REVIEW

Herbal Extracts and Phytochemicals: Plant Secondary Metabolites and the Enhancement of Human Brain Function[1]

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ABSTRACT

Humans consume a wide range of foods, drugs, and dietary supplements that are derived from plants and which modify the functioning of the central nervous sytem (CNS). The psychoactive properties of these substances are attributable to the presence of plant secondary metabolites, chemicals that are not required for the immediate survival of the plant but which are synthesized to increase the fitness of the plant to survive by allowing it to interact with its environment, including pathogens and herbivorous and symbiotic insects. In many cases, the effects of these phytochemicals on the human CNS might be linked either to their ecological roles in the life of the plant or to molecular and biochemical similarities in the biology of plants and higher animals. This review assesses the current evidence for the efficacy of a range of readily available plant-based extracts and chemicals that may improve brain function and which have attracted sufficient research in this regard to reach a conclusion as to their potential effectiveness as nootropics. Many of these candidate phytochemicals/extracts can be grouped by the chemical nature of their potentially active secondary metabolite constituents into alkaloids (caffeine, nicotine), terpenes (ginkgo, ginseng, valerian, *Melissa officinalis*, sage), and phenolic compounds (curcumin, resveratrol, epigallocatechin-3-gallate, *Hypericum perforatum*, soy isoflavones). They are discussed in terms of how an increased understanding of the relationship between their ecological roles and CNS effects might further the field of natural, phytochemical drug discovery. *Adv. Nutr. 2: 32–50, 2011.*

Introduction

Approximately one-half of all licensed drugs that were registered worldwide in the 25 y period prior to 2007 were natural products or their synthetic derivatives. However, only 3 of a total of 84 psychotropics registered in this period fell within this class (1). Although the contemporary medical pharmacological arsenal includes an array of synthetic psychotropic medications designed to modify aspects of brain function in specific pathological groups, to date there are few mainstream options in terms of improving brain function for cognitively intact populations. These groups include the growing segments of our aging societies that suffer from natural, age-related declines in brain function. Even sufferers from dementia are offered few treatment options for their more severe cognitive deficits. Those that are available are generally potentially toxic cholinesterase inhibitors that were initially derived from alkaloid phytochemicals (2). These chemicals generally have a less than favorable efficacy/side effect profile (3). Contrast this with the multitude of off-the-shelf herbal supplements that purport to improve aspects of brain function and are commonly used in developed societies. As an example, ~20% of the population of the US takes herbal products, often in the absence of any good evidence of their effectiveness, with 6 of the 10 most popular products being consumed in the belief that they will beneficially modify aspects of brain function (4).

A huge scientific literature focusing on psychoactive herbal extracts and their phytochemicals, encompassing hundreds of thousands of scientific papers, has emerged over recent decades. The vast majority of these papers describe in vitro investigations of the potential mechanisms of action of putatively psychoactive phytochemicals, whereas a much smaller proportion explores their effects in vivo in animals and only a tiny minority investigate their efficacy in humans.

The following comprises a review concentrating on those few nonprescription plant extracts and phytochemicals that have garnered enough evidence in human trials to arrive at some sort of indication of their efficacy in terms of improved brain function. Several polyphenols that are attracting huge scientific interest and that are in the first stages of the human trial process are included for completeness.

Curiously, one question that is almost completely ignored in the vast literature surrounding the effects of natural psychotropics is why plant chemicals affect human brain function. The answer to this fundamental question is not only of academic interest but also has a number of practical implications for future research and product development. This review therefore includes a consideration

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of why the plant chemicals that affect brain function, almost all of which can be classified as secondary metabolites, have their effects and how an exploration of this subject might help move this field of research forward.

The role of secondary metabolites in plants

Plants, and the evolutionarily more recent subdivision of flowering plants (angiosperms), have colonized the vast majority of the terrestrial surface, courtesy of rich levels of specialization and intricate relationships with other organisms. They make an exponentially larger contribution to terrestrial biomass by volume and weight than all other forms of life combined (5). However, as stationary autotrophs, plants have to cope with a number of challenges, including engineering their own pollination and seed dispersal, local fluctuations in the supply of the simple nutrients that they require to synthesize their food, and the coexistence of herbivores and pathogens in their immediate environment. Plants have therefore evolved secondary biochemical pathways that allow them to synthesize a raft of chemicals, often in response to specific environmental stimuli, such as herbivore-induced damage, pathogen attacks, or nutrient depravation (6,7). These secondary metabolites can be unique to specific species or genera and do not play any role in the plants' primary metabolic requirements, but rather they increase their overall ability to survive and overcome local challenges by allowing them to interact with their environment (8). An indication of how essential these secondary metabolites are to plants' survival can be seen in the energy invested in their synthesis, which is usually far in excess of that required to synthesize primary metabolites (9). Some of the roles of secondary metabolites are relatively straightforward; for instance, they play a host of general, protective roles (e.g. as antioxidant, free radical-scavenging, UV light-absorbing, and antiproliferative agents) and defend the plant against microorganisms such as bacteria, fungi, and viruses. They also manage inter-plant relationships, acting as allelopathic defenders of the plant's growing space against competitor plants. More complex roles include dictating or modifying the plant's relationship with more complex organisms (8,10,11). Their primary role here is often viewed as being one of feeding deterrence, and to this end many phytochemicals are bitter and/or toxic to potential herbivores, with this toxicity often extending to direct interactions with the herbivore's central and peripheral nervous systems (12). In this regard, secondary metabolites often act as agonists or antagonists of neurotransmitter systems (11,13) or form structural analogs of endogenous hormones (14). However, equally importantly, plants also have to foster a number of symbiotic relationships in order to survive. The most obvious role here is attraction of pollinators and other symbiotes via colors and scents or the provision of indirect defenses for the plant by attracting the natural enemies of their herbivorous attackers. This may take the form of providing an attractive chemical milieu for the predator or, alternatively, may be in direct response to tissue damage by the herbivore, which results in the synthesis and release of a cocktail of phytochemicals that attract the natural predators of the herbivore (8,10,11).

In terms of the evolutionary forces that have shaped the plant's selection of phytochemicals, it is notable that plants live within their own microenvironment, replete with a comparatively warm and humid microclimate rich in chemical emissions (15). Their interactions with animals are most often with the rich palette of invertebrates that coexist alongside them, and in particular with the arthropod, or insect, subgroup. The insect group itself comprises more than one-half of all of the species of multi-cellular life identified on earth thus far (16). Nearly one-half of all of these insect species are herbivorous, with the feeding habits of most species restricted to a small number of plant species (17). Many of the remainder live courtesy of either direct symbiotic relationships with plants or predation on other herbivorous insects. On the other side of the coin, two-thirds of flowering plants are entirely reliant on symbiotic insect interactions for pollination (15). Not surprisingly, plants and insects have coevolved in terms of physical and chemical diversity over their 400 million year common history (15,18).

In contrast to the pivotal role of insects in the life of plants, it is notable that vertebrates make up a mere 4% of species on earth and are physically outweighed by insects by a factor of 10 to 1 across temperate areas of the earth (5). Although there are many examples of plant secondary metabolites interacting with vertebrates, the evolutionary imperative underlying these instances naturally become less prevalent to the majority of plants as the size of the animal increases and frequency of contact decreases. In these terms, humans have been inconsequential to the plant kingdom until the very recent past (in evolutionary terms) and the advent of agriculture some 12,000 y ago, with the ensuing deforestation and transformation of the earth's surface.

