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PLANT-DERIVED PHYTOCHEMICALS TO ENHANCE COGNITIVE FUNCTION AND ALERTNESS

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- Psychoactive plant-derived phytochemicals are "secondary metabolites" that play ecological roles for the synthesizing plant.
- The effects of the three predominant structural groups – phenolics (including polyphenols), terpenes and alkaloids – on human brain function correspond broadly to their differing ecological roles.
- Polyphenols are the primary beneficial component in fruit, vegetables and plant-derived foods/drinks, and improve cardiovascular and cerebrovascular function. Cognitive and mood effects are less clear.
- Volatile terpenes, such as monoterpenes from a number of culinary herbs, diterpenes from *Ginkgo biloba*, and triterpenes from ginseng and bacopa, can exert beneficial effects on cognitive function and alertness relevant to sport.
- Among the toxic alkaloids, only nicotine and caffeine are both legal and show some efficacy in terms of relevant aspects of brain function. However, their use is potentially confounded by habituation and withdrawal.

INTRODUCTION

Optimal sports performance clearly depends in part on several aspects of cognitive functioning. Psychomotor function and other aspects of attention/concentration, spatial and informational working memory, and executive function (the overarching set of higher-order cognitive processes that control all aspects of behavior) are all intrinsic components of sporting performance, with the comparative contribution of each dependent on the demands of differing sports. Similarly, high alertness and low mental fatigue will naturally have a ripple effect on cognitive function, motivation and performance. All of these aspects of cognitive function and psychological state are amenable to modulation by the consumption of selected plant-derived "phytochemicals."

These phytochemicals are typically "secondary metabolites" (i.e., they have no role in primary metabolism) that fulfill "ecological" roles for the synthesizing plant, increasing its ability to survive by allowing it to interact with its environment. Most phytochemicals fall into one of three structural groups that can be differentiated by the ecological roles that they play. "Phenolics" are present in all plant material where they play primarily protective roles in the face of environmental stressors. They provide color, antioxidant, anti-ultraviolet light and antimicrobial protection, particularly in the outer layers of leaves, fruits, etc., and manage the plant's relationships with symbiotic microbes in the soil. "Terpenes" play dual roles depending on the plant tissue and mode of delivery: the simpler, volatile terpenes act as attractants for pollinators or other symbiotic animals at low, airborne doses, and as toxic deterrents at the higher concentrations found in plant tissue and on the surface of leaves. The more complex terpenes tend more toward toxic deterrence of herbivorous insects and invertebrates, including via interactions with their nervous and hormonal systems. The final structural group, "alkaloids," play almost exclusively toxic roles, again potentially via direct interactions with the nervous systems of herbivores (Kennedy, 2014a).

The differing ecological roles of these phytochemicals have parallels in their effects in humans; therefore, the following brief review of their psychoactive effects in this Sports Science Exchange article is subdivided accordingly. As there are very little data collected in a sporting context, the following is based on the wider human-controlled-trial literature (see Kennedy, 2019 for an expanded review). It would be difficult to argue that most of the findings from this body of research did not apply equally to a sporting context.

PHENOLICS

The most intensively studied group of phytochemicals, the 'phenolics,' can incorporate one (simple phenolics) or more (polyphenols) phenyl aromatic hydrocarbon ring within their structure. The polyphenols can then be further subdivided, with most falling into the flavonoid subgroup (itself subdivided into flavanones, flavones, flavonols, isoflavones, flavanols, and anthocyanins). The single molecule units of several of these subgroups can link themselves together into more complex dimers, oligomers or polymers (two, several, and many units, respectively) which then typically have to be dismantled into smaller units by gut microbiota in the consumer's large intestine.

