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Homo medicus: The transition to meat eating increased pathogen pressure and the use of pharmacological plants in *Homo*

Edward H. Hagen[1] | Aaron D. Blackwell[1] | Aaron D. Lightner[1,2] | Roger J. Sullivan[3]

[1]Department of Anthropology, Washington State University, Pullman, Washington, USA

[2]Department of the Study of Religion, Aarhus University, Aarhus, Denmark

[3]Department of Anthropology, California State University, Sacramento, California, USA

Correspondence
Edward H. Hagen, Department of Anthropology, Washington State University, Pullman, WA, USA.
Email: edhagen@wsu.edu

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Abstract

The human lineage transitioned to a more carnivorous niche 2.6 mya and evolved a large body size and slower life history, which likely increased zoonotic pathogen pressure. Evidence for this increase includes increased zoonotic infections in modern hunter-gatherers and bushmeat hunters, exceptionally low stomach pH compared to other primates, and divergence in immune-related genes. These all point to change, and probably intensification, in the infectious disease environment of *Homo* compared to earlier hominins and other apes. At the same time, the brain, an organ in which immune responses are constrained, began to triple in size. We propose that the combination of increased zoonotic pathogen pressure and the challenges of defending a large brain and body from pathogens in a long-lived mammal, selected for intensification of the plant-based self-medication strategies already in place in apes and other primates. In support, there is evidence of medicinal plant use by hominins in the middle Paleolithic, and all cultures today have sophisticated, plant-based medical systems, add spices to food, and regularly consume psychoactive plant substances that are harmful to helminths and other pathogens. We propose that the computational challenges of discovering effective plant-based treatments, the consequent ability to consume more energy-rich animal foods, and the reduced reliance on energetically-costly immune responses helped select for increased cognitive abilities and unique exchange relationships in *Homo*. In the story of human evolution, which has long emphasized hunting skills, medical skills had an equal role to play.

KEYWORDS
immunity, recreational drugs, self-medication, spices, traditional medicine, zoonotic disease

1 | INTRODUCTION

Every day, most adults deliberately consume plant substances that contain few, if any, macronutrients but that have potent pharmacological properties. Globally, farmers grow over one million tons of black pepper (*Piper nigrum*) and other *Piper* species every year, for example, along with 6.5 million tons of tea (*Camellia sinensis*), 10 million tons of coffee (*Coffea* spp.), 6.7 million tons of tobacco (*Nicotiana tabacum*), and 1.7 million tons of areca nuts (*Areca catechu*) (Food and Agriculture Organization, 2019).

Apparently mundane black pepper contains numerous bioactive compounds that are effective against a wide range of pathogens and have other medically useful effects. Many of these effects are linked to the alkaloid piperine (Takooree et al., 2019), which is also psychoactive, crossing the blood brain barrier and modulating γ-aminobutyric acid (GABA) type A receptors (Eigenmann et al., 2016). Tea, the world's most popular beverage after water, has about 700 bioactive compounds, including catechins, theanine, caffeine, and volatiles (Wei et al., 2018), with numerous health and psychoactive effects and antimicrobial activity (Bansal et al., 2013; Nonthakaew et al., 2015; Zhang et al., 2019). Over 90% of a large representative US population sample had urinary biomarkers of caffeine (Rybak et al., 2015). Beyond these substances, other plant-based "recreational" drugs such as cannabis, cocaine, and opioids, as well as hundreds of additional spices, are widely consumed on a daily basis for their psychoactive and other effects.

Traditional medicine, a cross-cultural universal (Brown, 1991), also involves the consumption of pharmaceutical plant substances administered by specialists such as healers and shamans. Because access to Western medicine is limited in low- and middle-income countries (LMICs), where about 85% of the global population resides, most people depend on traditional medicinal knowledge when sick (Johns, 1990; Kim, Kim, et al., 2020; WHO, 2019). Traditional medicine even informs drug discovery in Western medicine (Atanasov et al., 2015, 2021; Porras et al., 2021; Silva et al., 2016). Willow bark, for instance, has been used to treat pain for thousands of years. The active ingredient, isolated in the nineteenth century, is aspirin (Desborough & Keeling, 2017). The 2015 Nobel Prize in Medicine was awarded to Chinese scientist Tu Youyou for isolating the antimalarial compound artemisinin from sweet wormwood, a traditional Chinese medicine used to treat fevers (Nobel Prize, 2015). Traditional plant-based medicines often work.

Although Westerners classify some of these substances as foods (black pepper), some as recreational drugs (tobacco), and some as medicines (willow bark and sweet wormwood), all of them are plant substances rich in pharmacological compounds. We will argue here that the ubiquitous use of these substances is a behavior that evolved from the self-medication strategies used by ape ancestors to fight pathogens (Huffman, 2003). Currently, 9149 pathogen species are known to infect 1835 mammal host species (Farrell et al., 2020), with the human species infected by the greatest number (2064). See Figure 1.

Humans have experienced a number of major epidemiological transitions throughout our evolution. Currently, humans are experiencing an unprecedented decline in morbidity and mortality from infectious diseases following the 19th century discovery of the germ theory of disease and the development of sanitation technologies, vaccines, and antibiotics. At the same time, there is a rapid

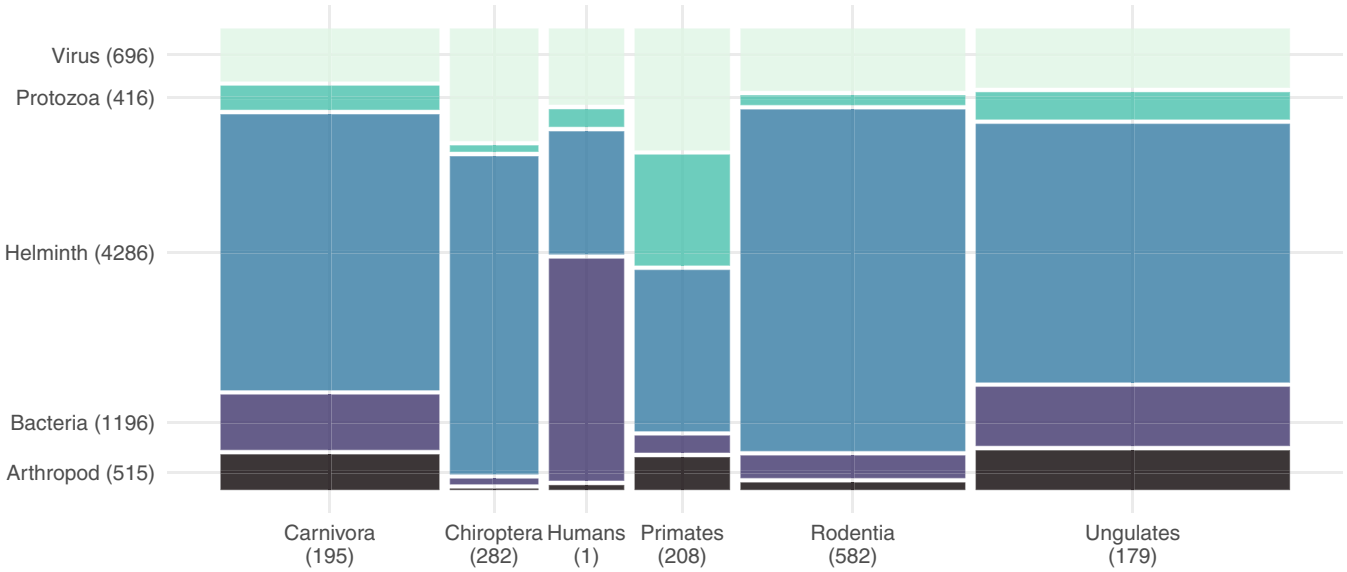

FIGURE 1 Associations of pathogen species with mammalian host species, with pathogens grouped by major categories and mammals grouped by Order, except that humans are plotted separately from other primates. The widths of the bars are proportional to the number of associations in that Order (i.e., a combination of the number of species per mammalian Order and the number of pathogens that infect each species). The heights of the bars indicate the proportions of associations with each pathogen category. Numbers indicate the number of distinct species in each category of pathogens (rows) or mammal Order (columns). The numbers for humans are biased upward by research effort. Data from Farrell et al. (2020) filtered to display only the most speciose mammalian Orders and most common pathogen categories.

emergence of new human infectious diseases and the evolution of antimicrobial drug resistant pathogen strains (Barrett et al., 1998). Much earlier, during the Neolithic, c. 10 thousand years ago (kya), greater sedentism, population size, population density, and animal domestication increased human exposure to zoonotic pathogens and created conditions required for sustained human-to-human transmission (Barrett et al., 1998; for some genetic evidence, see Domínguez-Andrés et al., 2021). Prior to this, it has been thought, small nomadic populations of dispersed Pleistocene hunter-gatherers could not sustain the acute communicable pathogens common in large sedentary communities. This transition might have started as modern humans colonized Eurasia, however (Houldcroft & Underdown, 2016), as there is evidence of strong selection during the Upper Paleolithic on human proteins that interact with viruses (Enard & Petrov, 2020; Souilmi et al., 2021).

Here, we focus on an epidemiological transition that likely occurred long before these better known transitions: a shift and perhaps increase in zoonotic pathogen pressure as the human lineage transitioned from a mostly plant-based diet to a more carnivorous niche, triggering changes in life history and social organization, near the beginning of the Pleistocene, c. 2.6 mya. We propose that this transition selected for changes in investment in immunity, which provides the critical benefit of eliminating pathogens, but also causes tissue damage and incurs substantial energetic costs that must be traded off against other important energy-consuming investments, such as growth and reproduction (Blackwell et al., 2010; Demas et al., 1997; Garcia et al., 2020; Martin et al., 2011; McDade et al., 2016; Muehlenbein et al., 2010; Nystrand & Dowling, 2020; Schulenburg et al., 2009; Shattuck-Heidorn et al., 2017; Urlacher et al., 2018). To reduce these costs, we argue that there was selection for increased use of antiparasitic plant compounds in the form of traditional medicines, spices, and "recreational" plant drugs. Along with cooking, use of these compounds permitted greater consumption of energy-rich meat and reduced energetically expensive immune responses, thus helping create the conditions for a dramatic increase in brain size in the human lineage.

