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Review Article

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Cognitive Enhancers Derived from Edible Crops

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Abstract

The concept of an effective cognitive boosting nootropic supplement is gaining traction with consumers, neuroscientists and regulators alike and it is therefore unsurprising that scientifically validated Nootropics are highly prized. New research demonstrates edible crops could be useful sources to mine for new nootropics; plant extracts enriched with an array of cognitive enhancing metabolites. There is merit in investigating these plant species. Metadata has identifies consuming specific fruit and vegetables positively affects cognitive function; therefore these same edible crop plants present as opportunities for developing nootropic formulations. This hypothesis is supported by positive data obtained through clinical testing [e.g. extracts of tomato (*Solanum lycopersicum*), herbs from the Genus *Salvia*, cocoa (*Theobroma*), tea (*Camellia sinensisor*) and coffee (*Coffea Arabica*). This review will discuss clinically tested cognitive enhancers derived from edible crop species and discuss their use alongside other classes of nootropics.

Keywords: Cognition; Nootropic; Plant-based

Introduction

There are a myriad of different supplements all targeted towards the consumer interested in cognitive enhancement. Some products have formulations rigorously tested to demonstrate efficacy, claims supported by clinical testing. Some products however lack test data and are often branded with 'soft' claims. Other nootropics are blends of known neuro-stimulants, although this may result in increased risk of side effects. There is a growing interest for supplements or bioactive compounds that originate from widely eaten plants species including crop plants e.g. tomato and tea [1,2], nootropics that are effectively already consumed as part of a healthy diet. This review will present peer-reviewed evidence for supplements derived from these sources in order to evaluate and compare supporting data and discuss potential for novel applications in the nootropic space.

A number of reviews have described the potential for beneficial effects on cognition of supplementation with nootropics [3,4]; published literature describes formulations prepared from chemically synthesised additives or botanicals [5,6] and reported effects link to neuroprotection and neurocognitive stimulation [7]. Additional review articles have discussed the relationship between diet and cognition [8] and attempts to dissect the link between nutritious content and neurobiological outcome [9]. It is however timely to review and discuss the application of targeted nootropics derived from edible crop species.

Compounds that stimulate cognitive function are under development or have been trialled as potential therapeutics in response to specific medically diagnosed conditions [6,10]. However, although tested for both efficacy and safety, in some instances misuse of prescriptive medicines as nootropic supplements may be result in harmful side effects. Nootropics are widely used with North America holding the leading share of sales (37%, 2018), however the Asia Pacific region is forcast to show the fastest growth in consumption increasing by 18% from 2019 to 2025 (Source: grandviewresearch.com). Product categories in space include memory enhancement, amelioration of depression or mood enhancement, boosting traits linked to attention and focus or alleviation of anxiety. This review will only focus on non-prescriptive nootropics in these spaces. Pharmaceutical products are not intended for use outside strictly defined medical conditions and will only be referred to as and when appropriate.

The term cognition covers many different aspects of the mental faculties [11]. Cognitive processes may be coordinated and co-regulated, or independent and distinct. This is an important consideration when deciding on appropriate compositions or formulations for multi-ingredient or stacked nootropics i.e. multiple different bioactives in one dose. The number of supplements and bioactive compounds that can affect cognition is also broad, with many different reported mechanisms of action. Demonstrations of efficacy for supplements range from no supporting research, those presenting with limited data and statistical analysis, to products tested and published in peer reviewed trials. We would suggest only the latter may be considered as proven nootropics, since it is only fully tested products that provide a robust demonstration of efficacy. The use of supplements without evaluated supporting validation should be considered with caution [12].

The aim of nootropic development is to assess and carefully select supplements or ingredient compounds that improve cognition, lack toxicity and show little or no disruption to healthy neurological processes. With this in mind sourcing compounds from widely available crop plants with existing dietary links to cognitive benefit, may be a useful strategy for developing extracts or identifying compounds with nootropic activity.