Phenolics are an unavoidable part of the human diet, and the primary health-promoting components of fruit and vegetables (alongside micronutrients and fiber). The greatest quantities are consumed in the form of beverages such as wine and tea, fruit and fruit juices, and vegetables, but they exist at low levels in processed and high-energy foods. Although typically described as antioxidants, their effects in consumers are attributable to their ability to interact within the cellular signal transduction pathways that carry information within cells, typically toward the nucleus. Examples include information about the cell's internal and external energy status, and external activity, stressors, inflammation, and infection. Phenolics do this by interacting with receptors (membrane or nuclear), or within the complex dominolike signaling cascades. The net effect is modulation of a wide range of cellular responses, which can result in, for instance, endogenous antioxidant, vasodilatory and anti-inflammatory responses in the body. In terms of the brain, the same mechanisms can include direct neurotransmitter receptor interactions, an increase in the growth factors that drive synaptic plasticity, and synthesis of the vasodilatory molecule nitric oxide (NO), leading to an increase in local cerebral blood-flow, which in turn fosters angiogenesis/neurogenesis. One further mechanism that is coming under increasing scrutiny is the role of phenolics in the modulation of the gut microbial communities, which play a bidirectional role in cardiovascular and brain function – a role that mirrors their management of nutrient-absorbing, symbiotic microbial populations in the plant's root system. (Kennedy, 2014b)

Individual epidemiological studies and meta-analyses clearly show that the consumption of polyphenols or polyphenol-rich foods is related to protection from all aspects of cardiovascular disease, the incidence of cerebrovascular disease and dementia, and improved cognitive function and reduced cognitive decline in middle-aged and older populations (Kesse-Guyot et al., 2012; Tresserra-Rimbau et al., 2014). The cardiovascular benefits have also been confirmed in a large body of controlled intervention trials, principally involving polyphenols derived from cocoa, which have demonstrated consistent beneficial effects across metabolic and cardiovascular parameters, including peripheral blood flow (Lin et al., 2016). These effects are achievable at doses between 200-500 mg of flavanols within 2 h of consumption of the first dose.

There is also consistent evidence, garnered from more than a dozen brain imaging studies, that single doses and chronic consumption of polyphenols at similar doses to the above can increase cerebral blood flow (Bowtell et al., 2017; Kennedy et al., 2010). However, while these studies also typically measured cognitive function, there is very little evidence of any concomitant cognitive benefits.

Looking at the wider literature, there is some evidence that single doses of polyphenols, derived, for instance, from cocoa and fruit, improve attention and spatial/working memory performance. However, several studies also fail to report any interpretable benefits. The best evidence comes from chronic consumption studies – in particular, a pair of methodologically identical studies carried out in 90 healthy elderly participants (Mastroiacovo et al., 2015) and 90 sufferers from age-related cognitive impairment (Desideri et al., 2012), respectively. Participants received drinks containing 520 mg or 990 mg flavanols or control for 4 wk. In both studies, the high-flavanol drink was associated with cardiovascular benefits and improved performance on one or two cognitive tasks that assessed attention and executive function. However, a number of studies assessing the longer-term effects of cocoa-flavanols and fruit polyphenols have generated either very subtle effects or null findings.

TERPENES

Terpenes are composed of units of the volatile, organic, 5-carbon compound isoprene. Monoterpenes and sesquiterpenes (2 and 3 isoprene units, respectively) are also volatile, evaporating into the air, and are synthesized by all plants as the main volatile components of the vapors, such as floral bouquets, that attract pollinators and symbiotic animals. A subgroup of plants use these volatiles in defensive roles, and as such they are delivered at much higher doses to herbivores via mechanisms such as bladder-like glandular trichomes on the insect-favored underside of the leaf. Often, the volatile terpenes used in these dual roles are the same chemicals that insects synthesize for their own "pheromone/allomone" communication purposes. A minority of plant clades have also evolved the specific use of higher molecular weight terpenes, such as diterpenes and triterpenes (4 and 6 isoprene units, respectively) in ecological roles. In both cases they exhibit insecticidal and antifeedant properties, potentially via direct interactions with the nervous system of herbivores. The triterpenes additionally disrupt the life cycle of insects and other herbivores due to their structural resemblance to animal hormones. This group can also interact with pathogenic and symbiotic soil microorganisms via bacterial/fungal "estrogen-like" receptors (Kennedy, 2014a).