2 | CARNIVORY IN *HOMO*

Although vertebrate meat eating is widespread across extant primates, with the most common prey species being, in order, birds (including eggs), reptiles, amphibians, mammals, and fish (Watts, 2020), meat is probably not an important source of either energy or protein even in chimpanzees, who are some of the most regular meat consumers among the non-human primates (invertebrates, on the other hand, are nutritionally important for many primate species, Rothman et al., 2014; Watts, 2020). African great apes, the closest living human relatives, subsist mostly on plants, primarily fruits and leaves (Berthaume & Schroer, 2017; Pontzer & Wood, 2021). The last common ancestor (LCA) of humans and chimpanzees, thought to have lived during the late Miocene, was therefore possibly a frugivore (Almécija et al., 2021; Young et al., 2015).

As African forests diminished, grasslands expanded, and seasonality intensified from the late Miocene into the Pliocene c. 6–5 mya, a new clade of apes—hominins—emerged with a more committed terrestrial lifestyle in open habitats. Craniodental traits, tooth wear patterns, and paleoecological contexts indicate a substantial shift in diet involving greater masticatory processing of food relative to extant apes, probably involving decreased consumption of C3 vegetation (e.g., fruits and leaves) and increased consumption of C4 vegetation (e.g., grasses, underground storage organs), albeit retaining dietary flexibility (considerable uncertainty remains in dietary reconstruction, however, Daegling et al., 2013; Lacruz et al., 2019; Quinn, 2019; Wynn et al., 2016).

The earliest fossil evidence of *Homo* coincides with the transition from the Pliocene to the Pleistocene 2.6 mya (Antón et al., 2014), when the Earth entered full glacial/interglacial cycles with hemispheric glaciations, strongly impacting African vegetation and herbivore communities (Couvreur et al., 2021). The brain and body of early *Homo* were somewhat bigger compared to australopithecines, and dentition reduced (Antón et al., 2014), indicating that our lineage had again entered a new dietary niche, this time involving less masticatory processing. A range of evidence, including stone tool cut marks on bones, leave little doubt that vertebrate meat, much of it from large mammalian prey like megaherbivores and grazers, was an important component of *Homo* diets (Antón et al., 2014). Although *Homo* might have acquired up to 70% of its calories from meat (Ben-Dor et al., 2021), the prevailing view is that it evolved as a diet generalist, able to flexibly adapt to different trophic levels as conditions required (e.g., Antón et al., 2014; Crittenden & Schnorr, 2017; Pontzer & Wood, 2021). Nevertheless, compared to <5% meat in chimpanzee diets (Watts, 2020), the proportion of animals in the diet of contemporary hunter-gatherers is quite high, ranging from 40%–60% (Pontzer & Wood, 2021).

3 | MEAT EATING LIKELY INCREASED ZOONOTIC PATHOGEN PRESSURE

Ancestrally, meat likely harbored more pathogens than plant foods. Although plant foods are often contaminated with animal pathogens, for example, in feces, the threat from plant pathogens themselves is relatively low. A few plant pathogens appear capable of cross-kingdom infections, but human infections with plant pathogens mostly occur in immunocompromised or physically injured individuals. In general, the substantial differences between plant and animal cell walls and immune systems are major barriers to pathogen spillover from plants to animals (Kim, Yoon, et al., 2020). Moreover, as we discuss in detail later, plant foods are infused with anti-infective compounds.

Prey animals, in contrast, would often have been infected with pathogens adapted to primates and other mammals that had a high risk of spillover. There are numerous well-documented examples of spillover from prey to predators, with some carnivore populations suffering catastrophic declines. Spillover outcomes in predators can vary from asymptomatic infections, such as feline immunodeficiency virus

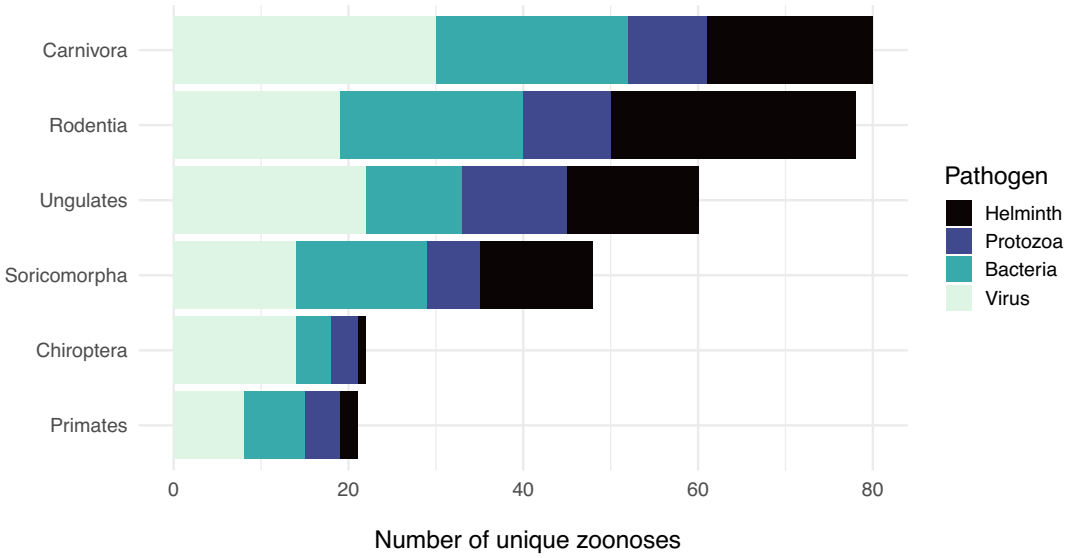

FIGURE 2 The number of unique zoonoses caused by each pathogen type in the six most species-rich mammal groups: the carnivores, bats (Chiroptera), primates, rodents, shrews and moles (Soricomorpha), and the hoofed mammals (ungulates, which combine the orders Perissodactyla and Artiodactyla and exclude domesticated species). Data and caption from Han et al. (2016).

in pumas preying on bobcats, to variable clinical outcomes, such as anthrax in wolves preying on bison, to virulent infections, such as bovine tuberculosis in coyotes preying on white-tailed deer (Malmberg et al., 2021). There is even evidence that some chimpanzee and bonobo viruses spilled over from their primate prey (Calvignac-Spencer et al., 2021). Once killed, prey is further colonized by pathogenic bacteria from the dead animal itself, the animals that fed on it (including insects), and the soil, water, and air (Ragir et al., 2000; Smith et al., 2015).

To reduce infections from prey, predators have evolved special physiological and behavioral resistance mechanisms. Although evidence of increased investment in cellular immunity is mixed, at least among captive carnivores (Nunn et al., 2003), carnivores have exceptionally low gastric pH and avoid preying on closely related species (Malmberg et al., 2021). Carnivores frequently kill other carnivores, for example, but rarely eat them, probably due to the heightened risk of infection (Moleón et al., 2017).

In contrast to australopithecines, members of genus *Homo* would have had intimate, near-daily contact with mammalian prey and predators, and their pathogens and arthropod disease vectors. Most human infectious diseases indeed originate in non-human animals (Han et al., 2016). Many zoonoses are enzootic (stably established) in animal populations and transmit from animals to people but then have little or no subsequent person-to-person transmission (Karesh et al., 2012). Rabies, for example, is a deadly zoonotic virus infecting the central nervous system (CNS) (Fisher et al., 2018) that humans acquire from infected carnivores or bats but do not transmit to other humans. Today, about 60,000 people die every year from rabies acquired from infected dogs (Hampson et al., 2015). Other deadly zoonoses, such as HIV, have substantial person-to-person transmission. Between 1940 and 2004, over 300 infectious diseases emerged in the global human population, 60% of which came from animals, mostly wildlife (the remainder were newly evolved strains and previously rare pathogens that increased in prevalence, Jones et al., 2008).

On average, about 10% of mammalian species within the most specious orders are zoonotic hosts, with rodents and bats being the most specious, and therefore hosting a large fraction of zoonotic diseases. Ungulates—common human prey species—stand out, however, in that 32% of species are zoonotic hosts, as are a large fraction of primate and carnivore species (Han et al., 2016; Han et al., 2021). See Figure 2.

A key predictor of bacterial and viral zoonotic status is having a host that is a short phylogenetic distance from humans, an effect driven largely but not entirely by primates (Olival et al., 2017; Shaw et al., 2020). For helminths, on the other hand, diet class is the strongest predictor of a wild species sharing a helminth species with humans. Specifically, herbivores and carnivores are more likely to share helminth parasites with humans than are wild omnivorous and insectivorous mammals, probably because the life cycles of many helminths depend on trophic interactions – consumption of their eggs and cysts, or by contact with larvae (Wells et al., 2018). Modern hunter-gatherers tend to avoid hunting primates, carnivores, and rodents (Bugir et al., 2021), perhaps due in part to the higher risk of spillover.

3.1 | Increased zoonoses in commercial hunters (bushmeat), Congo Basin foragers, and workers in animal-related occupations

Hunting is widely considered to be a major risk factor for zoonotic spillover. Bushmeat—wildlife hunted for human consumption—

provides food for hundreds of millions of rural people living in poverty, and in the Congo Basin alone involves more than a million tons of meat per year (Saylors et al., 2021). Bushmeat activities have been linked to numerous virulent disease outbreaks, including Ebola, HIV, monkeypox, SARS-CoV-1, and possibly SARS-CoV-2 (Guan et al., 2003; Kurpiers et al., 2016; Peros et al., 2021). Pathogen spillover from bushmeat can occur through consumption, but major risks come from exposure to body fluids and feces during handling and butchering (Milbank & Vira, 2022). A study investigating the origins of SARS-CoV-1 in a key market, for example, found that 31% of individuals involved in wild animal trade or slaughter had SARS-CoV-1 antibodies whereas only 5% involved in trading vegetables did (Guan et al., 2003). A review found 133 reports of disease involving 60 pathogens in 58 bushmeat species, mostly mammals (95%); the most common zoonotic pathogens were helminths (37%) and bacteria (33%), followed by viruses and protozoa (15% each) (Peros et al., 2021). An important caveat is that although such spillovers are a global phenomenon, in only about half the cases was evidence linking specific spillovers to wild meat processing and consumption of good quality (Milbank & Vira, 2022).