Biological similarities across taxa

The common ancestry of all multi-cellular organisms has endowed them with a wide range of conserved cellular processes, including similarities in most pathways for the synthesis and breakdown of proteins, nucleic acids, carbohydrates, and lipids. A number of molecules that function as neurochemicals within the mammalian central nervous sytem (CNS), for instance acetylcholine (ACh),[2] also originated in common ancestors and are ubiquitous across all eukaryotes (19). At a molecular level, the extensive cytochrome P450 group of enzymes occurs in all living organisms and is involved in the biosynthesis, detoxification, and metabolism of compounds (20). Similarly, a raft of inter-related, ancestral, signaling molecules and pathways are preserved in both plants and animals (21). For instance, nitric oxide (NO) plays a key cellular signaling role in all animals and plants (22). Additionally, multiple aspects of cellular and redox signaling are conserved between the taxa (23,24), including similar gene expression in response to cellular stressors, which are regulated by common transcription factors (24). Glutathione in its various forms plays a role as the predominant nonprotein thiol across the taxa, acting as an important endogenous antioxidant (23). Of potentially pivotal relevance here, the fatty acid-derived, growth-regulating jasmonate family of plant signaling molecules (cis-jasmone, jasmonic acid, and methyl jasmonate) and many mammalian paracrine molecules, including prostaglandins and other eicosanoids, are synthesized via the same genetically preserved pathways (25), with both groups of chemicals playing a role in the response to physical and biotic stressors in their respective taxa (26,27). One common, key, relevant function of NO, redox signaling molecules, and the jasmonates in plants is also in the induction and synthesis of secondary metabolites (28,29).

Naturally, humans share greater similarities with insects than plants. For instance, most 'human' neurochemicals, such as neuropeptides (30), hormones (31), and neurotransmitters, including dopamine (DA), serotonin (5-HT), glutamate, γ-aminobutyric acid (GABA), and ACh (32,33), can be found in insects. Even

[2] Abbreviations used: 5-HT, serotonin; ACh, acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer's Disease; CNS, central nervous sytem; DA, dopamine; EGCG, epigallocatechin-3-gallate; GABA, γ-aminobutyric acid; GB, Ginkgo biloba extract; GE, ginseng extract; HP, *Hypericum perforatum*; MO, *Melissa officinalis*; SI, soy isoflavone; SL, *Salvia lavandulaefolia*; VE, valerian extract.

the uniquely nonvertebrate neurotransmitter/modulator octopamine is functionally and structurally analogous to noradrenaline (34). These common neurochemicals can play similar or at times different roles in humans and insects. So, for instance, across the taxa, glutamate functions as a key excitatory neurotransmitter (35) and ACh plays a key role in memory and neural plasticity (36,37), but 5-HT activity has opposite effects on aggressive behavior (31) and dopaminergic neurons are implicated in aversive learning in insects but reward in mammals (38). The underlying neuronal functional apparatus governing synaptic release and recycling, receptor interactions, and signal transduction mechanisms are also preserved in both taxa (33), including the role of NO as a secondary messenger (37). As an example, long-term memory is dependent on the same process of long-term potentiation in insects as seen in mammals (39) and this is underpinned by the same molecular processes, such as NO and cAMP signaling (37,40) and the involvement of glutamate and N-methyl-D-aspartic acid receptors (41). Even the cognitive architecture of the insect brain shares similarities with that of the vertebrates, with common principles of modularity within the CNS in terms of specific sensory domains, and higher order structures integrating information (42).

Courtesy of these similarities and the comparative simplicity of their nervous systems, invertebrates, including insects, have been deployed for more than fifty years as a model for unraveling many of the fundamental processes in the CNS and resultant behaviors (32). Insects have also been employed as standard models for the investigation of cognitive processes (42), with the honeybee serving as a model for the study of an "intermediate level of cognitive complexity" both in terms of behavior and neural mechanisms (43). Insects have also been used as models to study behavioral responses to, among others, addictive drugs (33,42), alcohol (44), diet (45), sleep deprivation (46), and age-associated cognitive decline (47) and the behavioral effects of serotonergic (48), dopaminergic (49), glutamatergic (50), GABAergic (51), and cholinergic (36) pharmacological agents. So, for instance, pharmacological agents that upregulate activity in the nicotinic and muscarinic cholinergic systems improve memory processes in both mammals and insects, whereas downregulation of the same systems has the opposite effects (52).

Hypotheses: why secondary metabolites affect human brain function

These similarities suggest 2 broad, alternate, but complementary hypotheses as to the factors underpinning the effects of secondary metabolites on human brain function.

The first is simply that any effects might be due to the similarities between plant and mammalian biochemistry and molecular functioning, in particular the many molecular signaling pathways that are conserved between the taxa and play roles in secondary metabolite synthesis within plants (53).

The second is that the effects are predicated on the similarities between the nervous systems of humans and those of the most prevalent, natural herbivores of plants, in particular, insects. In this case, phytochemicals whose synthesis has been retained by a process of natural selection on the basis of their ability to interact with the CNS of herbivorous or symbiotic insects will also interact with the human CNS system via the same mechanisms, with either similar, or in some cases dissimilar, behavioral effects.

Current status of knowledge

A vast number of natural, plant-based extracts and chemicals are purported to have beneficial effects on human brain function. Zhang (54) identified extracts and constituents from 85 individual medicinal plants that have demonstrated potential efficacy for treating psychiatric disorders on the basis of animal behavioral models alone. However, few plant-based products have been assessed in methodologically adequate human trials. A simple literature search using the individual names of the few extracts and compounds reviewed below (excluding nicotine and caffeine) generates some 30,000 publications. The 3 single polyphenols [epigallocatechin-3-gallate (EGCG), curcumin, and resveratrol] alone contribute 15,000 of these papers, the vast majority of which have been published in the last 10 y. This represents a huge amount of research and naturally raises the question of the ultimate efficacy of the interventions in question. The following comprises a brief review of the evidence surrounding the handful of herbal extracts and phytochemical supplements that have garnered enough evidence of efficacy or have been subjected to adequate levels of research to allow any conclusion as to their efficacy in terms of improved brain function. The polyphenols are included on the basis of the enormous interest they are generating currently.

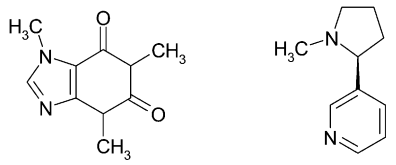

Figure 1 Structures of the alkaloids caffeine and nicotine.

The palette of secondary metabolites can be subdivided into a number of distinct groups on the basis of their chemical structure and synthetic pathways, and these groups can, in turn, be broadly differentiated in terms of the nature of their ecological roles and therefore their ultimate effects and comparative toxicity in the consuming animal. The extracts/phytochemicals are therefore grouped below by the chemical nature of their putative active components. In this regard, the largest and most prevalent of phytochemical groups are the alkaloids, terpenes, and phenolic compounds.

Alkaloids

Alkaloids are a structurally diverse group of over 12,000 cyclic nitrogen-containing compounds that are found in over 20% of plant species (55). Although no single classification exists, alkaloids are often distinguished on the basis of a structural similarity (e.g. indole alkaloids) or a common precursor (e.g. benzylisoquinoline, tropane, pyrrolizidine, or purine alkaloids).

The recorded use of alkaloids for medicinal purposes stretches back some 5000 y (56) and this chemical group has contributed the majority of the poisons, neurotoxins, and traditional psychedelics (e.g. atropine, scopolamine, and hyoscyamine, from the plant *Atropa Belladonna*) and social drugs [e.g. nicotine, caffeine, methamphetamine (ephedrine), cocaine, and opiates] consumed by humans (57). This group also provides the cholinesterase inhibiting treatments routinely prescribed for the cholinergic dysregulation of Alzheimer's Disease (AD), such as galantamine, huperzine, physostigmine, and rivastigmine (2).

In terms of their ecological roles, alkaloids primarily act as feeding deterrents and toxins to insects and other herbivores (8), in many cases by directly interacting with molecular targets within the nervous system (13). For instance, individual alkaloids act as agonists and antagonists to a variety of neurotransmitter systems via, for instance, direct binding to neuroreceptors and interference with neurotransmitter metabolism (e.g. cholinesterase inhibition), signal transduction, and ion channel function (13) or by

mimicking the structure of endogenous neurochemicals (11). A number of specialized herbivorous species have adapted to either tolerate or sequester alkaloids from their host plant. However, plant-derived alkaloids, by function and chemical nature, are toxic to mammals (12). Hagen et al. (58) point out that the psychoactive effects of alkaloid addictive drugs are predicated on their ecological role as insect deterrents/toxins and suggest that their addictive properties may partly arise as a consequence of the divergence of some of the roles of DA in insects and mammals.