Monoterpenes

The *Nepetoideae* subfamily of the *Lamiaceae* family of plants, which provides most of our culinary herbs and many essential oils (distilled volatile terpenes), is a particularly rich source of plants that use volatile terpenes in dual ecological roles. Members include psychoactive herbs such as rosemary, lemon-balm, sage, and peppermint. This group typically synthesizes monoterpenes and sesquiterpenes such as 1,8-cineole, α-pinene camphor, geraniol, geranial, borneol, camphene and ß-caryophyllene. Extracts from this family of plants share common (but variable) mechanisms of action relevant to the brain, for instance, inhibiting acetylcholinesterase and binding allosterically to *gamma*-aminobutyric acid ($GABA_A$, part of a ligand-gated ion channel complex), nicotinic, and muscarinic receptors (Kennedy, 2014a). Members of this group (e.g., lemon balm [*Melissa officinalis*]) that have anxiolytic/sedative properties, due to GABAergic properties, would be unlikely to have beneficial effects on cognitive function in a sporting context.

Sage *(Salvia officinalis/lavandulaefolia).* Whole extracts and volatile terpene essential oils (25-50 µl) have both consistent cholinesterase inhibitory properties and beneficial effects on cognitive function and/or mood. For the essential oils, this has included improved working memory, executive function and increased alertness (Kennedy & Wightman, 2011). In the most recent placebo-controlled study, the consumption of single doses of 50 µl of monoterpene essential oil, high in 1,8-cineole, led to improved memory and attention task performance alongside increased alertness and reduced mental fatigue over the next 4 h (Kennedy et al., 2011).

Rosemary *(Rosmarinus officinalis).* Psychoactive properties may relate to cholinergic receptor binding and cholinesterase inhibitory properties. The bioavailability of monoterpenes via pulmonary absorption during aromatherapy have been confirmed in two studies in which plasma levels of 1,8-cineole increased alongside exposure to rosemary essential oil vapor, and correlated with subsequent changes in performance of attention, working memory, prospective memory and executive function tasks (Moss, 2017). Comparatively low single and chronic doses (500-750 mg) of dried rosemary leaf have also been shown to enhance subjective or objective measures of memory performance and improve alertness or mood, but with evidence that these benefits were reversed at higher doses (Pengelly et al., 2012).

Peppermint *(Mentha piperita).* Peppermint essential oils, or menthol alone, have cholinesterase inhibitory and interactive properties at nicotinic, 5-hydroxytryptamine (HT_3), $GABA_A$, glycine and κ-opioid receptors. Pilot studies have previously shown that peppermint tea and peppermint essential oil dripped on the tongue, both in comparison to water, can improve memory and attention functioning and physical performance within minutes of consumption. In the only double-blind, placebo-controlled study to date, young participants received encapsulated peppermint essential oil (50 µl/100 µl) that had been selected on the basis of its *in vitro* ability to inhibit cholinesterase and bind to nicotinic and $GABA_A$ receptors. Consumption of the highest dose of essential oil resulted in improved performance of a focused attention task and improved serial subtraction task performance and mental fatigue within the first 3 h post-dose (Kennedy et al., 2018,).

Diterpenes

Ginkgo biloba. While there are a number of psychoactive diterpene synthesizing plants, the only member of this group with evidence of relevant psychological benefits is *Ginkgo biloba*. Standardized extracts typically contain 6% diterpene ginkgolides and their bilobalide derivative (alongside 24% polyphenols). Meta-analyses suggest that Ginkgo extracts may exert promising cognitive and behavioral effects in dementia sufferers. In healthy populations, extracts taken for several weeks have been shown to increase cerebral blow flow and enhance cognitive function, including in terms of attention task performance following single doses and longer-term consumption (Kennedy & Wightman, 2011). As an example, 12 wk of Ginkgo supplementation improved attention, memory and subjective ratings of physical health in 300 participants (Grass-Kapanke et al., 2011).

Triterpenes

Many of the triterpenes' ecological interactions and physiological effects in humans can be attributed to their structural similarity to the triterpene hormones endogenously synthesized by humans (e.g., human sex and glucocorticoid hormones), insects, invertebrates and plants. Many triterpene-containing herbal extracts are traditionally classified as "adaptogens" – a term which denotes that they primarily function by protecting the consuming organism from the negative impact of physical, biological, chemical and psychological stress by modulating the hypothalamic-pituitary-adrenal (HPA) axis. In this regard, a number of these triterpenes have been shown to interact with multiple mammalian steroid hormone receptors, including ubiquitous estrogen and glucocorticoid receptors. These interactions could underlie their multifarious interactions they enjoy with the nervous system function, including bolstering NO synthesis and modulating neurotransmission (Kennedy, 2014a).