Congo Basin foragers are also at increased risk of acquiring zoonotic infections compared to neighboring farmers, and infections are strongly associated with severe bites from apes during hunting. Viral zoonoses include simian foamy virus (Betsem et al., 2011) and human T-lymphotropic virus type 1 (HTLV-1) (HTLV-1 originates from simian T-lymphotropic virus type 1, Filippone et al., 2015). There is also a higher prevalence of antibodies to monkeypox among Aka foragers compared to neighboring farmers (Reynolds et al., 2007), probably because Aka are more likely to engage in behaviors, such as visiting the forest and interacting with animals, that expose them to monkeypox (Guagliardo et al., 2019). In a population of Efe foragers, the prevalence of antibodies to Ebola virus, a zoonotic pathogen whose animal reservoir is probably bats, are among the highest ever reported (18.7% vs. 2%–3.5% in the Republic of the Congo and the Democratic Republic of the Congo, Mulangu et al., 2016; Steffen et al., 2019).

In a more cosmopolitan perspective, veterinarians have a higher risk of zoonotic infections than control groups (Baker & Gray, 2009), and members of other occupations that involve animals, such as livestock farm laborers, livestock/dairy producers, slaughterhouse workers, and animal carers and forestry workers, also have higher infectious disease risk (albeit not all zoonoses, Acke et al., 2021; Vonesch et al., 2019). Taken together, all these patterns indicate that, compared to earlier hominins, the more carnivorous *Homo* experienced increased zoonotic pathogen pressure, likely selecting for increased invetment in immunity.

4 | CARNIVORY-RELATED SHIFTS IN HUMAN LIFE HISTORY AND SOCIAL ORGANIZATION ALSO AFFECTED PATHOGEN PRESSURE AND INVESTMENT IN IMMUNITY

The Plio-Pleistocene transition to carnivory in *Homo* was accompanied by increases in body size and longevity, and changes in climate variability, range size, population size, population density, and social organization (Antón et al., 2014), all of which could also have altered pathogen pressure, thereby also selecting for changes in investment in immunity. We consider each of these in turn.

Intuitively, large, long-lived animals would have greater lifetime exposure to pathogens and greater somatic investment, and should therefore invest more in immunity (although there are many complications, Banerjee et al., 2017; Donnelly et al., 2015, 2017; Downs, Schoenle, et al., 2020; Han et al., 2015; Kieft & Simmons, 2015; van Boven & Weissing, 2004). Empirically, body size is positively associated with the prevalence of viruses and bacteria in primates and ungulates, with macroparasites in primates and carnivores (Han et al., 2015), and with pathogen diversity, an index of pathogen pressure (Bordes & Morand, 2009), across animal, plant, and fungal hosts (Kamiya et al., 2014).

Most studies of the fossil record conclude that body size in the human lineage increased in the evolutionary transition from *Australopithecus* to *Homo*, probably as a consequence of the higher quality diet (Grabowski et al., 2015; McHenry, 1992; Püschel et al., 2021; Will et al., 2017). Indeed, carnivores tend to have large body sizes (Cooke et al., 2022). Longevity is much harder to infer from the fossil record, but a reasonable conjecture is that increased body size in *H. erectus* entailed an increase in longevity (briefly reviewed in French & Chamberlain, 2021). Modern humans fall toward the higher end of the distribution of mammalian body masses and have one of the longest lifespans, traits that are correlated across species. Even given our large body size, the long lifespan of modern humans is an outlier among primates (Miller et al., 2019).

Empirical evidence that larger animals invest more in immunity is starting to emerge. A study of 26 felid species found that larger species, several of which evolved in ecological niches overlapping with those of early *Homo* (lions, leopards, cheetahs), had greater white blood cell counts (an index of investment in immunity) than smaller species (Naidenko & Alshinetskiy, 2020). Mammal metabolic rate scales hypometrically with body mass ($Y = aM^b$, $b < 1$), but neutrophils, part of the innate immune system, scale hypermetrically with body mass in over 250 mammalian species ($b > 1$), clear evidence of a size-related increase. Lymphocytes, which participate in both the innate and adaptive immune systems, scale nearly isometrically ($b \sim 1$) (Cornelius Ruhs et al., 2021; Downs, Dochtermann, et al., 2020; see also Ruhs et al., 2020), as does antibacterial activity in serum in over 160 terrestrial mammals (Downs, Schoenle, et al., 2020). These patterns suggest size-related increases in immune investment.

Pathogen diversity is also positively related to both host range size and population density across animal, plant, and fungal hosts (except range size in arthropods, Kamiya et al., 2014). These patterns have opposite implications for changes in pathogen pressure in early *Homo*. The population range sizes of early *Homo* species are estimated to be about seven to 10 times larger than those of *Australopithecus* species (Antón et al., 2002), suggesting increased pathogen pressure.

Larger terrestrial vertebrates, including mammals, typically have lower population densities (Santini et al., 2018), on the other hand,

suggesting that, compared to its smaller hominin ancestors, *Homo* did too. Carnivory would have further reduced population density because transfer of energy and nutrients from lower to higher trophic levels is inefficient (10,000 kilograms of prey supports about 90 kilograms of a given species of carnivore, Carbone & Gittleman, 2002). As the proportion of meat in the diet increases, population density in ethnographically known hunter-gatherers decreases (Zhu et al., 2021), and in high productivity environments (e.g., tropics, subtropics), lower population density is associated with lower pathogen stress (Tallavaara et al., 2018; but see critique in Zhu et al., 2021). As a larger-bodied *Homo* increased in trophic level in the Lower Paleolithic its population density would therefore likely have decreased relative to its smaller-bodied hominin predecessors with plant-based diets. Decreased population density would have decreased pathogen pressure in *Homo*; pathogen pressure could also limit population density. (Much later, in the Upper Paleolithic, population densities of *Homo sapiens* appear to have increased, French, 2016).

Pathogen pressure is also affected by climate change because many species survive by moving, bringing their pathogens into contact with new species (Carlson et al., 2022). Climate variability increased during the Pleistocene because the distribution of the continents and low atmospheric greenhouse gas concentrations made the climate susceptible to changes in insolation due to the orbital forcing on 40 kyr and later 100 kyr cycles (Potts, 2012; von der Heydt et al., 2021). There is also evidence for more rapid, and sometimes abrupt unidirectional changes in the environment of early *Homo* (Lupien et al., 2020, 2021). Increased Pleistocene environmental variability might therefore have increased the frequency of spillovers into the human lineage.

Lastly, across primates and carnivores, mating promiscuity is positively associated with increased investment in immunity, probably due to increased risk of sexually transmitted infections (STIs) (Nunn, 2002; Nunn et al., 2003). Theoretical results indicate that under various conditions, STIs can select for a shift toward a monogamous mating system (Kokko et al., 2002; McLeod & Day, 2014). The reduced sexual dimorphism in *Homo erectus* compared to earlier Australopithecines suggests a shift in their mating system, perhaps toward greater monogamy (Villmoare et al., 2019), which is also widespread in carnivores (Macdonald et al., 2019). Given that one of the today's most dangerous epidemic diseases, HIV, is a zoonotic STI, and that one of the most common STI's is from a Pleistocene spillover event (HSV-2 and genital herpes – see below), it is possible that increased zoonotic spillovers of STIs in *Homo* contributed to a shift toward monogamy.

In summary, meat-eating, increased body size, lifespan, range size, and climate variability would likely have increased pathogen pressure and investment in immunity in *Homo*, although lower population density could have partially offset these increases. Increased pathogen pressure might then have been one selection pressure for a shift in the mating system toward monogamy, which would also have reduced pathogen pressure. Overall, most changes point to an increase in pathogen pressure and investment in immunity.

5 | EVIDENCE OF CARNIVORY-RELATED PLEISTOCENE SPILLOVERS INTO HOMININS

Taeniid tapeworms, characteristic parasites in carnivorous mammals, are one of the clearest examples of carnivory-related spillover to early *Homo*. Cestodes (tapeworms) are parasites that, as adults, live and produce eggs in their definitive host(s). The eggs are shed (e.g., in feces) and enter an intermediate host in which the larvae develop. The life cycle completes when the intermediate host is eaten by a definitive host. Humans are the definitive host for *Taenia saginata*, *T. asiatica* and *T. solium*, with domesticated ruminants as intermediate hosts. These species are responsible for considerable disease burden in contemporary human populations, especially when they infect the nervous system (Carabin et al., 2017), a topic to which we shall return. Morphological and genetic evidence suggests that these *Taenia* species switched their definitive host, probably hyenas and/or lions, to hominins who were hunting the same ungulate prey species (Hoberg, 2006; Hoberg et al., 2001; Terefe et al., 2014).

Other possible examples of Pleistocene spillovers into humans include herpes simplex virus 2 (HSV-2), which infects about 11% of the population, causes most cases of genital herpes, and appears to have spilled over from bonobos into the human lineage around 1 mya, after bonobos diverged from chimpanzees c. 2.1 mya (Wertheim et al., 2021). *Helicobacter pylori*, which infects the stomachs of about half of all humans, causes inflammation and increased risk for stomach cancer, appears to have spilled over into the human lineage from an unknown host c. 88–116 kya, just prior to human migration out of Africa (Linz et al., 2007; Moodley et al., 2012). The rare human T-cell lymphotropic virus type II, found mainly among some Congo Basin foragers, Native American populations, and intravenous drug users, appears to have spilled over from a primate species at least 400 kya (Vandamme et al., 2000). Other spillovers include various hepatitis viruses (A, B, C, and GB viruses) (Houldcroft & Underdown, 2016; Reperant et al., 2013), enteroviruses such as poliovirus (Reperant et al., 2013), and *Schistosoma* spp (due to increasing use of open environments, Mitchell, 2013). For reviews, see Houldcroft and Underdown (2016), Mitchell (2013), Ledger and Mitchell (2019), Harkins and Stone (2015), Reperant et al. (2013), Blerkom (2003), and Brinkworth and Alvarado (2020).

5.1 | Infections of the CNS and the virulence of newly emerged zoonotic pathogens

The transition to carnivory in the human lineage was accompanied by a rapid increase in brain size, indicating that biological fitness depended much more heavily on CNS functions. There are reasons to believe that the carnivory-related increase in spillover risk increased the risk of especially virulent infections, especially of the CNS.