Examples of some alkaloid secondary metabolites that are in common usage as psychotropic medicines, social drugs, or hallucinogens and have been used in insect studies either as simple tools for the modulation of specific neurotransmitter targets or, alternatively, in insect models of drug abuse and addiction are shown in **Table 1**. Given their toxicity profile and low levels of efficacy in terms of benefits to brain function, few alkaloid-based psychotropics are appropriate for use as nootropics in healthy populations. Two potential exceptions are caffeine, which is ubiquitously consumed by humans, and nicotine, the psychoactive constituent of tobacco. The chemical structure of caffeine and nicotine are shown in **Figure 1**.

Caffeine (and co-occurring phytochemicals). Caffeine is a purine alkaloid. Its ecological roles include chemical defense against pathogens and herbivores (59) and as a potential intra-plant allelopath whereby it inhibits the growth and fertility of competitor plants (60). In insects, caffeine increases arousal, reduces sleep (46,61), and decreases tonic immobility (62), with these effects mediated by interactions with adenosine and DA D_1 receptors (63). Similarly, in mammals, caffeine is a competitive antagonist of inhibitory adenosine A_1 and A_2 receptors, which in turn leads to activation via increased dopaminergic and glutamatergic activity (64). Caffeine also has a vaso-constricting effect on peripheral and cerebral blood flow via inhibition of vascular adenosine A_{2a} receptors (65). Chronic caffeine consumption may lead to increased adenosine receptor populations and/or sensitivity, and this may underlie subsequent withdrawal effects (66), which include increases in basal cerebral blood flow (67). For humans, caffeine is the most widely consumed psychoactive substance across the globe and is a popular additive to products for its purported stimulant effects. It has attracted a huge amount of research and, at low doses, is generally seen to increase subjective alertness and performance on attention tasks, although it has been suggested that these effects merely represent the alleviation of withdrawal as a consequence of using deprived habitual caffeine consumers in many experimental paradigms (68). However, caffeine has also been shown to demonstrate similar effects even when there is no evidence of withdrawal in habitual consumers (66,69,70). At higher doses, caffeine leads to increased anxiety, restlessness, insomnia, tachycardia, and psychomotor agitation and ultimately to caffeine intoxication, and, in extreme cases, death (71).

Co-occurring phytochemicals. Caffeine is one potentially active constituent in many foods and extracts that contain other phytochemicals, including tea (*Camellia sinensis*), guarana (*Paulinia cupana*), maté (*Ilex paraguariensis*), and cocoa (*Theobroma cacao*). Where the effects of caffeine in these forms has been investigated, the results have demonstrated either psychoactive effects that are not attributable to the caffeine content of the treatment, e.g. following single doses of guarana that contain comparatively high levels of terpenoids but low levels of caffeine (72), or the direct modulation of the effects of caffeine by the co-occurring phytochemicals. As an example, coadministration of the amino acid L-theanine, which is found in tea, attenuates the negative effects of caffeine on blood pressure (73) and cerebral blood flow (D. O. Kennedy and C. F. Haskell, unpublished data) and potentiates its cognitive effects (74).

Nicotine. Nicotine is a pyridine alkaloid from the American plant *Nicotiana tabacum* that is induced as an insecticide and antiparasite agent by leaf wounding and insect damage (55). Nicotine is highly toxic to mammals, and although very low doses are delivered by smoking, nicotine can be administered at lethal doses transdermally or orally. In insects (Drosophila), volatilized nicotine causes hyperactivity at low doses and reduced activity and paralysis with ascending dose. These effects are mediated by excitatory direct binding to nicotinic ACh receptors and increased dopaminergic activity (33). In mammals, nicotine binds directly to nicotinic ACh receptors, increasing the release of a number of neurotransmitters, including ACh, glutamate, and 5-HT, with increased DA activity in the ventral tegmental area underlying nicotine's addictive properties (75). Nicotine's effects on attention and memory are mediated by cholinergic projections to the prefrontal cortex and direct binding to receptors in the amygdala and hippocampus, respectively (76,77). In terms of improved brain function, much of the early research was confounded by similar withdrawal issues pertaining to caffeine research. However, Heishman et al. (78) meta-analyzed 50 methodologically adequate, double-blind, placebo-controlled studies that assessed the effects of nicotine administered via various methods in nondeprived smokers, minimally deprived smokers, or nonsmokers. They concluded that nicotine consistently improved cognitive performance in a number of domains, including attention, episodic memory, and working memory. Trans-dermal nicotine treatment has also been proposed for the behavioral deficits and cognitive decrements associated with old age and a number of conditions, including attention deficit hyperactivity disorder, AD, and schizophrenia (79). However, given its addictive properties and hypertensive/vascular effects, it seems unlikely as a candidate phytochemical for improved brain function in healthy, nonelderly adults.

Terpenes

Terpenes are a diverse group of more than 30,000 lipid-soluble compounds. Their structure includes 1 or more 5-carbon isoprene units, which are ubiquitously synthesized by all organisms through 2 potential pathways, the mevalonate and, more recently identified, deoxy-*d*-xylulose pathways (102). Terpenoids are classified according to the number of isoprene units they contain; isoprene, which itself is synthesized and released by plants, comprises 1 unit and is classified as a hemiterpene; monoterpenes incorporate 2 isoprene units, sesquiterpenes incorporate 3 units, diterpenes comprise 4 units, sesterpenes include 5 units, triterpenes incorporate 6 units, and tetraterpenes 8 units.

As a broad group, terpenes exhibit a range of toxicity from deadly to entirely edible and this is in keeping with their broad range of ecological roles, which include antimicrobial properties and a range of properties that attract symbiotes for the purposes of pollination, seed dispersal, and secondary protective roles. These latter roles include the provision of airborne chemical signals and scents, flavor, and taste. Monoterpenes can also function as antigerminative, phytotoxic allelopaths (103,104).

Terpenes also exhibit a wide range of effects within the insect CNS. For instance, the neurotoxic deterrent properties of many monoterpenes in insects have been shown to include interactions with the octopamenergic system (analogous to the noradrenergic system in vertebrates), cholinesterase inhibition, and multiple

Table 1. The comparative mechanisms of action and behavioral effects of alkaloid secondary metabolites in insects and humans/mammals