Evidence for Nootropics derived from extracts of crop species

(see table 1 for examples of different trials reporting nootropic activity testing extracts derived from these sources).

Source	Reference	Partici-pants	Cogantive measures	Functional ingre-dients	Study conclusions
Coffee	Lieberman, *et al.* [23]	68	Visual Vigilence, four choice visual reaction time, matching to sample working memory task and a repeated acquisition test of motor learning and memory.	100, 200 or 300 mg caffeine	Caffeine (200 and 300mg) significantly improved visual vigilance, choice reaction time, repeated acquisition, self-reported fatigue and sleepiness with the greatest effects on test of vigilence, reaction time, and alertness.
	Sands, *et al.* [25]	29	Mood and psychomotor assessments were carried out at baseline and 30 minutes postdrink. Bond-Lader visual analogue scales (VAS) and caffeine research VAS were used to assess mood, while three simple motion tasks (using an accelerometer device to record dynamic bodily movement) were used to assess psychomotor control.	150 mg caffeine	Moderate consumers reported significantly worse headaches and experienced more tremors on accelerometer. Following caffeine, ratings of calmness significantly decreased.
	Cropely, *et al.* [30]	39	Mood and cognitive process as measured by behavioral tasks and event - related potentials.	224 mg CGA, 5 mg caffeine; 521 mg CGA and 11 mg caffeine; 244 mg CGA, 167 mg caffeine	Non-caffeine compounds in coffee such as the chlorogenic acids may be capable of excerting some acute behavioral effects.
Cocoa	Karabay, *et al.* [35]	63	Spatial working memory	250 mg or 500 mg cocoa flavanols	Behavioral measures of accuracy and reaction time were not found to be significantly different between treatment groups, significantly different between groups during memory encoding, the working memory hold period and retrieval.
Sages	Tildesfey, *et al.* [37]	44	Congnitive drug research computerised test battery.	25, 50, 100 and 150 microl of a standardized essential oil extract	50 µl dose of salvia essential oil significantly improved immediate word recall in both studies.
	Pengelly, *et al.* [38]	28	General cognitive performance	750 mg, 6000mg of rosemary	Dose-dependents effect in measures of speed of memory: 750 mg of rosemary statistically significant beneficial effect, whereas the highest dose (6000mg) had a significant impairing effect.
Dietary association	Calil, *et al.* [42]	96	Brief cognitive Screening Battery, Mini-Mental State examination.	Mediterranean and MIND diet	Moderate adherence to the Mediterranean and MIND dietary patterns may be associated with better cognition among healthy seniors.
	Torres, *et al.* [43]	249	Cambridge Cognitive Examination.	Dietary pattern	A diet high in processed foods was associated with some level of cognitive impairment.
	Samieri, *et al.* [45]	16058	Telephone Interview for cognitive Status.	Dietary pattern	Long-term MeDi adherence was related to moderately better cognition but not with cognitive change.
Tomato	Nilsson, *et al.* [47]	40	Working memory capacity, selective attention, and psychomotor reaction time.	150g blueberries, 50g blackcurrant, 50g elderberry, 50g lingonberries, 50g strawberry, and 100g tomatoes	Subjects performed better in the working memory test after supplementation relative to placebo.
	Chapman, *et al.* [1]	17	Detection speed and scores identification speeds and scores, visual learning speeds and scores.	290mg tomato extract (Nomato ™)	Significance reported for overall effects of treatment (detection speeds, and scores) and additionally for the identification speed. A suggestion of treatment effects was observed for identification scores.

Table 1: Examples of types of trial undertaken, statistically significant data returned ($P<0.05$) and conclusions from each study

Tea as a beverage or Tea extracts (*Camellia sinensis*)

Tea, one of the most widely consumed beverages worldwide. Ingredient bioactive compounds identified in tea include flavonols and polyphenols [13]. Interestingly different cultivars or processing techniques have been shown to alter the relative level of these compounds [13]. Teas such as Oolong include an oxidization step, which may differ between processing methodology and change metabolite composition [14]. Therefore it is likely that effects of any supplement derived from tea may depend on the processing methodology used in preparation.