Theoretical models of the evolution of virulence assume that there is a tradeoff between virulence and transmission: faster replicating pathogens create larger populations, increasing their transmission rate, but cause more host damage, increasing host mortality and thus

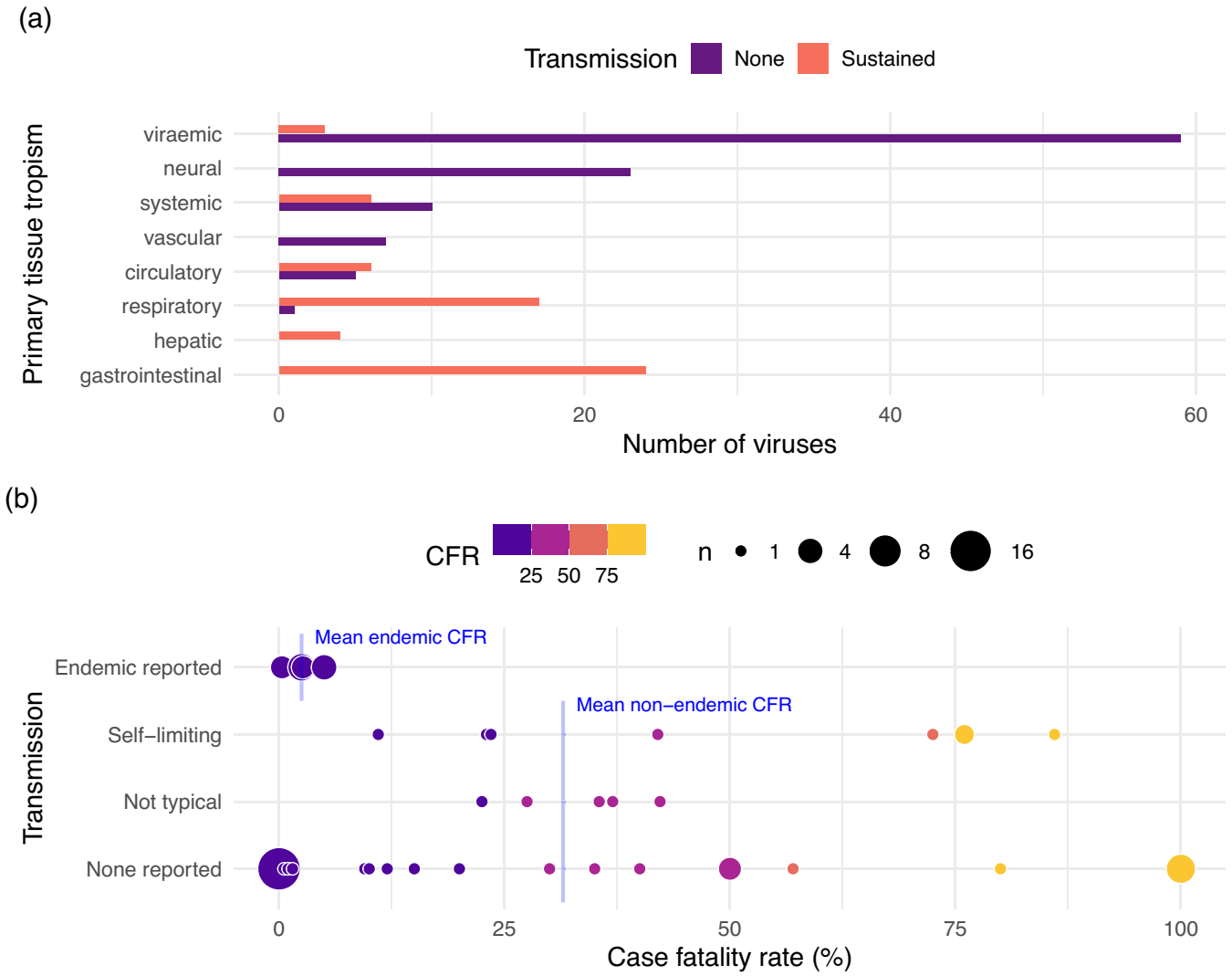

FIGURE 3 (a) Human RNA virus primary tissue tropism versus transmission. Primary tissue tropism indicates the dominant organ system the virus typically infects or targets (viraemic: only blood presence is known). No transmission: the virus infects humans but does not transmit to other humans. Sustained transmission: sustained human-to-human transmissibility. (Viruses with intermediate transmission not depicted.) Data from Brierley et al. (2019). (b) Zoonotic virus case fatality rate (an index of virulence) versus degree of human-to-human transmission. Each dot is one virus species, or group of species with identical CFRs and degrees of transmission. Dot size represents the number of overlapping data points. Dot color represents the CFR. Blue vertical lines represent mean CFRs for viruses with endemic and non-endemic transmission. Data from Guth et al. (2019).

decreasing the time for the infected host to contact susceptible hosts (reviewed in Cressler et al., 2016). Empirical evidence to date supports the existence of this tradeoff (albeit with complexities, Geoghegan & Holmes, 2018; Visher et al., 2021). In human zoonotic viral infections, for instance, there is indeed a negative association between the capacity for human-to-human transmission and case fatality rate (CFR), an index of virulence (again, with caveats, Brierley et al., 2019; Geoghegan et al., 2016). Pathogens should therefore evolve to optimize virulence to maximize the number of hosts they can infect (Visher et al., 2021).

Newly emerging zoonotic pathogens, however, are unlikely to have phenotypes that optimize the virulence-transmission tradeoff in the new host. They will therefore vary widely in their virulence and transmission rates (Brierley et al., 2019; Bull & Ebert, 2008; Visher et al., 2021). In addition, when the pool of susceptible hosts is large there can be transient selection for greater virulence in newly emerging pathogens (Berngruber et al., 2013; Bolker et al., 2010). An analysis of zoonotic viruses found that those with limited or no reported human-to-human transmission, suggesting they were poorly adapted to humans, had CFRs ranging from 0% to 100%, with mean = 31.5%, whereas those with reported endemic transmission, suggesting they were better adapted to humans, all had relatively low CFRs, with mean = 2.5% (Guth et al., 2019). The highest CFRs after spillover were caused by zoonotic viruses from the hosts more distantly related to humans, and thus less well-adapted, such as viruses from ungulates, which were common prey species, and from

bats, which inhabited the same caves as human ancestors (Guth et al., 2019). See Figure 3b.

Importantly, novel and thus poorly adapted pathogens might "accidentally" infect host tissues, such as the CNS, that fail to support onward transmission of the pathogen. Nevertheless, the host immune system must defend those infected tissues. In a study of human RNA viruses, for example (Brierley et al., 2019), the most common primary tissue tropism for viruses with the lowest transmission level, indicating they were poorly adapted, was viraemic (only blood presence is known) and neural. The highest transmission level, indicating well-adapted, was gastrointestinal and respiratory – tissues that can easily support onward transmission via feces, droplets, and aerosols. See Figure 3a. Onward transmission pathways from neural tissue are limited, but infection of neural tissue could be very costly to the host. Indeed, neural tropism in RNA viruses is associated with high virulence (Brierley et al., 2019). As already noted, rabies is a zoonotic RNA virus infecting the human CNS with no onward transmission, indicating poor adaptation to this host, and that is lethal.

Interestingly, larvae of *T. solium*, one of the tapeworm species that switched definitive hosts from a carnivore into the human lineage, can infect the brain. Ingested eggs hatch and migrate to various tissues, including the CNS, a condition termed *neurocysticercosis*. Once in the CNS the larval cyst might continue to grow, or die due to immune response or treatment and then degenerate and calcify (Sinha & Sharma, 2009). The clinical manifestations of neurocysticercosis range from completely asymptomatic in the majority of cases, to headaches, seizures, increased intracranial pressure, focal deficits, meningitis, pressure on the spinal nerve, dementia and other mental changes, dizziness, stroke, and death (Sinha & Sharma, 2009). Neurocysticercosis, a common cause of epilepsy in rural, low income settings (Stelzle et al., 2022), is a neglected tropical disease that has been difficult to diagnose (Gripper & Welburn, 2017). Only now are MRI-based population studies beginning to emerge, which have found prevalence rates of 10%–20% in rural villages where raising pigs is common (Brutto et al., 2017; Moyano et al., 2016). Even though most cases of neurocysticercosis appear to be asymptomatic in these cross-sectional studies, symptoms could appear over time, and there might be undetected cognitive deficits in apparently asymptomatic individuals. We will return to *T. solium* as a key example for our self-medication hypothesis.

More generally, encephalitis (inflammation of the brain parenchyma) is a major source of disease burden globally (Feigin et al., 2019), with mortality rates ranging from 5%–15% (mostly in children, Venkatesan et al., 2019). A variety of pathogens are implicated, which in children include enterovirus, parechovirus, bacterial meningoencephalitis, influenza, herpes simplex virus, and *Mycoplasma pneumoniae* (Britton et al., 2020), and in adults include herpes simplex virus, Varicella-zoster virus, Japanese encephalitis virus, *Mycobacterium tuberculosis* and *Listeria monocytogenes* (Boucher et al., 2017). Arthropod-borne viruses such as Zika and chikungunya are also increasingly implicated (Venkatesan et al., 2019). Zoonotic SARS-CoV-2 seems to infect the brain, causing encephalitis in a few individuals but perhaps "long covid" symptoms in many more (Bauer et al., 2022; Davis et al., 2023). There is also increasing evidence that a number of pathogens establish latent infections in the CNS, that is, survive but do not replicate until a later date. These include *T. gondii*, which provides the textbook example of parasite manipulation of behavior (Johnson & Johnson, 2021; Poirotte et al., 2016), and is implicated in the death of a 2000-year-old hunter gatherer boy from South Africa (Rifkin et al., 2020), as well as *M. tuberculosis*, HIV, West Nile virus, herpes simplex virus, and *Treponema pallidum* (syphilis) (Forrester et al., 2018).

Increased zoonotic spillovers in *Homo* might therefore have selected for increased investment in immunity and especially defense of the CNS through both immunological and behavioral mechanisms.

6 | PHYSIOLOGICAL AND GENETIC EVIDENCE FOR HUMAN-SPECIFIC IMMUNE DEFENSES IN RESPONSE TO CHANGES IN PATHOGEN PRESSURE

There is physiological and genetic evidence that immunity in humans has diverged from apes and other primates, possibly in response to increased meat eating and life history changes c. 2 mya, which supports arguments we make later that behavioral immunity also diverged for the same reasons.

Physiologically, human stomach acid, which functions as an important barrier to entry of pathogens into the gastrointestinal tract (Martinsen et al., 2005), has a low pH, much lower than seen in herbivores and omnivores, and on par with that seen in scavengers and generalist carnivores (Beasley et al., 2015). Innate immune responses also differ. Compared to most other mammals, the human immune system is highly sensitive to lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria, mounting a robust immune response to quantities about 1/10 of those needed to activate similar responses in macaques, baboons, and other mammals (Brinkworth & Valizadegan, 2021). Although chimpanzees might be as sensitive to LPS as humans (Brinkworth & Valizadegan, 2021), and both species show stronger and more generalized innate immune responses to viral and bacterial stimulation than macaques and baboons, many more human genes are differentially upregulated in response to LPS than in the chimpanzees, macaques, and baboons (Hawash et al., 2021).