Phytochemical (group)	Genus, family, or plant	Insect models		Human/mammal models	
		Mechanism	Effect on behavior	Mechanism	Effect on behavior
Atropine (tropane alkaloid)	Family: *Solanaceae* Plant: e.g. *Atropa belladonna* (deadly nightshade)	Muscarinic ACh receptor antagonist (80)	Impaired memory retrieval (one trial olfactory conditioning) (81)	Muscarinic ACh receptor antagonist (82)	Impairs memory in primates and humans (83)
Caffeine (purine alkaloid)	Plants: e.g. *Coffea arabica, Camellia sinensis* (tea), *Paulinia cupana* (guarana), *Ilex paraguariensis* (Maté), *Theobroma cacao* (Cocoa)	Adenosinergic (63) and dopaminergic (84) receptor interactions, specifically involving DA D_1 receptor signaling (63)	Increased arousal and decreased sleep (46,61), decreased tonic immobility (62)	competitive antagonist of inhibitory adenosine A_1 and A_2 receptors → increased dopaminergic and glutamatergic activity (64)	Increased alertness and improved attention in humans (69)
Cocaine (tropane alkaloid)	Plant: *Erythroxylum coca (Coca)*	DA synthesis and binding – plus interaction with tyramine (85)	Increased drosophila grooming (86) and dancing in bees (87) at low doses. Increased and erratic acivity, paralysis and death with increasing dose.	Increased extracellular DA by blockade of DA transporter (88)	Increased alertness, euphoria, motor activity in humans (89)
Ephedrine (alkaloid)	Family: Ephedraceae Plant: e.g. *Ephedra sinica* Synthesized as Methamphetamine	Increased dopaminergic signaling (90) via DA D_1 receptors (63)	Increased arousal/decreased sleep (63,90)	Interact with adrenergic receptors (91) increase DA efflux and inhibit monoamine oxidase (88)	Increased alertness, arousal, motor activity, concentration, well-being in humans (89)
Morphine (isoquinoline alkaloid)	Plant: *Papaver somniferum*	Opioid receptor binding (92)	Decreased protective reaction to noxious stimuli (92) and increased feeding behavior (93)	Opioid receptor binding (94)	Euphoria, analgesia, sedation in humans (89)
Nicotine (pyridine alkaloid)	Plant: *Nicotiana tabacum* (tobbaco)	Agonist nicotinic ACh receptor binding (95)	hyperactivity at low doses - hypokinesis and akinesis at higher doses (96)	Agonist nicotinic ACh receptor binding → ACh, glutamate, 5-HT and DA activity (75)	Stimulant effects and improved attention and memory (78)
Physostigmine (indole alkaloid)	Plant: *Physostigma venenosum* (Calabar bean)	Cholinesterase inhibitor and direct agonistic nicotinic ACh receptor binding (97)		Allosteric nicotinic ACh receptor agonist, but at higher doses blocks open channels (98)	Improves memory in aged primates and humans (83)
Pilocarpine (imidazole alkaloid)	Genus: *Pilocarpus*	Muscarinic ACh receptor agonist (80)	Improved memory (nestmate recognition) (36)	Muscarinic ACh receptor agonist (82)	Improved cognitive function inc memory in old rats (99) and young primates (but high level of side effects) (100)
Scopolamine (tropane alkaloid)	Family: *Solanaceae* Plant: e.g. *Atropa belladonna* (deadly nightshade)	Muscarinic ACh receptor antagonist (80)	Memory decrements (one trial olfactory conditioning) (80) decrements in memory (nestmate recognition) (36)	Muscarinic ACh receptor antagonist (101)	Human cognitive and memory decrements (101)

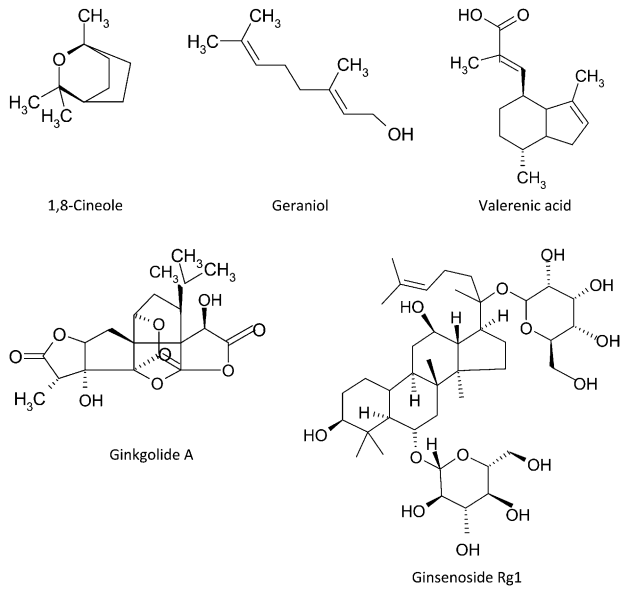

Figure 2 Structures of selected terpenes, including the monoterpenes 1,8-cineole and geraniol, the sesquiterpene, valerenic acid, the diterpene, ginkgolide A, and the triterpene, ginsenoside Rg1.

direct interactions with the GABA system, including blockade of GABA-gated chloride channels and both agonistic and antagonistic, direct and allosteric binding to $GABA_A$ receptors (12). Plants also synthesize a wide range of ecdysteroids from sterol that are structural analogs of insect hormones and may play a defensive role by interfering with the life course and behavior of herbivorous insects by, for instance, delaying pupation, metamorphoses, and molting (105). However, one of the terpene conundrums is that some phytochemicals can act as both deterrent and attractant. As an example, 1,8-cineole, a monoterpene found in psychoactive sage and lemon balm extracts, acts as a toxin to coleoptera and some species of flies but not as a consequence of its cholinesterase inhibitory properties. It is also harmless to some other taxa, for instance honeybees, and acts as a fragrant attractant for insect pollination. It may also contribute to the indirect defense mechanism of attracting the natural insect predators of attacking herbivores by the emission of an induced cocktail of chemicals. (106). It seems very unlikely that attractant chemicals would have a negative effect on the functioning of the nervous system of symbiotes, and it may well be that cholinesterase inhibition by terpenes' secondary metabolites can be advantageous in behavioral terms to insects that have a symbiotic relationship with the emitting plant (106). It is interesting to note that many terpenoids also exhibit considerable toxicity to some insects but very low toxicity to mammals (12), and this group of chemicals are present in a host of spices, flavors, and foods that form essential components of our diets both in terms of the provision of taste and healthy eating. Obvious examples here are the carotenoids, with β-carotene being endogenously converted to the human vitamin A.

One other key property of terpenoids is that they are generally present in complex mixtures that play multiple, differing, or additive ecological roles for the plant (11). In many cases, they have also been shown to act synergistically. For instance, the activity of naturally occurring monoterpenoid combinations have been shown to outweigh the combined activity of their constituent chemicals in the inhibition of the growth of competitor plants (107) and of toxicity (108), repellent (109), and deterrent properties in insects (110) and their mammalian cholinesterase inhibitory properties (111,112). Many terpenoid-containing herbal extracts have therefore resisted the identification of a single active component, while adequate standardization of herbal extracts has also proved elusive. The chemical structure of a selection of terpenes are shown in **Figure 2**.

Ginkgo biloba. Ginkgo biloba leaf extracts (GB) have been used medicinally for several millennia and are of some the most commonly taken herbal products globally. They are prescribed routinely in parts of Europe as a nootropic in old age and dementia (113). GB contains a number of biologically active, species-specific terpenes: bilobalide and ginkgolides A, B, C, and J (114), and a range of flavonoid glycosides. Within the plant, these constituents are associated with insecticidal (115), antifeedant (116), and antimicrobial (117) activities and are induced by environmental stressors (118,119).

The potential CNS relevant mechanisms of action of GB include antagonism of platelet activating factor, enhanced constitutive NO bioavailability and consequent beneficial effects on peripheral and cerebral blood flow parameters in humans, modulation of a number of neurotransmitter systems [including inhibition of monoamine oxidase A and synaptosomal uptake of DA, 5-HT, and norepinephrine], scavenging and inhibition of free radicals, both in vitro and in vivo neuro-protective properties, including inhibition of amyloid-β neurotoxicity, and protection against hypoxic challenges and increased oxidative stress (120–122). In humans, a number of randomized control trials have demonstrated cognitive enhancement in young adults following single doses of GB (123–127) and in both younger (128) and older (129,130) cognitively intact populations administered GB for 7 d or longer, although evidence of this is not unequivocal (131,132).

In terms of the many trials assessing the efficacy of GB with regards to cognitive function in dementia, a comprehensive Cochrane review (133) meta-analyzed 33 studies that involved cohorts suffering from dementia or age-related cognitive impairment. The authors concluded that "Overall there is promising evidence of improvement in cognition and function associated with Ginkgo." However, in a recent update and reanalysis, the authors (134) modified their inclusion criteria and analyses and concluded that the evidence was "inconsistent and unconvincing." This finding was supported by the recent Ginkgo Evaluation of Memory Study, where no difference in rate of change of memory, attention, visuospatial abilities, language, and executive functions was observed between 3069 72–96 y olds taking either 120 mg ginkgo twice daily or placebo. However, Kaschel (135) notes that the vast majority of dementia and age-associated cognitive decline trials have merely reported global measures, thereby obscuring effects specific to individual cognitive domain. In his own review, he included 29 methodologically adequate randomized controlled trials that provided this information and concluded that chronic treatment with GB resulted in improvements in attention, executive function, and long-term memory.