Ginseng *(Panax ginseng).* The active components here are triterpene 'ginsenosides.' While evidence of ergogenic effects is somewhat equivocal, meta-analyses show that ginseng may be an effective treatment for ischemic heart disease and erectile dysfunction. In terms of human brain function, a number of randomized, controlled, balanced-crossover single-dose (200-400 mg extract) trials have demonstrated consistent improvements in the accuracy of memory tasks, the speed of attention task performance, and improved the performance of difficult working memory/executive function tasks. Cognitive benefits in terms of working memory and mood (calmness) following 7 or more days of supplementation have also been reported (Kennedy & Wightman, 2011).

Bacopa *(Bacopa monnieri).* The active constituents here are triterpene bacosides/bacopasides, which may interact with acetylcholine, opioid, and GABA neurotransmitter systems and the HPA axis (Kennedy, 2014a). In humans, a recent meta-analysis of the data from nine chronic dosage (> 12 wk) randomized, controlled trials found that supplementation with ~300 mg/day of Bacopa extract improved attention task performance and speed of processing (Kongkeaw et al., 2014).

Other triterpenes: A meta-analysis showed that chronic consumption of asiaticoside-containing *Centella asiatica* (Gotu kola) extracts engendered significant increases in subjective alertness and calmness (Puttarak et al., 2017). Single studies have also demonstrated relevant improvements in cognitive function following a single dose (800 mg) of an *Avena sativa* (wild green oat) extract and 2 months administration of Withania somnifera and Rhodiola rosea – all of which contain triterpenes.

ALKALOIDS

Alkaloids are a structurally diverse group of low molecular weight compounds that contain one or more nitrogen atoms, typically as part of an amine group. They are synthesized in exclusively toxic, defensive roles against herbivorous insects and invertebrates by approximately a fifth of all plant species. Interference with all aspects of neurotransmission is one of the hallmark functions. Because of this, the group includes many psychotropic medicines and most of our social and illicit drugs. Given their toxicity, legal status and psychopharmacological properties, few alkaloids would confer any potential benefits in a sporting context, with two exceptions.

Nicotine

Nicotine binds agonistically to ubiquitous acetylcholine nicotinic receptors, with downstream effects throughout numerous neurotransmitter systems. Regular use will result in addiction, and habituation/

withdrawal effects as nicotinic receptor populations and sensitivity change. While nicotine exerts cardiovascular effects potentially relevant to improved physical performance in nicotine-naïve consumers, there is little persuasive evidence of actual performance improvements (Johnston et al., 2017). The story regarding brain function is better. A meta-analysis of the data from 50 studies demonstrated that, irrespective of withdrawal, nicotine led to consistent improvements in cognitive performance in a number of domains, including fine motor tasks, the speed of response on attention, and working memory tasks and the accuracy of attention and short term memory tasks (Heishman et al., 2010).

Caffeine

The most commonly consumed psychoactive phytochemical, caffeine, unlike other co-occurring methylxanthines, has rapid and consistent central nervous system effects due to inhibitory binding to adenosine A_1 and A_2 receptors (McLellan et al., 2016). Caffeine, particularly in anhydrous form, has well-established ergogenic properties and has been shown to enhance performance of both endurance exercise and high-intensity and intermittent exercise. These benefits are attributed primarily to its effects on the central nervous system at moderate/high doses (~3-6 mg/kg or 225-450 mg for a 75 kg person) (Goldstein et al., 2010). However, lower doses of 32 mg and above have been shown to enhance brain function, with effects plateauing at 300 mg. Caffeine's effects on psychological function are generally limited to increased subjective arousal/alertness, and improved performance of psychomotor tasks and "simple" attention, focused attention and vigilance type tasks. Caffeine has inconsistent effects on working memory and executive function tasks and no interpretable effect on memory function (McLellan et al., 2016). As with nicotine, the use of caffeine in a sporting context is complicated by habituation and withdrawal in regular consumers.