In general, the immune system also "sees" meat as dangerous: animal foods are generally pro-inflammatory whereas plant foods are anti-inflammatory (Alcock et al., 2012). See Figure 4.

Genetically, viruses appear to have driven ~30% of all adaptive amino acid changes in the part of the human proteome conserved within mammals (Enard et al., 2016). There is human-chimpanzee divergence in regulatory sequences related to immune genes (He et al., 2016; Jin et al., 2018), including in microglia (brain immune cells, Xu et al., 2018), and there are human-specific

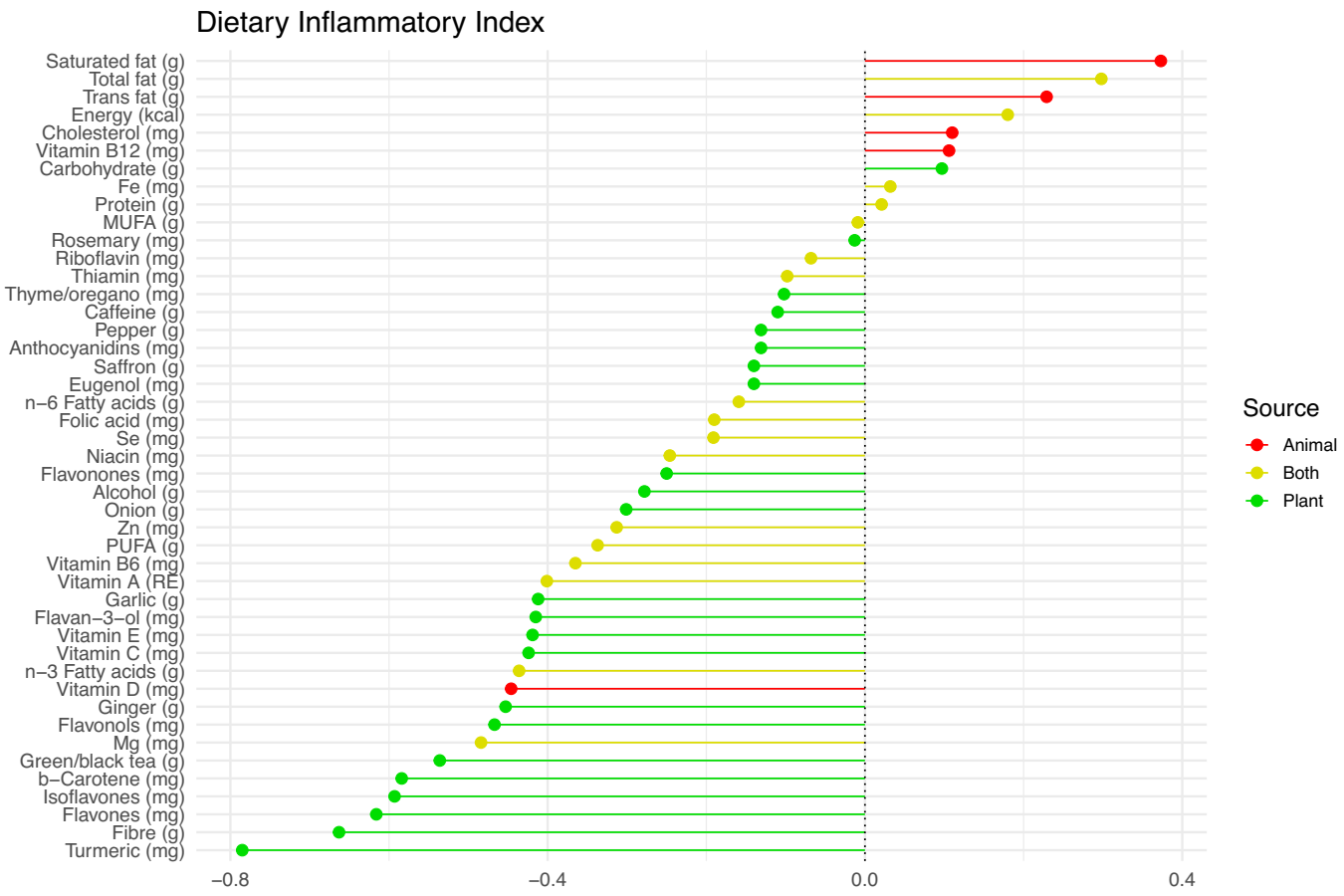

FIGURE 4 Overall inflammatory effect score from the Dietary Inflammatory Index. Positive values indicate the food component is pro-inflammatory; negative values indicate the food component is anti-inflammatory. Colors indicate primary source. MUFA: monounsaturated fatty acid. PUFA: polyunsaturated fatty acid. Saturated fat and Vitamin D are mostly (but not exclusively) from animal foods and are therefore coded as "Animal". Values from Shivappa et al. (2014).

coding genes related to immunity (Costantini et al., 2019), including one expressed in microglia (Hayakawa et al., 2005). Because positive selection on immune-related genes is common in primates (van der Lee et al., 2017), divergent evolution of immune genes could simply be due to Red Queen dynamics. About 2 mya, however, there was a loss-of-function mutation in CMAH in the human lineage that eliminated biosynthesis of the common mammalian sialic acid Neu5Gc, which was a target for pathogens such as Plasmodium, Escherichia coli, and coronaviruses; related genes also evolved. Similar evolution of these genes in apes has not occurred, nor has there been recent evolution of these genes in humans (Moon et al., 2018), suggesting that the selection pressure was increased carnivory-rated spillover c. 2 mya (Khan et al., 2020). There is also evidence that resistance to *Bacillus anthracis*, a zoonotic bacterium that spills over from ruminants into humans, evolved early in modern human evolution (Choate et al., 2021). Finally, unlike chimpanzees and other vertebrates, humans have three high frequency apolipoprotein E alleles, which are linked to meat-eating and improved immune defense, among other things (Finch & Stanford, 2004; Vitek et al., 2009; cf. Huebbe & Rimbach, 2017).

7 | THE BEHAVIORAL IMMUNE SYSTEM INCLUDES CONSTITUTIVE AND INDUCIBLE CONSUMPTION OF PHARMACOLOGICAL SUBSTANCES

The behavioral immune system is a motivational system that reduces infection risk, and therefore the energetic and other costs of immune activation, by promoting pathogen avoidance via changes in cognition, affect, and behavior – pathogen disgust is the canonical example (Ackerman et al., 2018, 2021; Buck et al., 2018; de Roode & Lefèvre, 2012; Schaller & Park, 2011). Meat avoidance is another possible example. Meat is seen as dangerous across cultures. A study of food taboos among horticulturalists and foragers in the Democratic Republic of the Congo, for example, found that nearly all involved animal foods, and many aimed to prevent illness and death (Aunger, 1994). A study of food taboos in 78 cultures found that 85% involved meat, likely due to the risk of pathogen transmission (Fessler & Navarrete, 2003). Because spoilage risk is similar for different animal foods, taboos regarding specific animal species are generally thought to be maladaptive (albeit imposing only a small nutritional cost, Aunger, 1994). It is possible, though, that the taboos are not due

to spoilage risk but instead originated after spillover events from particular species, which would warrant avoiding those species. Pork taboos are common, for instance, perhaps because pigs host various zoonoses, including *Taenia solium* – avoidance of pork and Muslim faith (but not Christian faith) are both negatively associated with CNS infections of this parasite (Stelzle et al., 2022; cf. Harris, 1997).

Cooking, which reduces pathogens in meat prior to consumption (Attwell et al., 2015; Smith et al., 2015), is another possible example of behavioral immunity; cooking also detoxifies food and increases net energy extraction. Although cooking would reduce exposure to pathogens in food that was about to be eaten, it would not have reduced exposure to potential zoonoses when tracking, killing, and butchering animals and scavenging meat. Moreover, even the earliest (but highly contested) dates for the possible controlled use of fire, 1.7–1.5 mya, are about 1 million years after evidence of increased meat eating c. 2.6 mya, and clear archeological evidence for the regular, controlled use of fire use only appears after 1 mya, with most evidence after 500 kya (reviewed in Hlubik et al., 2019; MacDonald et al., 2021). Further, several ethnographically known hunter-gatherer populations eat raw animal foods (McCauley et al., 2020), and even in modern populations that regularly cook animal foods, those who hunt and butcher wildlife are at increased risk of zoonotic disease.

To consider how *Homo* might have evolved to reduce the costs of zoonotic spillover that could not be mitigated by cooking, we further develop the behavioral immunity concept, which is based on an analogy with physiological immunity. In physiological immunity, there is an important distinction between constitutive and inducible immune defenses. Constitutive defenses, which in humans include skin, saliva, and restriction factors, are always active, thereby incurring a fixed cost to develop and maintain whether they are needed or not. They pay substantial dividends, however, if they prevent pathogens from infecting and multiplying in the host, which would necessitate a much costlier immune response and risks severe illness and death. Inducible defenses, on the other hand, which in humans include pathogen pattern recognition receptors and costly proliferation of leukocytes, only incur a cost when activated upon contact with a pathogen, but the delay in efficacy enables the pathogen to multiply and cause damage, thereby requiring a substantial and costly immune response (the two systems overlap to some extent) (Boots & Best, 2018; Hamilton et al., 2008; Shudo & Iwasa, 2001; van Loon et al., 2006; Westra et al., 2015).

7.1 | Plant chemical defenses as a "pharmacy" for animals

In analogy with the inducible and constitutive arms of the physiological immune system, we propose that as *Homo* experienced increasing pathogen pressure, it increased investment in behavioral immunity by more intensively co-opting plant secondary compounds through consumption (Billing & Sherman, 1998; Hagen et al., 2009; Hagen et al., 2013; Hardy, 2019; Huffman, 2003; Rodríguez et al., 1982; Sullivan et al., 2008; Sullivan & Hagen, 2002). We conceptualize regular consumption of pharmacological plant substances, regardless of infection status, as a constitutive defense, and consumption upon infection as an inducible defense.