Melissa officinalis (Lemon balm). *Melissa officinalis* (MO) has been in medicinal use as a mnemonic and anxiolytic psychotropic for more than 2 millennia (136). Its potentially active components primarily include monoterpenoids and sesquiterpenes, including geranial, neral, 6-methyl-5-hepten-2-one, citronellal, geranyl-acetate, β-caryophyllene and β-caryophyllene-oxide, and 1,8 cineole (137). The specific ecological properties of the constituents of MO essential oils include toxic deterrents to nematodes (138) and insects

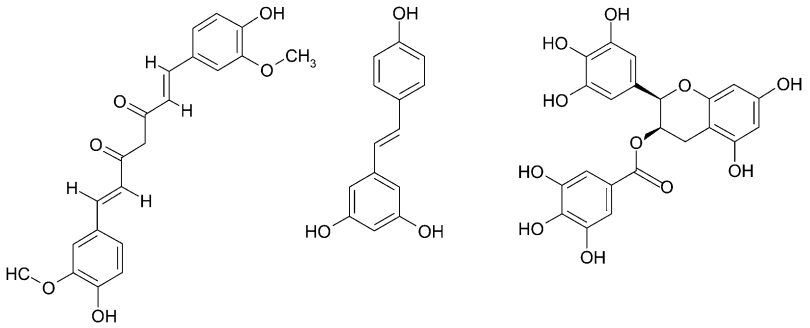

Figure 3 Structures of selected phenolic compounds.

(139) and as phytotoxic plant allelopaths (103), although individual components have also been identified as contributors to symbiotic attraction (see Sage below).

The CNS-relevant in vitro effects of MO extracts include antioxidant properties (140,141), demonstrations of direct nicotinic and muscarinic cholinergic receptor binding properties in human brain tissue (142,143), and acetylcholinesterase (AChE) inhibitory properties (141,142,144) arising from synergies between components (111). MO extracts also have an affinity for $GABA_A$ receptors (145) and inhibit the enzyme GABA transaminase, leading to increased GABA activity (146). These properties may underlie observations of a reduction in both inhibitory and excitatory transmission, with a net depressant effect on neurotransmission, in cultures of rat cortical neurons (147) and anxiolytic properties in terms of rodent behavior (148). It is notable that β-caryophyllene is also a cannabinoid type 2 receptor ligand and thus offers potential for the prevention and treatment of inflammation (149).

In humans, 2 randomized, double-blind, placebo-controlled, balanced-crossover trials have demonstrated dose-dependent memory decrements (150) and anxiolytic-like modulation of mood (150, 151) following single doses of an ethanolic MO extract with no cholinergic receptor binding properties. A subsequent trial selected and assessed an encapsulated dried leaf with ACh nicotinic and muscarinic binding properties (in human brain tissue) and demonstrated a dose-related improvement in memory task performance and ratings of mood (152). These results suggest that MO extracts have consistent anxiolytic properties but that cholinergic receptor binding is required for overall improvements in brain function.

Two double-blind, placebo-controlled studies have also assessed the effects of MO in sufferers from dementia, with Ballard et al. (153) finding improvements in agitation and quality of life following essential oil aromatherapy in 71 patients suffering from severe dementia. Akhondzadeh et al. (154) also demonstrated reduced agitation and improved cognitive (Alzheimer's Disease Assessment Scale, cognitive subscale) and behavioral function (Clinical Dementia Rating) following a 16-wk administration of a MO alcoholic tincture to a small cohort (n = 35) of mild to moderate dementia sufferers.

Panax ginseng. Extracts made from the roots of *Panax ginseng*, the most widely consumed member of the *Araliaceae* family, have a 5000 y medicinal history (155). The putative major active components comprise 40 or more species-specific triterpene saponins known as ginsenosides (156). Within the plant, ginsenosides have antifungal/-viral/bacterial, insecticidal, and molluscicidal activity and exert allelopathic and antifeeding effects (157,158).

Ginseng extracts (GE) exert neuro-protective and cardiovascular properties and modulate the hypothalamic-pituitary-adrenal axis and neurotransmission via a plethora of mechanisms at a cellular level, including modulation of NO synthesis (156,159). Animal behavioral models suggest that ginsenosides have antistress, antidepressant, and anxiolytic effects; moderate fatigue; improve memory in impaired rodents, and improve learning by fostering neurogenesis and modulating long-term potentiation in the hippocampus (156,159,160).

To date, the evidence of any effects of GE on physical performance or measures of mood and quality of life in humans is equivocal, but this may be attributable to methodological inconsistencies in the literature (159). In terms of human cognitive performance, a number of randomized, double-blind, placebo-controlled, balanced-crossover trials of single doses of GE have demonstrated consistent improvements in the accuracy of memory task performance (161–163), improvements in the speed of performing attention tasks (163), and decreased latency of evoked potentials and topographical modulation of electrical activity as measured by electro-encephalography (164). Reay et al. (165,166) also demonstrated that GE improved the performance of difficult mental arithmetic tasks and the resultant mental fatigue in fasted individuals. These effects were accompanied by concomitant reductions in fasted blood glucose levels but were abolished by the coadminstration of glucose (166). A recent study (167) also extended the treatment period to 7 d and focused on working memory performance, demonstrating improved mood in terms of calmness following both doses of GE investigated (200 and 400 mg) and improved performance of the 3-back task following the higher dose, but slower performance following the lower dose. There was no evidence of an increased effect due to the longer treatment period.

Salvia officinalis and Salvia lavandulifolia (sage). Sage's history as a cognition enhancer and treatment for cognitive decline stretches back to the ancient Greeks. The 2 most commonly used species of sage, *Salvia officinalis* and *Salvia lavandulaefolia* (SL), share a similar composition, with the exception that SL contains very little of the potentially toxic $GABA_A$ receptor-antagonizing monoterpenoid thujone (168). Common active components include several polyphenolic compounds and a range of monoterpenes (e.g. 1,8-cineole, terpeneole borneol, limonene, camphor α-pinene, and geraniol) (111,169). The latter group exerts a complex pattern of ecological effects, including neurotoxic deterrence to some phytophageous insects, and attraction of symbiotic insects for pollination and indirect defensive purposes, with cholinesterase inhibition potentially playing a role in both attraction and deterrence (106).

Both essential oils and hydro-alcoholic extracts of sage have been shown in vitro to inhibit human AChE (111,112,169,170)

and butyrylcholinesterase (112), with in vivo inhibition also being demonstrated in rodent brains following oral administration (171). 1,8-Cineole has been shown to be the most potent single component in terms of cholinesterase inhibition (111) but with synergistic interactions (and antagonisms) among the components increasing the overall potency (111,172). α-Pinene and geraniol also exhibit antiinflammatory activities and the whole extract of SL and its geraniol component have demonstrable estrogenic activities (173).

A number of double-blind, placebo-controlled, randomized, balanced-crossover studies in healthy humans have demonstrated improved memory (174–176), attention/executive function (176,177), and mood (175,177) following single doses of cholinesterase-inhibiting sage extracts or essential oils. The most recent study investigated the effects of a monoterpenoid SL essential oil with high levels of 1,8-cineole and an IC_{50} for AChE inhibition at one-tenth of the concentration previously seen. Single doses administered to healthy adults were shown to improve attention, memory, and working memory/executive function task performance and to increase subjective alertness (106). A single, double-blind, placebo-controlled trial in a small cohort ($n = 30$) of AD patients also demonstrated improved cognitive functioning (Alzheimer's Disease Assessment Scale, cognitive subscale) and behavioral function (Clinical Dementia Rating) following a16-wk administration of a *Salvia officinalis* alcoholic tincture (178).