Caffeine interactions. Caffeine consumed in other naturally occurring forms, such as coffee, is also effective for improving performance during endurance exercise (Higgins et al., 2016). Evidence also suggests that caffeine may enjoy additive or synergistic relationships when co-consumed with other bioactive compounds. For instance, the brain function effects of caffeine are differentially modulated, or vice versa, by the co-consumption of other phytochemicals (Haskell et al., 2013), and a host of other food components. Low doses of caffeine have also been shown to increase the bioavailability of a number of phenolic compounds. A recent human study found that when caffeine was co-consumed with cocoa-flavanols, plasma flavanol metabolites and cardiovascular effects were increased in comparison to cocoa-flavanols alone. Caffeine alone had no effects (Sansone et al., 2017).

Guaraná (Paullinia cupana): Guaraná is a good example of a potential caffeine/phytochemical interaction. The cognitive and mood effects of extracts are typically attributed to their caffeine content, despite the presence of high levels of polyphenols and triterpene saponins. Research shows that guaraná extract (75 mg) can improve attention, executive function and working memory tasks, and engender dose-related (37.5, 75, 150 and 300 mg guaraná) increases in alertness, 'contentedness' and memory task performance, with the most effective doses containing the levels of caffeine associated with a cup of decaffeinated coffee (4.5-9 mg) (Haskell et al., 2007). A recent study also showed that a guaraná plus multivitamin/minerals improved executive function/attention task more than its caffeine content alone (Pomportes et al., 2014).

PRACTICAL APPLICATIONS

- It is clear that consuming more polyphenols, either in the diet or as supplements (optimal dose 200-500 mg), can be associated with almost immediate, wide-ranging benefits to cardiovascular function and cerebral blood flow. There is a high probability that these factors will result in improved brain function over the long term. However, the evidence regarding improvements in cognitive function and psychological state following short-term supplementation is currently somewhat equivocal.
- Edible terpenes are not associated with any negative side effects. Beyond sage, rosemary and peppermint leaf, and essential oil (effective dose: sage 50 µL, peppermint 100+ µL), it is possible that other edible monoterpene-rich herbs exert beneficial psychoactive effects. However, those with traditional uses as anxiolytics or sedatives, such as lemon balm, should be avoided. For the triterpenes, both single doses of ginseng extract (200-400 mg) and chronic dosage (300+ mg) with bacopa have established beneficial effects, but there is little information about the opposite treatment regimen for either.
- The regular use (for instance during training) of nicotine and caffeine may cause habituation and potential withdrawal effects that are likely to confound any acute benefits. Products combining low doses of caffeine with other phytochemicals (e.g., guaraná, flavanol-rich chocolate/extracts) may exert benefits that are greater than those associated with their components, but it remains an unexplored possibility that these effects would also attenuate in regular consumers of caffeine.

SUMMARY

A number of phytochemicals have cognitive and alertness/arousal effects that may be relevant to improved sporting performance. Broadly, these effects relate to the ecological roles of the phytochemical groups. Phenolics, which currently attract by far the most research attention, are intrinsic to good health and cardiovascular/cerebrovascular function as part of the everyday diet. However, the evidence of additional benefits to cognitive function and mood following short-term supplementation is currently weak. This profile of functional effects is in keeping with their plant roles as general protectants. Terpenes and alkaloids, which are not a natural, unavoidable component of the diet, serve ecological roles that include interactions with the central nervous systems of symbiotes and/or herbivores and therefore might be expected to exert more striking effects on brain function. Terpenes tend to be overlooked, but the evidence of beneficial cognitive and mood effects is promising for several edible, monoterpene-expressing herbs such as sage, rosemary and peppermint; diterpene-rich Ginkgo biloba; and several triterpene-rich extracts, including ginseng and bacopa. While research is lacking in some respects for all of these extracts, they are all safe and well-tolerated and none are associated with significant negative effects on any parameter. Alkaloids, as the archetypal plant defence compounds, often have intense effects on neurotransmission in both herbivores and human consumers. Their potency, toxicity, and legal status mean that only nicotine and caffeine currently have any obvious potential role in cognitive enhancement in a sporting context. However, nicotine is addictive, and the contribution of habituation and withdrawal effects, and therefore dosage patterns, for both compounds need to be considered. Some interesting data is emerging in regard to potential additive effects and synergies when phytochemicals and lower doses of caffeine are co-consumed, and phytochemical or nutrient rich extracts containing low doses of caffeine might be a rational approach for enhancing cognitive function.

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