The plant kingdom contains an estimated $10^5 - 10^6$ chemically unique structures, with 5000–15,000 structures per species, dwarfing all other major taxonomic categories for known specialized metabolites (Medema et al., 2021). Primary metabolic pathways—those producing compounds vital for plant survival such as proteins, lipids, and carbohydrates—are widely conserved across plant lineages and therefore contribute little to this chemical diversity, most of which comprises lineage-specific secondary compounds – those involved in, for example, plant-pollinator signaling and herbivore defense (Li & Gaquerel, 2021). Even fruits and nectars, which evolved to attract seed and pollen dispersing animals, are chemically defended against unwanted consumers (Cipollini, 2000; Dalling et al., 2020; González-Teuber & Heil, 2009; Valenta et al., 2017). Plant defensive toxins typically target protein functions in plant consumers, including animal neural receptors and other steps in neural signaling (Wink, 2015).

Plants are attacked by the same broad classes of pathogens that attack humans and other animals: viruses, bacteria, protozoa, fungi, helminths, and arthropods. Plant chemical defenses might therefore also be effective against the pathogens of humans and other animals. Indeed, a substantial fraction of anti-infective drugs approved in the last four decades are either derived from plant or microbial products, or inspired by them (Cicka & Quave, 2019; Harvey et al., 2015; Newman & Cragg, 2020; Porras et al., 2021). The increase in antibiotic resistant strains of pathogenic bacteria in particular, combined with new high-throughput screening technologies, has renewed drug discovery efforts focused on plant products (Atanasov et al., 2021; Porras et al., 2021; Silva et al., 2016).

Over the course of evolution, local flora would have represented a "pharmacy" for members of the human lineage and other animals (Boppré, 1984). It is therefore plausible that there has been selection over deep time to not only extract macronutrients from plants but also to co-opt plant secondary compounds for their anti-infective effects. Such self-medication could also allow some energy to be redirected from immunity to growth, higher reproductive rate, or other fitness-enhancing processes and activities. In a model insect system, for example, use of antibiotics down-regulated immune-related genes, upregulated growth-related genes, and increased growth (Galarza et al., 2021). In humans, it would also have improved an ability to safely exploit energy-rich animal foods, which along with reduced immune costs would have helped enable the evolution of a larger brain.

7.2 | Spices as a constitutive pharmaceutical toolkit to manage enteric pathogen risk

Humans routinely add spices—plant substances high in secondary compounds but low in macronutrients—to food, typically meat-based dishes. Billing and Sherman (1998) proposed that because spices have antimicrobial properties, and because foods, especially meat, contain

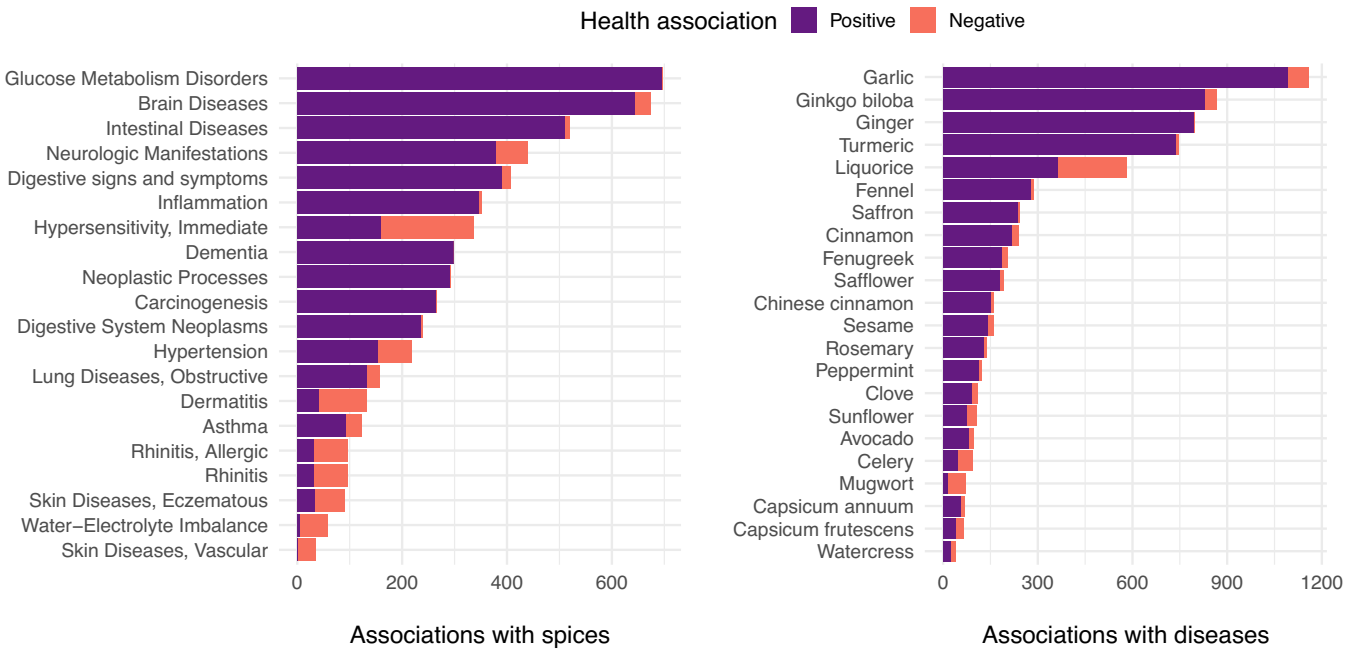

FIGURE 5 Top positive and negative health associations with spices (positive: spice associated with improved outcome; negative: spice associated with worse outcome). Left. Disease categories with the most positive and negative health associations with spices, ranked according to their total number of associations. Right: Spices with the most positive and negative health associations with diseases, ranked according to number of associations. The number of positive health associations for spices outnumber the number of negative associations, indicating that spices, in general, have been reported with beneficial health effects. Data from Rakhi et al. (2018).

dangerous microbes, this practice is adaptive, a hypothesis supported, in part, by a positive association between mean national temperature, a proxy of food-borne pathogen risk, and various indices of national spice use. On this view, the routine addition of spices and other medicinal substances to foods is a constitutive pathogen defense – it is always active, incurring the cost of potential interference with physiological functions but providing benefits by deterring infection and subsequent pathogen growth.

A reanalysis of Billing and Sherman (1998) that included additional data and appropriately controlled for autocorrelation from shared cultural ancestry and spatial proximity, and other potential confounds, found no significant association between temperature and spice use. Instead, spice use was associated with global patterns of poverty and health outcomes (Bromham et al., 2021). These authors went too far, though, in claiming "Patterns of spice use are not consistent with an infection-mitigation mechanism" (p. 1), especially since, accounting for autocorrelation, they found associations between mean spice use and incidence of foodborne illness, incidence of diarrhea in young children, and use of spices and meat-based dishes. The problem with both studies is that their data are aggregated (mostly) at the nation level (36 countries in Billing & Sherman, 1998; 70 cuisines in Bromham et al., 2021). These sample sizes are simply too small to tease apart the impact of what Bromham et al. (2021) themselves characterize as a "jungle of entangled variables that covary with culture, history and geography" (p. 6), such as temperature, disease, poverty, biodiversity, and population.

In our opinion, the current adaptationist approach to spice use has placed undue emphasis on temperature and food spoilage, as there are major, temperature-independent risks of contaminated food that could be ameliorated by spices, such as zoonotic pathogens infecting the living animal, and fecal-oral transmission of pathogens (animal-to-human and human-to-human) via contaminated plant or animal foods. Despite some costs, there is considerable evidence for the beneficial biological activity of spices, especially against intestinal diseases (Rakhi et al., 2018), including evidence that spices can control pathogens already resident in the gut, such as *H. pylori*, which infects the stomachs of about half the world's population. Evidence of efficacy against *H. pylori* includes antibacterial activity in vitro and anti-growth activity in vivo in laboratory animals, but clinical evidence is still lacking (Zaidi et al., 2015). See Figure 5.

Although the extent to which prehistoric and contemporary hunter-gatherers have used spices is not clear, there is some evidence that it might be a longstanding practice. Chimpanzees have been observed to chew leaves when eating freshly killed animals (Krief et al., 2015), compounds in Neanderthal dental calculus that have been interpreted as "medicines" might be better conceptualized as "spices" (Krief et al., 2015), spices were combined with hunted foods by European foragers and early agriculturalists (Saul et al., 2013), and contemporary Congo Basin foragers use wild plants as spices (Fils et al., 2020; Gallois et al., 2020; Tanno, 1981). We propose an expanded adaptationist hypothesis that preferences for spices (and perhaps salt, which is also antimicrobial, Albarracin et al., 2011)

evolved to constitutively manage overall enteric pathogen risk from whatever source.

7.3 | Self-medication as an inducible defense

When constitutive defenses fail to prevent infections and illness, inducible (therapeutic) uses of plant substances could help bring infections under control, albeit with risk of poisoning. There is increasing evidence that invertebrates and vertebrates, including obligate carnivores, have evolved to co-opt plant and fungal toxins to prevent or treat their own infections, a phenomenon termed *self-medication*, *zoopharmacognosy*, or *pharmacophagy* (Boppré, 1984; de Roode et al., 2013; Huffman, 1997, 2017; Neco et al., 2019; Rodríguez & Wrangham, 1993; Villalba & Provenza, 2007; Wrangham & Nishida, 1983; Yoshimura et al., 2021). A systematic review of self-medication in mammals found reports of self-medication in 71 species from 7 mammalian orders, with the most reports in Primates (46 species), Carnivores (10 species), and Rodents (5 species). Types of self-medication included ingestion of whole leaves to expel parasites from the digestive system (mostly apes and elephants), rubbing fur with toxic plants (non-human primates), placement of bay foliage around the nest to reduce ectoparasites (rodents), and use of specific plants to attenuate negative effects of food ingestion (artiodactyls). Results suggest that self-medication evolved independently at least four times, and is associated with traits that increased in the human lineage in the Pleistocene: body size, brain size, and longevity (Neco et al., 2019).

7.3.1 | Possible self-medication by Middle Paleolithic *Homo*

Middle Paleolithic hominins might have self-medicated, perhaps more intensively than other apes. An analysis of dental calculus from five Neanderthals found azulenes and coumarins in one, consistent with yarrow and chamomile, bitter-tasting plants with no nutritional value that might instead have been used as medicines (Hardy et al., 2012). An analysis of ancient DNA in the dental calculus of this same individual, who had a dental abscess, found sequences of poplar, which contains salicylic acid (the active ingredient in aspirin), a chronic gastrointestinal pathogen, and antibiotic-producing *Penicillium rubens*, suggesting this person might have been self-medicating both their abscess and a gastrointestinal infection (Weyrich et al., 2017).