Valeriana officinalis L. (valerian). Valerian extracts (VE) have a long traditional history as mild sedatives and anxiolytics (179), with these properties attributed to a range of monoterpenes and sesquiterpenes, including the genus-specific valepotriates and valerenic acid. Root extracts also contain appreciable levels of GABA (180). Although specific ecological roles have not been delineated for most of these constituents, the valepotriates have been shown to be induced in response to a number of biotic and physical stressors (181). Constituents bind to a variety of neurotransmitter receptors (182), including the 5-HT_{5A} receptor (183), which is implicated in circadian rhythms and anxiety. They also act as allosteric modulators of subunit-specific $GABA_A$ channels (184) and adenosine A1 receptors (185). Valerenic acid and derivatives have been shown to have potent anxiolytic effects in rodents models (186), with these effects underpinned by in vivo binding to a specific subunit (β3) of the $GABA_A$ receptor (187).

In humans, single doses of valerian have been shown to disrupt vigilance and information processing task performance after 1–2 h (188) but not the morning after administration (188,189). In 1 study, valerian was also shown to be equipotent to benzodiazepines in sleep quality and waking symptoms in insomnia outpatients (190) and evidence suggests specific efficacy when coadministered with hops (191,192). However, reviews of the studies assessing the efficacy of VE have been somewhat inconclusive, with only 1 eligible, methodologically adequate study of anxiolysis (193). Reviews of VE efficacy in sleep disturbance have concluded that the evidence is "promising but not fully conclusive" on the basis of 9 included trials (194) and that the evidence only "suggested" that valerian improved sleep quality on the basis of 16 eligible randomized, controlled trials (195). A recent meta-analysis that included 18 studies (196) found that VE significantly improved sleep quality when measured by a simple subjective yes/no question but that evidence from typical, validated sleep questionnaires was lacking. In general, research in the area is replete with methodological inconsistencies but suggests VE is associated with few negative side effects.

Phenolics

Phenolics are ubiquitously found across the plant kingdom, with ~10,000 structures identified to date. With a few notable exceptions, phenolic compounds are synthesized from precursors produced by the phenylpropanoid pathway. Structurally, they share at least 1 aromatic hydrocarbon ring with 1 or more hydroxyl groups attached. The simplest compound with this structural motif is the phenol molecule, which itself does not occur in plants. Phenolics range from simple low-molecular weight compounds, such as the simple phenylpropanoids, coumarins, and benzoic acid derivatives, to more complex structures such as flavanoids, stilbenes, and tannins. Of these, the flavonoids represent the largest, most diverse group, encompassing some 6000 compounds, all of which share a common underlying structure of two 6-carbon rings, with a 3-carbon bridge, which usually forms a 3rd ring. Flavanoids can then be subdivided according to modifications of this basic skeleton into chalcones, flavones, flavonols, flavanones, isoflavones, flavan-3-ols, and anthocyanins (197).

The ecological roles of phenolic compounds include constitutive and induced roles in toxicity and feeding deterrence in insects (198,199). However, they also contribute to a more benign palette of intra- and inter-plant protective, symbiotic, and attractant/deterrent effects. For instance, they are induced in the face of bacterial or fungal attack; provide scent, color, and flavor to attract symbiotic insects and deter herbivores; act as phagostimulants; act as allelopathic agents in intra-plant relationships; and manage symbiotic relationships with soil bacteria. Alongside these roles, many phenolic compounds also play roles in antioxidant defenses and the absorption of UV light (198,199).

In terms of CNS function, a wide range of phenolic compounds interact directly with neurotransmitter systems. As an example, in animal models, a diverse range of individual and combined flavonoids that occur in traditional medicinal extracts exert sedative/anxiolytic effects via direct binding to $GABA_A$ receptors (200, 201), cognitive enhancement via antagonistic $GABA_A$ receptor binding and resultant cholinergic upregulation (202), and antidepressant effects via monoamine oxidase inhibition and resultant increases in levels of 5-HT, DA, and noradrenaline in select brain areas (203). Plants also synthesize a range of phenolic phytoestrogens, including isoflavonones, flavones, stilbenes, and lignans (204,205), which function as defense chemicals against herbivory by disrupting the endocrine functions of the insect and modifying their life course (205). Similarly, in mammals and other vertebrates, phytoestrogens modulate hormonal systems, and therefore brain function, via a variety of mechanisms (see Soy isoflavones below) (205).

Phenolics, and flavanoids in particular, are ubiquitous in plants and therefore represent an important component of a normal human diet. Epidemiological studies have suggested associations between consumption of phenolic-rich foods or beverages and various diseases, such as stroke, cardiovascular disease, and cancer (206) and neurologic disorders such as dementia/AD (207,208). Cognitive performance in elderly populations has also been shown to be associated with tea, but not coffee, consumption (209) and the consumption of polyphenol-rich foods such as chocolate, red wine, and tea (210).

Naturally, multiple phenolic compounds coexist in foods. Many investigations utilizing animal models have demonstrated, for instance, that berry extracts with high levels of anthocyanins or other polyphenols can reverse brain insult- and age-related cognitive decrements in rodents and that the actives can cross the blood brain barrier (211). Similarly, in healthy humans, complex mixtures of

cocoa-flavanols have been shown to increase peripheral vaso-dilation and cerebral blow flow during task performance, as indexed by functional MRI (212), and improve performance on cognitively demanding tasks (213). It has been suggested that flavonoid-rich foods may limit neurodegeneration and prevent or reverse normal or abnormal deteriations in cognitive performance (214). However, the majority of the research in this area is concentrated on the effects of single molecules and the following includes a review of evidence surrounding the 3 most promising single molecule candidates. The chemical structure of curcumin, EGCG and resveratrol are shown in **Figure 3**.

Curcumin. Curcumin, a curcuminoid polyphenol responsible for the bright yellow color of the Indian spice turmeric (*Curcuma longa* L.), has been utilized for centuries within the Ayurvedic system of medicine for the treatment of a whole host of ailments, including inflammation (215). Within the plant, curcumin is associated with potent suppression of bacteria, funghi, and viruses, with these effects also observed both in vitro and in animal models (216).

Curcumin exerts varied and wide-ranging effects on molecular targets (217). These include transcription factors such as NF2, a master regulator of the antioxidant response; the protein kinase-enzymes, which are involved with the majority of cellular pathways, especially those involved with signal transduction; enzymes such as heme oxygenase 1, a stress response protein whose expression is upregulated after curcumin consumption and associated with neuroprotection (218); invasion and angiogenesis biomarkers such as matrix metalloproteinase 9, which are associated, among numerous other activities, with tissue repair; and inflammatory mediators such as NF-κB and cytokines such as TNFα and IL-1 and IL-6 (219). Curcumin (in vitro) has also been observed to inhibit the metabolism of amyloid precursor protein (220) and dose dependently inhibit amyloid-β fibril formation and extension, as well as destabilizing existing fibrils (221).

In animals, some of the physiological effects attributed to curcumin include activity against a range of neurologic diseases in animal models, including AD (222), multiple sclerosis (223), Parkinson's disease (224), age-associated neurodegeneration (225), schizophrenia (226), and depression (227). In animals, curcumin is also associated with the prevention of cognitive deficits (228) and an ability to improve learning and memory in mouse models of AD and reverse scopolamine-induced amnesia in rats (229). An epidemiological study of over 1000 60- to 90-y-old, nondemented Asians provided further tentative evidence of better cognitive performance by frequent or occasional curry consumers compared with nonconsumers or rare consumers of curry (230). Of course one has to consider that other ingredients in curry may be providing these effects alone or in synergy with curcumin.

Despite a wealth of in vitro and in vivo animal evidence, to date there is lack of evidence of clinical benefits in humans, leaving open the issues of bioavailability and biotransformation (231). To the present, over 40 small pilot trials in humans have been completed assessing pharmacodynamics/kinetics and efficacy in a variety of small patient groups (217). Curcumin is currently the subject of a wide range of ongoing clinical trials. These include assessments of its efficacy in the treatment of AD as a monotherapy and in combination with GB (232).