Many different health promoting properties such as energy-homeostasis, cardio protection has been assigned to tea [15]. Effects may at least in part link to levels of the ghrelin receptor agonist's tea ghrelin [15]. Ghrelin activity is linked to appetite and has been demonstrated to impact the modulation of pancreatic secretions [16] and may impart explain those health promoting processes reported in the literature [17]. Interesting new research has identified that the Ghrelin pathway may have positive neurocognitive effects of the Hippocampus region of the brain; combatting degenerative processes such as those found in Alzheimer's disease by eliciting an ameliorative and regenerative response [18]. Ghrelin has also been found to modulate cognitive processes in other brain areas with stimulatory effect reported for memory retention [19]. Further research is required to elucidate if neuronal stimulatory effects tie with activity in promoting energy-homeostasis.

Caffeine (Coffee / tea)

Caffeine is a well-known and well-studied bioactive identified in Coffee beans and tea leaves. Traditionally consumed in drinks, Caffeine is also popular as an additive to nootropic supplements. Doses of up to 300 mgs pf Caffeine have been shown to enhance different aspects of cognitive activity, including attention mood and reaction times [20-22] while preventing decrements in alertness and attention [23]. Further testing identified that doses of caffeine improved both speed and scores in detection skills testing [24]. Although caffeine has been reported to positively affect traits such as psychomotor function, ratings of alertness, it should be noted that negative traits such as tremor and jitteriness also significantly increase, while reported ratings of calmness significantly decrease [25]. Sleep patterns may also be disrupted by caffeine consumption, especially if caffeine is ingested during exercise or in the evening [26]; lack of sleep is known to impair attention and working memory and may impact on other neurological functions, such as long-term memory [27]. The caffeine substitutes Methylliberine, sharing similarities with caffeine in chemical structure, is hypothesized to have similar beneficial and negative physiological properties [28]. Therefore, while caffeine or Methylliberine may positively correlate with improvements in some cognitive skills, effects of treatment may also result in counter-productive side effects diminishing these same attributes.

It should be noted that Coffee is also rich in a number of other secondary metabolites of interest e.g. such as polyphenols, chlorogenic acids with health promoting properties [29]. Clinical testing has assessed effects of treatment with chlorogenic acids on cognitive function; administration of beverages enriched with these polyphenols positively affected mood and mood-related behaviour [30]. Recent research suggests that long-term consumption of chlorogenic acids may improve cognitive function in the elderly [31]. This research demonstrates the potential for finding not one, but many nootropics within crop species possessing a diverse array of secondary metabolites; each with possible different mechanisms of action.

Cocoa (Genus *Theobroma*)

Cocoa is a popular and globally consumed food-stuff. Although widely known as a crop species producing beans used in the confectionary industry, this plant also possesses metabolites linked to improved cognition. Some compounds are functional ingredients with mechanisms of action described in this review such as methylxanthine caffeine [32]; cocoa beans however are also a rich source of flavonoids such as epicatechin and catechin [33]. These flavonoids may exert effects on cognition via a range of mechanisms e.g. protecting neurons from oxidative damage, neuronal regeneration and differentiation resulting in improved long-term potentiation and traits such as memory [34]. Positive effects on cognitive skills have been demonstrated in a number of clinical studies including placebo controlled tests to evaluate cocoa drinks containing 500mg and 250mg flavanols when dosed over a 30-day test period. This study identified improved working memory function after flavanol treatment [35]. A second study testing cocoa drinks containing 494mg and 23 mg flavanols administered daily over a 28-day period concluded that supplementation provided beneficial effects on global cognition following high-flavanol treatment [36]. Collectively this data suggests that flavanols present within Cocao improve aspects of cognition and that these effects are dose dependant. This research also further supports the notion that crop species such as Cocao may possess many different types of compounds with nootropic activity.