Hardy (2019) classified plants from seven Near Eastern archeological sites dating from the lower Paleolithic to the early Neolithic into edible, edible/medicinal, and medicinal/poisonous categories. Medicinal plants were quite common across sites (>50% species), and much more common than in plants used by chimpanzees (~30%) or among wild flora (~12.5%). Some of the medicinal plants might have been regularly added to food, that is, they were "spices" (Krief et al., 2015). In modern populations, foods and medicines also overlap. Among the Hausa, for example, 30% of plant foods are used as medicines, and 89% of plants used to treat malaria are also part of the diet (Huffman, 2003; see also Roulette et al., 2018).

7.4 | Ethnopharmacology as a form of transgenerational immune memory

Inducible immune responses have traditionally been divided into innate immune responses, which respond to pathogens rapidly and nonspecifically, and adaptive immune responses, which respond more slowly but are pathogen-specific and form immunological memory for rapid responses upon re-exposure (again, there is some overlap in these systems) (Netea et al., 2016; Netea et al., 2019). Transgenerational transmission of immunity is seen in invertebrates and vertebrates. In mammals this involves antibody provisioning via transplacental transfer and breastfeeding (Atyeo & Alter, 2021; Clements et al., 2020; Erickson, 2022), maternal microchimerism, and antigen exposure in utero, phenomena termed "transgenerational immune priming" (Blackwell, in prep; Roth et al., 2018). These mechanisms suggest that there is widespread selection for pathogen defenses that learn about specific pathogens and transmit this information to offspring.

We propose that, analogous to transmitted immune memory, increased pathogen pressure in the human lineage was a major selection pressure for the cognitive mechanisms underlying cultural transmission. Huffman (2003) proposed that ethnomedicine, such as culture-specific and traditional plant uses, is linked to hominid self-medication strategies – in fact, some traditional plant medicines are used by both humans and African great apes (Huffman, 2003; Salali et al., 2016). Our proposal builds on his idea, arguing that in the context of social communication, transmitted information routinely includes locally adaptive medicinal knowledge, and can be viewed as a socially transmitted form of transgenerational immune memory (for related ideas, see Hurtado, 2021).

Medicine is a human universal (Brown, 1991), and traditional medicines and practices are still very widely used, especially in low- and middle-income countries (Porras et al., 2021). Although traditional medicine rarely outperforms Western medicine, Western medical services are often unavailable and traditional medical knowledge provides considerable value (Blackwell & Purzycki, 2018; Kim, Kim, et al., 2020). Studies of Tsimane horticulturalists found that parental ethnobotanical knowledge was positively associated with child health (McDade et al., 2007), including increased BMI (Reyes-García et al., 2008), with some mixed results in a later study (Reyes-García et al., 2016). Similarly, in a study of Congo Basin foragers, mothers with greater knowledge of medicinal plants used to treat respiratory diseases had children with higher BMI (Salali et al., 2016).

Traditional medicines, furthermore, have many advantages for drug discovery over other approaches (Atanasov et al., 2015). There are an estimated 374,000 plant species, 28,000 (7.5%) of which are used in traditional medicine. This subset is likely enriched in compounds that are both effective against human diseases and also relatively safe for humans (Porras et al., 2021). Databases of plants used

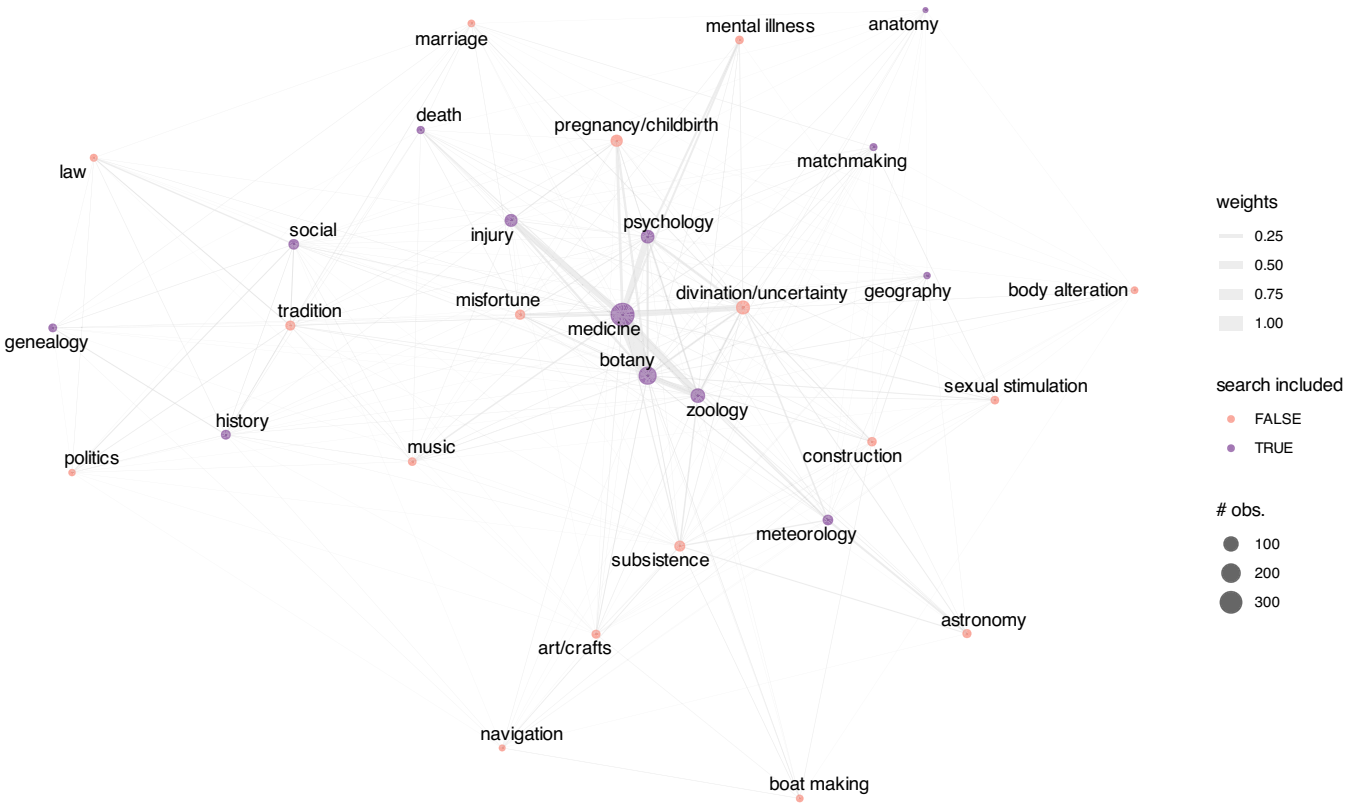

FIGURE 6 Commonly occurring domains of knowledge and skill that occurred in ethnographic text records of 55 traditional cultures. Vertices indicate domains that occurred in at least 10 text records, and vertex size corresponds to the number of text records including that domain. Vertex colors indicate whether or not the domain was included in the original search query. Each edge indicates that a pair of knowledge/skill domains co-occurred in at least one text record. Edge widths correspond to the frequency with which each domain pair co-occurred (as determined by the number of text records describing them together, normalized by the maximum frequency = 113). Figure from Lightner et al. (2021a).

in traditional medicine are widely screened for medically useful compounds (Anand et al., 2019; Pushpangadan et al., 2018; Wink, 2015; Yeung et al., 2020). Although the "jungle medicine" narrative has its share of hype, Western romanticism, and exploitation (Voeks, 2018), and some systematic assays of ethnomedicines have been disappointing (e.g., Applequist et al., 2017), there have been about 60,000 publications on ethnopharmacology, with research increasing dramatically on inflammation, infection, pain, toxicity, cancer and diabetes (Yeung et al., 2020).

7.5 | The evolution of medical specialization

Evolutionary theories of cultural transmission emphasize widespread knowledge that is used on a near-daily basis, such as locally adaptive subsistence practices (including spice use), toolmaking skills, and cooperative social norms (Henrich & McElreath, 2003; Richerson & Boyd, 2008; Richerson & Boyd, 2020). Medical problems are different. Because the immune system, perhaps combined with the constitutive behavioral defenses we described earlier, prevents most pathogens from causing serious illness, the substantial investment in individual and social learning required to effectively treat specific illnesses with specific plant substances would only occasionally be useful to the individual. The costs of acquiring medical knowledge would likely outweigh the benefits. Serious illnesses nevertheless unpredictably strike some individuals, who would benefit from diagnosis and treatment. To profit from a substantial investment in medicinal knowledge, it would be necessary for a few medical specialists to cultivate a large, medically naive clientele that is willing to "pay" for medical services on the rare occasions they need them. For this dynamic to have contributed to encephalization in the human lineage, it would have to be the case that "payments" took the form of increased mating success for healers (i.e., sexual selection) or substantially increased material or social resources. Selection for division of labor is a related dynamic (Nakahashi & Feldman, 2014).

In support of this perspective, medical knowledge, though clearly culturally evolved, is not evenly distributed within and across communities. Among Baka foragers in the Congo Basin, informants had almost the same amount of knowledge about plant uses for food and material culture, whereas knowledge of medicinal plants was mostly different, and some individuals had markedly more knowledge than others (Hattori, 2020). Similarly, among BaYaka Congo Basin foragers, knowledge of medicinal plants was primarily shared with families, unlike knowledge of food plants and social norms/beliefs, which was

shared among camp members regardless of family ties (Salali et al., 2016). Medical knowledge also differs substantially across language groups, even within geographic regions (Cámara-Leret & Bascompte, 2021).

In the ethnographic record, most knowledge specialists are medicinal knowledge specialists, such as shamans and traditional healers (Lightner et al., 2021b), whose expertise is often linked to other useful knowledge domains, such as botany, zoology, and psychology (see Figure 6). Medical specialists typically provide valuable medical services to a dedicated clientele, often in exchange for payments of various sorts (Lightner et al., 2021b; Sugiyama & Sugiyama, 2003), including social, material, and mating benefits (albeit with limited evidence for the latter, Lightner et al., 2021a). Medicinal knowledge specialists therefore often treat their knowledge as a proprietary and secretive resource, in contrast to the prestigious mentorships provided by specialists in domains requiring commonly used skills, such as subsistence or toolmaking (Lightner et al., 2021a).