EGCG. A number of the catechin polyphenols that are abundant in tea (*Camellia sinensis* L.) are reputed to have pharmacologically active properties. The 4 main tea flavanols are: (-)-epigallocatechin, (-)-epichatichin, (-)-epichatechin-3-gallate, and EGCG, with EGCG generally thought to be the main and active component in green tea. Within the plant, catechins are purported to be involved in the defense against invading pathogens, including insects, bacteria, fungi, and viruses (233), and have been observed to displace native plant species when exuded from the root of the *Centaura maculosa* (spotted knapweed) (234). Protection against bacterial and viral infection has also been observed against human pathogens (235,236) as well as a plethora of other health parameters in humans [for review, see (237)].

The potentially neuropotective effects of EGCG include direct effects seen in vitro in metal chelation (238), as an antiinflammatory agent (239), and in the reduction of amyloid-β and amelioration of amyloid-β induced neurotoxicity (240,241), with these neuroprotectant properties being in part mediated via the activation of cell survival genes and modulation of protein-kinase c signaling (238). EGCG has also been shown to facilitate cholinergic transmission (242), enhance neurite outgrowth (243), and modulate cerebral blood flow parameters in healthy humans (E. L. Wightman, C. F. Haskell, J. L. Reay, J. S. Forster, R. Veasey, D. O. Kennedy, unpublished data).

In vivo evidence from animal models suggests neuroprotective properties in the face of AD (244–246) and Parkinson's disease (247) and following schemia/reperfusion injury (248,249). Long-term administration of green tea catechins (63% EGCG) has also been shown to improve cognitive performance and increase antioxidant capacity in normal rats (250) and rats infused with amyloid-β (251). EGCG was also found to significantly increase the lifespan of *Candida elegans*, although, interestingly, this was observed only during situations of increased heat and oxidative stress (252). This might suggest that the life-extending (and perhaps other) effects of EGCG are due to antioxidant actions and an upregulation of stress resistance-related proteins such as heme oxygenase 1. Indeed, pretreatment of cells with EGCG is associated with an increase in levels of heme oxygenase 1 (253). Despite the relatively small number of investigations into the neuroprotective properties of EGCG in humans, epidemiological evidence reports that higher consumption of tea/green tea is associated with a reduced risk of neurodegenerative disorders (254) and a lower prevalence of cognitive impairment (210). In terms of direct intervention, despite a recent pilot study observing no cognitive effects of EGCG after acute administration of 135 and 270 mg to healthy, young participants (E. L. Wightman, C. F. Haskell, J. L. Reay, J. S. Forster, R. Veasey, D. O. Kennedy, unpublished data), this null finding could be seen as the result of acute bolus consumption by cognitively intact participants. Future research should therefore consider both acutely and chronically supplementing green tea catechins to young, healthy participants as well as to those with cognitive senescence.

Hypericum perforatum (St. John's Wort). Extracts of *Hypericum perforatum* (HP) have been in recorded medicinal use from the time of the ancient Greeks (255). HP contain a wide variety of potentially bioactive constituents, including phenolic acids (e.g. chlorogenic acid), and a wide range of flavonoids (quercetin, quercitrin, isoquercitrin, rutin, hyperoside, epigenanin), structurally related phloroglucinol derivates such as hyperflorin (256), and naphthodianthrones such as hypericin. The antidepressant and antiinflammatory effects of HP were initially attributed to the naphthodianthrones (257) and more recently to hyperforin (258,259) and the range of flavonoid constituents (260). It is now widely accepted that the various potential actives act synergistically (261,262). In ecological terms, many of these phytochemicals are induced by biotic and environmental stressors (263) via a NO and jasmonic acid pathway (264) and exert antimicrobial and antiviral activity [with these and antiretroviral effects extending to

animal models also (257)] and antiherbivore activity, including via the induction of photosensitivity in the consuming animal (265).

Beyond pronounced antiinflammatory and antibiotic properties (259), HP exerts a number of effects directly relevant to mammalian brain function, including inhibition of the neuronal reuptake of 5-HT, DA, norepinephrine, GABA, and L-glutamate and increased neurotransmitter sensitivity and receptor binding (266). Functional effects include neuroprotective effects, an attenuation of cognitive impairment, and improved cognitive performance in rodents (267).

In humans, the vast majority of research has focused on the antidepressant effects of HP extracts. In this domain, a number of reviews and meta-analyses have confirmed the efficacy of HP in the treatment of mild-to-moderate depression (268). In the most recent Cochrane review by Linde et al. (269), a total of 29 methodologically adequate controlled trials were included. In common with the previous reviews, the authors conclude that HP extracts seems to be more effective than placebo and as effective as standard antidepressants for treating major depression. HP also engendered significantly fewer side effects than synthetic antidepressants.

Resveratrol. The phytoalexin resveratrol (3, 4′, 5 trihydroxystilbene) is produced within a range of edible plants in response to tissue damage and environmental stressors such as fungal and viral attack (270,271). Antifungal effects have also been observed against human pathogenic fungi (272) and antiviral effects against the herpes simplex virus (273,274).

Consumption of resveratrol is associated with numerous protective health benefits in mammals, including increased longevity (275), antiinflammatory (276) and antiviral properties (277), and protection against cancer and tumorogenesis (278), cardiovascular disease (279), and atherosclerosis (280). With regards to these latter 2 effects, resveratrol has been associated with the French paradox, whereby the consumption of red wine in some cultures has been suggested to contribute to a relatively low incidence of coronary heart disease despite a diet high in saturated fats (281,282).

Potential neuroprotective mechanisms of action include improving blood flow and perfusion (283–287) and the promotion of antioxidant defenses (288), which in vivo are likely to be as a result of resveratrol bolstering the bodies' own endogenous antioxidant defenses (289) via upregulation of a host of antioxidant enzymes (290–292). This may be partly a consequence of activation of the Nrf2 transcription factor, which plays a central role in the regulation of cellular redox status (291) and modulation of the protein kinases, which were observed to be involved with neuroprotection against amyloid-β–induced toxicity (293) in vitro (294) and in vivo, specifically in the hippocampus (295). In vivo, oral administration has also been shown to diminish amyloid-β plaque formation in a region-specific manner in a transgenic mouse model (296).

Regarding cognitive performance, a number of in vivo studies in rodents have demonstrated preserved behavior and cognitive performance in aged rats (297) and following laboratory-induced brain insults (298–302). In humans, a recent, double-blind, placebo-controlled, balanced cross-over study from our own research group assessed the effect of single doses of resveratrol on cerebral hemodynamics in healthy humans using near infrared spectroscopy. In this study (303), doses of 250 and 500 mg increased cerebral blood flow in the frontal cortex of the brain in a dose-dependent manner, as indexed by hemoglobin concentrations, during tasks that activate this brain region. Both doses also led to increased concentrations of deoxy-hemoglobin, indicating increased uptake of oxygen. This demonstration of the effects of resveratrol on human brain function confirms that this polyphenol may have beneficial effects both in healthy humans and those suffering diseases, including AD and other neurological disorders, that feature decrements in cerebral blood flow.

Soy isoflavones. Soy extracts contain a number of soy isoflavones (SI), including genistein, diadzein, and glycetin, which are structurally similar to estrogen (304) and exhibit estrogen-like effects, including binding directly to estrogen receptors, inhibiting aromatase, and disrupting estrogen signaling (205). In general, it is assumed that phytoestrogens act as defense chemicals against insect herbivory, disrupting endocrine function and modifying the insect's life course and fertility. There are also many examples of similar effects in vertebrate and mammalian herbivores (205).