Herbs – Sages

Genus *Salvia* commonly known as sage, a label with historic reference to purported cognitive enhancing properties. Tildesley *et al.* [37] reported a dose-specific effect on cognitive traits such as delayed word recall and speed of memory access. The widely consumed herb Rosemary is also classified in the genus *Salvia*. Cognitive testing of rosemary [*Rosmarinus officinalis*] [38] also identified beneficial effects on speed of memory recall in a placebo controlled trial. Collectively these studies demonstrate extracts sourced from plants in the genus *Salvia* have positive cognitive benefits [39]. Interestingly these effects may be due to a number of different effects on a number of diverse neurological pathways [40]. It should be noted that additional safety trials investigating extracts of *Salvia* also recorded increases in blood pressure in two patients with a history of hypertension [41]. This suggests benefits may be achieved with this supplement; however caution should be exercised when supplementing with Sage. Further research is therefore required to fully evaluate the link between the mechanism

of action and benefits to specific traits. A better understanding of the effects of supplementation with *Silvia* may allow optimised dosing or formulation as a nootropic i.e. together with other bioactive extracts.

Tomato [*Solanum lycopersicum*]

Diets rich in tomato such as the Mediterranean diet have been linked to improved cognitive skills in a number of different studies [41]. Adherence to the Mediterranean diet associated with higher scores on the brief cognitive screening battery test and mini-mental state examination test; data demonstrating nootropic effects in healthy test participants [42]. Other studies have reported benefits of tomato rich diets to individuals with mild cognitive impairment [43]. Reports suggest adherence to a Mediterranean diet associates with reduced rates of cognitive decline and a reduced risk of developing Alzheimer disease; conclusions supported by data demonstrated in 4 of 6 cross-sectional studies, 6 of 12 longitudinal studies, 1 trial, and 3 meta-analyses test [44]. Effects of conformation to this diet have also been linked to improvements in specific traits such as verbal memory score [45]. Research has been undertaken to try and dissociate different components of a Mediterranean diet and establish their relative impact on cognitive function, however attempts so far have met with only limited success [46].

Supplements containing either tomato extract or tomato as an ingredient have also been trialled in clinic. A study conducted by Nilsson *et al.* [47] enrolled 40 subjects [30 women and 10 men] tested the effects of supplementation of a fruit based beverage containing this fruit [150g blueberries, 50g blackcurrant, 50g elderberry, 50g lingonberries, 50g strawberry, and 100g tomato]. This trial identified statistically significant improvements in working memory performance after consuming this drink; in-brief, a five week intervention with this beverage improved performance in working memory when tested 30 min after breakfast by ~5% in comparison to the control beverage [$P = 0.039$] [47]. Additional testing using only tomato extract also identified cognitive benefits in rodent models which replicate age linked cognitive decline [48]. Collectively this data suggests that both tomato supplementations may have beneficial effects on cognitive skills in both human and *in-vivo* rodent models.

Tomato extracts derived from a specially selected edible cultivar tomato [Noomato™] and formulated as a supplement have also been trialled in recent research. This study was designed to identify benefits to individuals when undertaking controlled physical exertion [1]; a stressor known to negatively impact on cognition. Supplementation with capsules containing 290 mg tomato fruit extract improved [$P<0.05$] normalized detection scores and detection times after 90 minutes exercise. A positive effect was noted on normalised psychomotor scores and speed of responses. Additional improvements were also recorded when measuring identification task speed of response. This data presented for this extract [Noomato™] suggests that nootropic activity of compounds found in tomato extend to improvements in cognitive performance while under stress.

Some tomato extracts contain high levels of an inhibitor of the pro-inflammatory cytokine IL-6 [49]. IL-6 is a hormone-like cytokine with pleiotropic capabilities including signalling within the central nervous system [CNS] [50]. Interestingly, dysregulation of IL-6 has been linked with many different negative neurological effects; data consistent across a number of different trials consisting of large numbers of trial participants [51]. It is likely that IL-6 acts to impair neurogenesis, which intern impacts on neuronal health [52]. The large volume of data obtained using many different trial designs and reported in a number of different independent studies suggests pathways associated with IL-6 are frequently dysregulated within the population, across many different individuals and impact on many different cognitive traits.

