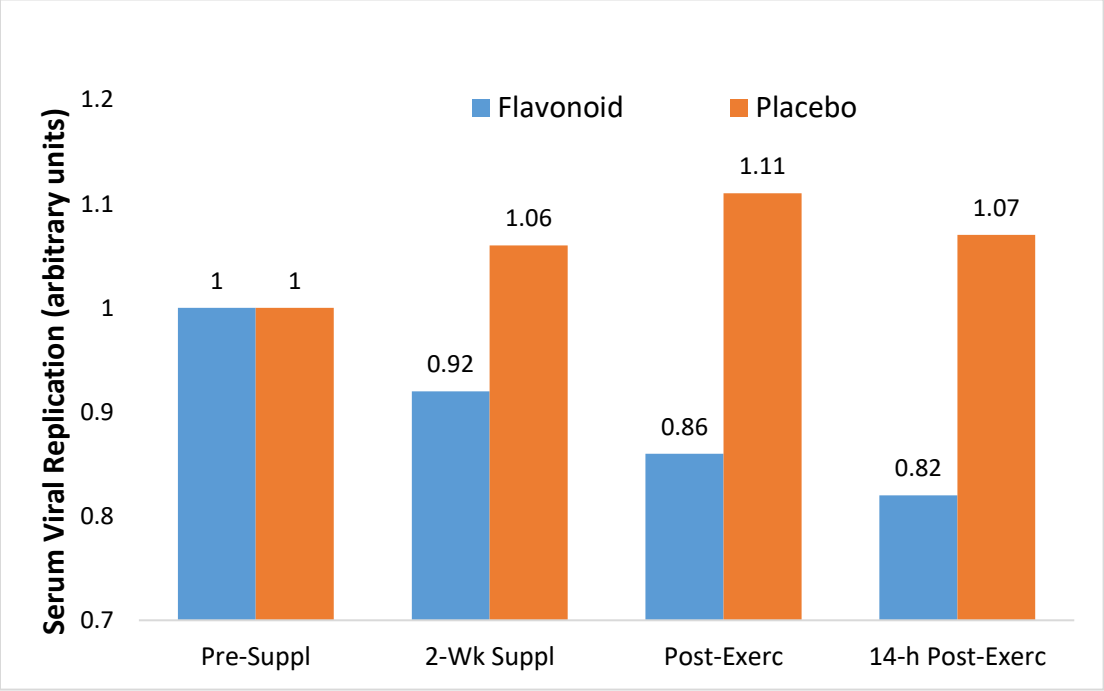


Figure 4: *Ingestion of a supplement with blueberry and green tea extract countered the exercise-induced increase in the capacity of viruses to multiply in the blood of athletes after a 3-day period of overtraining. Data from Ahmed, Nieman, et al. (2014).*

CONCLUSIONS

Taken together, there is strong literature support for the following claims regarding Bionuvo ingestion:

1. Improved vigilance, attention, working memory, reaction time, and psychomotor processing speed.

2. Decreased inflammation and oxidative stress in the general population, and in athletes after heavy exertion.

3. Support of good immune function and a reduction in acute respiratory illnesses for both athletes and nonathletes.

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