SI exert a number of effects relevant to general health, including modulation of enzymatic function, antioxidant activity, immune function, and the mechanisms underlying carcinogenesis (305). These factors may underlie putative neuroprotective effects and tentative epidemiological observations of a relationship between SI consumption and breast cancer (306). In terms of effects on brain function, it is theorized that isoflavones are potentially cognitive enhancing. In animal models, some improvements have been observed following SI in the memory function of ovariectomized rodents (307) and in middle-aged or older rats as a consequence of supplementation with both genistein (308) and SI (309), with concomitant improvements in cholinergic (309) and prefrontal dopaminergic function (308). In humans, supplementation with SI in females has been shown to significantly improve the physical, but not psychological, symptoms of premenstrual syndrome compared with placebo (310) and, in post-menopausal women, SI has been shown to improve ratings of quality of life (311), decrease follicle-stimulating hormone and luteinizing hormone, increase estradiol (312), and have modest positive effects on neurocognitive function and mood (313,314). However, it is notable that only 4 of 7 studies published between 2000 and 2007 reported a positive impact of isoflavones on cognitive function in this group (315). In hormonally intact humans, a diet rich in SI, as opposed to a depleted diet, for 10 wk improved short- and long-term memory tasks in males and females, with additional improvements in 2 executive function tasks for the females in the cohort (314). Most recently, SI supplementation for 6 wk in males was associated with selective improvement in a spatial working memory task in which females usually outperform males (316).

Conclusions

In general, the literature on the efficacy of the herbal extracts and phytochemicals reviewed here in terms of improving aspects of human brain function is somewhat equivocal. Research into the 2 alkaloids, caffeine and nicotine, is confounded by withdrawal effects and most of the remaining treatments have failed to progress beyond relatively small scale human studies. Indeed, in the case of the single molecule polyphenols (curcumin, resveratrol, EGCG), their huge and exponentially expanding literatures are singularly lacking in reports of relevant human intervention trials. Of the 3 treatments that have progressed to larger scale controlled trials and eventual meta-analyses, both GB and valerian are bedevilled by methodological inconsistencies and inadequacies that make conclusions difficult to draw (133,196), with only St. John's Wort consistently demonstrating efficacy (269).

One consistent feature across the phytochemical groups is a gradation seen in terms of ecological roles and toxicity. Although something of a generalization, it is possible to characterize alkaloids

as occupying the toxic extreme in terms of their deterrent effects in insects and other herbivores, with terpenes inhabiting the middle ground with a more mixed toxicity profile and a wider range of deterrent/attractant/protective ecological roles. Phenolics then occupy the more benign end of the spectrum, exerting many internal protective roles and managing nontoxic interactions with herbivores and symbiotes. The same gradation could be suggested for the factors underlying the CNS effects in humans. Many of the behavioral effects of low doses of alkaloids are evidently the consequence of modulation of the same CNS mechanisms in both insects and humans and they elicit similar behavioral profiles given the comparative complexity of the taxa (Table 1). Although little research has addressed the effects of terpenes and phenolic compounds on insect behavior, it is possible to speculate that the CNS effects of terpenoids may be balanced between those predicated on similarities between human and invertebrate herbivores, e.g. the cholinesterase inhibitory and direct cholinergic and GABAergic receptor binding properties of many terpenes, and also the similarities between human and plant molecular physiology. The phenolic compounds, particularly those like flavonoids that are ubiquitously consumed in plant-based foods, may then owe the balance of their CNS effects to the latter (but with notable exceptions in terms of hormonal effects and GABAergic effects). As well as the natural compatibility of molecules created by conserved stress signaling pathways common to both plants and humans, it is interesting to note that the induced antibacterial/fungal and viral effects of curcumin, EGCG, and resveratrol within the plant (216,233,271) may be mirrored by a similar protection conferred after exposure to similar pathogens in human cells and animal models (216,235,273). Although an exact concurrence between the mechanisms of action across the taxa has not yet been established, Friedman (233) has demonstrated that, in vitro, the antibacterial, antitoxin, antiviral, and antifungal properties of tea flavonoids were similar against all of the food-borne pathogens reviewed. These mechanisms ostensibly involved either binding to the invader and inactivating it or perturbing the membrane structure of the pathogen and causing leakage, with both resulting in preventing or limiting the deleterious effects of the bacteria, toxin, or virus.

With phenolic compounds in particular it is also interesting to note that humans are likely to have lost the ability to synthesize vitamins, which include several terpenoids and methylated phenols, because the ubiquity of these micronutrients in our diet made it more advantageous in evolutionary terms to sequester them from food rather than synthesize them de novo (317). The same argument has been made for all dietary antioxidants, including many nonvitamin phytochemicals (318), and this proposition could be extended to include the nonantioxidant properties of groups of phytochemicals that occurred as part of our natural ancestral diet. This would largely accommodate the phenolic compounds, and flavonoids in particular, that are ubiquitous in plant foods. It may be relevant that most phenolic compounds have low parent-molecule bioavailability but still exhibit in vivo bioactive effects (319,320). The rapid process of metabolism that takes place in the body could be viewed as the body processing the molecules into, for instance, glucuronidated and sulfated metabolites to more effectively transport and utilize them, in much the same way that vitamins are processed into their active metabolites and derivatives following consumption.

The gradation in toxicity and ecological/CNS functions is also seen in the comparative levels of research attention paid to the chemical groups. The alkaloid group has benefitted from intense research for over 200 y (57) and has provided a multitude of medicinal compounds with CNS activity (321). Interest in terpenes, on the other hand, has really only escalated in the last 25 y, during which time many advances have been made in terms of characterizing the constituents and activities of complex plant extracts that often have low toxicity, high bioavailability, and a multitude of potentially relevant physiological effects (322). Similarly, research into the health effects of phenolic compounds has only reached any considerable level within only the last 15 y (323). In the case of alkaloids, they have proven particularly amenable to research and drug discovery because of their comparatively straightforward, single molecule modes of action. Evidence suggests that extracts with largely terpene or phenolic actives owe their effects to multifarious synergies between their component chemicals (324,325) and this factor, along with an inability to reliably standardize extract constituents, has to date constrained their development and the clarity of the literature on their efficacy in humans.

Future directions

The development of effective plant-based products for improving human brain function is constrained by a number of issues, including a need to definitively identify relevant active components and understand synergies within them and an inability to adequately standardize replicable extracts. It is evident that insects such as Drosophila and the honeybee are sensitive to modulation by a full range of pharmacological agents. However, insect behavioral studies have only involved secondary metabolites either as a consequence of using them as simple tools for the modulation of specific neurotransmitter targets or alternatively in insect models of drug abuse and addiction (Table 1). It would seem appropriate that insect models could be utilized as simple, economical, time-efficient, and ethically acceptable tools for investigating the neuronal and behavioral consequences of individual phytochemicals and complex mixtures. It is also evident that there are many viable terpene/phenolic extracts that may have beneficial effects on CNS function without the toxicity associated with psychoactive alkaloids. These may include complex chemical mixtures that attract symbiotic insects and potentially offer them cognitive benefits (106). However, many phytochemicals simply do not function effectively as single molecules and there are many examples of synergies within and between the chemical groups. Insect models may provide ideal starting points for disentangling these synergies prior to animal and human studies.

Many secondary metabolites are also expressed as a consequence of environmental stressors, and an increased understanding of the many and varied ecological roles of secondary metabolites should, in the future, make it practical to upregulate and standardize the levels of desired active components by introducing a variety of stressors such as herbivore attack, salinity, UV light, bacteria, or fungi in carefully controlled environments.

Finally, the vast majority of the voluminous research relating to the topics briefly reviewed above is conducted in entirely discrete discipline "silos." In terms of research relevant to brain function, the vast majority is basic laboratory research conducted in vitro/vivo in an entirely atheoretical context, often with parent molecules or chemical concentrations that are highly unlikely to be seen in the human brain. Asking the simple question of why plant chemicals modulate brain function can only serve to focus some of this huge research effort, with the integration of thoughts and concepts from a diverse range of disciplines, including molecular biology/biochemistry, plant science, zoology, entomology, pharmacology, medicine, neuroscience and psychology potentially offering an intellectual synergy that might move this area a step forward.

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