Neurotransmitter / Neurotransmitter precursor class

Dopamine [Neuro-stimulant]

Dopamine is a neurotransmitter that binds to neuronal receptors to facilitate neuronal signalling [53]. This chemical acts within the central nervous system and acts to control movement, locomotion, learning and working memory [54]. Supplements linked to modifications of the dopamine pathway include the widely supplemented L-Tyrosine, a precursor to dopamine [55] and other neurostimulant compounds such as epinephrine [55]. L-Tyrosine is used as a supplement with mixed results to reduce the negative effects of physiological conditions that deplete dopaminergic resources, such as extreme stress [56]; reducing stress-induced impairments of working memory and tasks associated with attention [57]. However research has also identified that dopamine levels also widely vary between healthy individuals independent of task [51], suggesting that genetic variation may determine the effectiveness of L-Tyrosine supplementation. This hypothesis is supported by data suggesting that individuals carrying variants of key neuronal genes have varied endogenous dopamine levels [59].

Glutamate pathway

Glutamine is a precursor of the excitatory and inhibitory neurotransmitter glutamate [60]. This compound is a commonly used additive and widely offered as an easily-accessible nootropic. The glutamate pathway is involved in working memory, cognitive flexibility and executive functioning [61]. Mice lacking key glutamate receptors show impaired learning [62] and cell signaling events linked to dysregulated glutamate receptors may impair multiple aspects of the brain function [63].

Although the glutamate pathway is important to cognitive skills such as learning and memory [63], when supplements that affect glutamate are dosed at inappropriate or excessive levels, excessive stimulation of glutamate receptors can lead to excitotoxicity [64].

Genetic variation may play a role in determining responses to supplements linked to glutamate. Variation in sequence of genes along the glutamatergic pathway e.g. DTNBP1 associated with variation in verbal and visual memory in clinical testing [65]. A second gene GRM3 also significantly associates with episodic memory in similar tests [61]. It is likely that heterogeneity within these genes will impact on the effectiveness of glutamate as a supplement; genotype at these loci may also determine susceptibility or risk of negative side-effects.

Blending or stacking nootropics

A better level of cognitive enhancement may be achieved through blending different nootropics. This is a widely employed technique for many different supplements and may be used to obtain equivalent gains in efficacy, without risking adverse effects of elevated doses of one substance. Combinations of bioactives which act on distinct targets in the same pathway may result in adverse effects if incorrectly dosed. An example of biosimilar compounds included in multiple nootropic blends or 'stacks' is Methylliberine and caffeine. A combination of two interchangeable compounds could exceed a limit for an effect of pathway stimulation.

The level of cognitive boosting effects reported by the consumer may be complicated by the genetic background of individuals taking the supplement i.e. genetic variation within key pathway genes linked to the mechanism of action. Any perceived 'lack' of pathway effect may therefore be mitigated in part through the choice of compounds contained within the stack i.e. acting on a different target up-stream or down-stream within the pathway. Developing nootropics sourced from crops may be advantageous in this respect. Dietary compounds that show statistically meaningful effects on cognition within large trial sizes when consumed as a dietary component may present as good options for a stack. They will likely been consumed by wide number of people with different genotypes, retaining significant group-wide efficacy. Nootropics with these properties are likely relevant for use in a broad genetically diverse population.

Conclusions

Extracts sourced from edible crop species have demonstrable cognitive enhancing properties acting via diverse array of different mechanisms of action. Compounds found in tea may be linked to hormone growth receptors, while compounds found in tomato may suppress pro-inflammatory cytokines. These compounds are already widely consumed as part of a healthy diet and therefore present as new opportunities for blending together with existing nootropics possessing different mechanisms of action.

Collectively data published to date shows extracts prepared from edible crop plants have exciting potential for development as nootropics, new blending combinations with the potential to improve a range of different cognitive traits.

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