We propose that in the human lineage, the self-medication behaviors seen in other apes evolved into widespread daily consumption of pharmacological plants, that is, spices and "recreational" drugs (discussed next), that were behavioral analogs of constitutive defenses, and ethnomedical knowledge that was the behavioral analog of an inducible defense. Some ethnomedical knowledge to treat common infections, such as intestinal helminths, would have been widespread, but in modern humans, at least, much was probably possessed by shamans and traditional healers who treated specific but relatively uncommon illnesses in exchange for various sorts of payments.

8 | DEFENDING THE BRAIN FROM PATHOGENS WITH PSYCHOACTIVE DRUGS

The final category of pharmacological plant use that requires an evolutionary explanation is the widespread, habitual use of "recreational" drugs like caffeine, nicotine, and THC, which we also conceptualize as (mostly) a constitutive defense. Previously, two of the authors (EHH and RJS) and their colleagues proposed that use of these substances might have evolved as constitutive and inducible defenses against pathogens (Hagen et al., 2009; Hagen et al., 2013; Roulette et al., 2014; Sullivan et al., 2008). Here we extend this hypothesis to the behavioral defense of the CNS specifically, which tripled in size in the Pleistocene and might have been subject to increased virulent infections, as described earlier. This extension is based on the substantial differences in immune defenses of the brain vs. other tissues and organs.

Most tissues have mechanisms to restore functionality when damaged or infected, which typically involves the destruction and removal of injured or infected cells (D'Arcy, 2019; Deretic et al., 2013), and the generation of new cells (Clevers & Watt, 2018; Xia et al., 2018). Herpes simplex virus infection of skin cells, for example, results in massive immune- and virus-mediated cell death, followed by rapid replacement of the cells. Most human neurons, however, cannot be replaced in adulthood because loss of neurons entails the loss of functionality and often irreplaceable information, such as in Alzheimer's disease where neuronal cell death causes permanent loss of memory and other cognitive dysfunctions (Arendt et al., 2015). Although adult neurogenesis has been reported in a wide range of vertebrates, including birds, rodents, and primates, in humans it is very limited and perhaps non-existent (Denoth-Lippuner & Jessberger, 2021; Franjic et al., 2022; Gage, 2019; Lucassen et al., 2020; Moreno-Jiménez et al., 2019; Oppenheim, 2019; Sorrells et al., 2018). The unique value of neurons presents a conundrum to the immune system: how to defend the brain from pathogens if destroying infected neurons would cause permanent loss of critical learned information or other functionality (Miller et al., 2016; Solomos & Rall, 2016)? Moreover, CNS inflammatory responses interfere with CNS functions, sometimes permanently, even without neuronal death (Klein et al., 2017). Constitutive defenses are one solution (Paludan et al., 2021).

8.1 | The blood-brain barrier, a constitutive defense

The brain is defended by a physical blood brain barrier (BBB). The BBB prevents most blood-borne pathogens from infecting the brain. It also prevents most plant toxins and other xenobiotics from entering the brain (Banks, 2016; Iadecola, 2017; Villabona-Rueda et al., 2019), including most pharmaceuticals, which often chemically resemble plant toxins (Agúndez et al., 2014). These properties pose a considerable challenge to drug treatment of pathogens that do manage to infect the CNS (Pardridge, 2012; Terstappen et al., 2021). Certain small molecules can cross the BBB via lipid-mediated free diffusion, however, including widely used "recreational drugs" like nicotine and caffeine.

8.2 | CNS immune privilege and defense

For much of the last century, knowledge that the BBB prevented most pathogens from reaching the CNS and that tissue grafts implanted in the CNS parenchyma (functional tissue) did not provoke rejection, supported the view that the CNS was an "immune privileged" site. Recent discoveries that the brain parenchyma is connected to the peripheral immune system via meningeal lymphatic vessels have stimulated debate over the nature of immunity in the brain.

One mainstream view is that barriers establish compartments in the CNS that differ functionally in their access to the immune system and some are immune privileged and others are not (Engelhardt et al., 2017). The meninges surrounding the CNS parenchyma, for instance, contain a wide repertoire of immune cells, including monocytes and B cells from special skull and vertebral bone marrow reservoirs, that provide immune surveillance of the CNS (Alves de Lima et al., 2020; Brioschi et al., 2021; Cugurra et al., 2021). Although the CNS parenchyma can mount an inflammatory response to infection

via resident microglia (brain-specific macrophages) and other cells, as well as cells migrating from the meninges, it is characterized by a dearth of adaptive and innate immune responses relative to peripheral tissues (Engelhardt et al., 2017).

Immune privilege is a double-edged sword, however. Despite formidable CNS defenses such as the BBB, pathogens do manage to infect the CNS. The protection immune privilege provides to neurons also creates a niche in which pathogens that manage to infect the CNS can evade destruction by the immune system (Cain et al., 2019; Forrester et al., 2018). In fact, to maintain neuronal integrity, immune responses in the CNS might favor controlling pathogens rather than eliminating them (Matta et al., 2021; Miller et al., 2016).

8.3 | Habitual recreational drug use as a constitutive pathogen defense

Humans have evolved to be exceptionally reliant on learned information and other CNS functions across a lifespan that exceeds that of most other mammals, and they occupied a dietary niche with high exposure to potentially zoonotic pathogens, including those that infect the CNS. Yet immune defense of the CNS is constrained. Chemoprophylaxis and chemotherapy with compounds that are harmful to CNS pathogens but well-tolerated by the CNS would complement the immune system. Such an evolved chemoprotective strategy for the CNS requires antipathogenic compounds that can cross the BBB.

Most common recreational drugs, including caffeine, nicotine, THC, and arecoline in betel nut, are plant defensive neurotoxins (ethanol, a yeast fermentation product, is the major exception). Sullivan, Hagen, and colleagues argued that the prevailing evolutionary "hijack hypothesis" of recreational drug use, in which evolutionarily novel substances incidentally activate dopamine reward circuits (Kelley & Berridge, 2002; Wise, 1998), was implausible because similar compounds have been part of primate diets for millions of years (Hagen et al., 2009; Hagen et al., 2013; Sullivan et al., 2008; Sullivan & Hagen, 2002).

Psychoactive substance seeking might instead be an evolved self-medication strategy to defend against intestinal helminths and other pathogens (Hagen et al., 2009; Hagen et al., 2013; Sullivan et al., 2008; Sullivan & Hagen, 2002). All globally popular recreational drugs are toxic to helminths, as are some hallucinogenic plants used by Amazonian peoples (Rodríguez et al., 1982); nicotine was widely used to deworm livestock prior to the development of modern anthelmintics, and has the same mechanism of action as some commercial anthelmintics; an aqueous solution of tobacco is still used to deworm livestock in some low-income settings (efficacy quantitatively verified); tobacco is widely mentioned as an anthelmintic in ethnomedical texts; treatment of intestinal helminths in hunter-gatherers transiently reduces tobacco use, and tobacco and cannabis use is negatively associated with worm burden and reinfection; and there is a switch-like transition by virtually all humans to regular use of one or more of these pharmacologically potent substances in adolescence once teratogenic risks to the developing brain have dropped (Hagen et al., 2009; Hagen & Sullivan, 2018; Roulette et al., 2014; Roulette, Kazanji, et al., 2016; Sullivan et al., 2008; Sullivan & Hagen, 2002). In this model, females avoid culturally identified teratogenic substances such as tobacco during pregnancy and their reproductive years, increasing use postmenopause (Hagen et al., 2016, 2013; Hagen & Tushingham, 2019; Placek et al., 2017). See Figures 7 and 8.

Helminths are an important class of CNS parasites, and of course all recreational drugs cross the BBB. Here we extend the antiparasite hypothesis of recreational drug use to pathogens that infect the CNS, focusing on the helminth *T. solium* as a key example. Humans, dogs, and other animals infected with *Taenia* and other tapeworm species have often been treated with arecoline hydrobromide (Gemmell, 1958; Li et al., 2012). Arecoline is an agonist of muscarinic acetylcholine receptors, which have numerous roles including in neuromuscular junctions. Arecoline's mechanism of action against cestodes is probably to induce paralysis (Liu et al., 2016). Arecoline readily crosses the BBB and is the primary psychoactive alkaloid in the seed of *Areca catechu* palm, which is typically chewed with the leaf of the *Piper betle* and slaked lime, a concoction termed betel quid or *paan* (Volgin et al., 2019). Betel quid is widely consumed in Asia and the Pacific and is probably the fourth most widely used psychoactive substance after caffeine, alcohol, and tobacco (Arora & Squier, 2019; Gupta & Warnakulasuriya, 2002; Mehrtash et al., 2017). Areca seeds, often combined with pumpkin seeds, were one of several frequently mentioned treatments of *Taenia* infections in Chinese medical texts dating back about 2000 years (Zou & Ye, 2014). In a controlled study in humans this combination was found to be close to 90% effective at expelling *Taenia* tapeworms (Li et al., 2012). Whether arecoline also kills *Taenia* larvae in the brain is unknown, and killing larvae in the brain induces inflammation, potentially creating more problems than it solves. However, most of the medical community has accepted that the benefits of antiparasitic treatment of neurocysticercosis outweigh the risks (García et al., 2003). In an observational study of individuals suffering epileptic seizures, many of whom probably had neurocysticercosis based on the local prevalence of this disease, chewers of *Areca catechu* (1/3 of the sample) had 59% fewer seizures in the month prior, compared to non-chewers (a mean of 1.4 vs. 3.3 seizures, respectively, Mateen et al., 2017).

It is intriguing that a tapeworm that humans acquired from carnivores in the Pleistocene, and which infects the CNS and other tissues, is potentially treatable with the active compound in one of the world's most popular "recreational" drugs, used on a daily basis by a sizable fraction of the world's population, and that among those with seizures, use of the drug is negatively associated with seizure frequency. It is also intriguing that caffeine, the world's most popular drug, inhibits growth of *T. gondii* (Munera López et al., 2019), another common neurotropic pathogen. Consumption of ethanol, like consumption of pharmacological plant substances, could also be a self-medication strategy: it is a potent antimicrobial compound, and there is evidence that it mitigates infections of *H. pylori* in vitro and in vivo (Liu et al., 2016; Xia et al., 2020).

Extending previous work (Hagen et al., 2009; Hagen et al., 2013; Sullivan et al., 2008), we propose that when the benefits exceed the

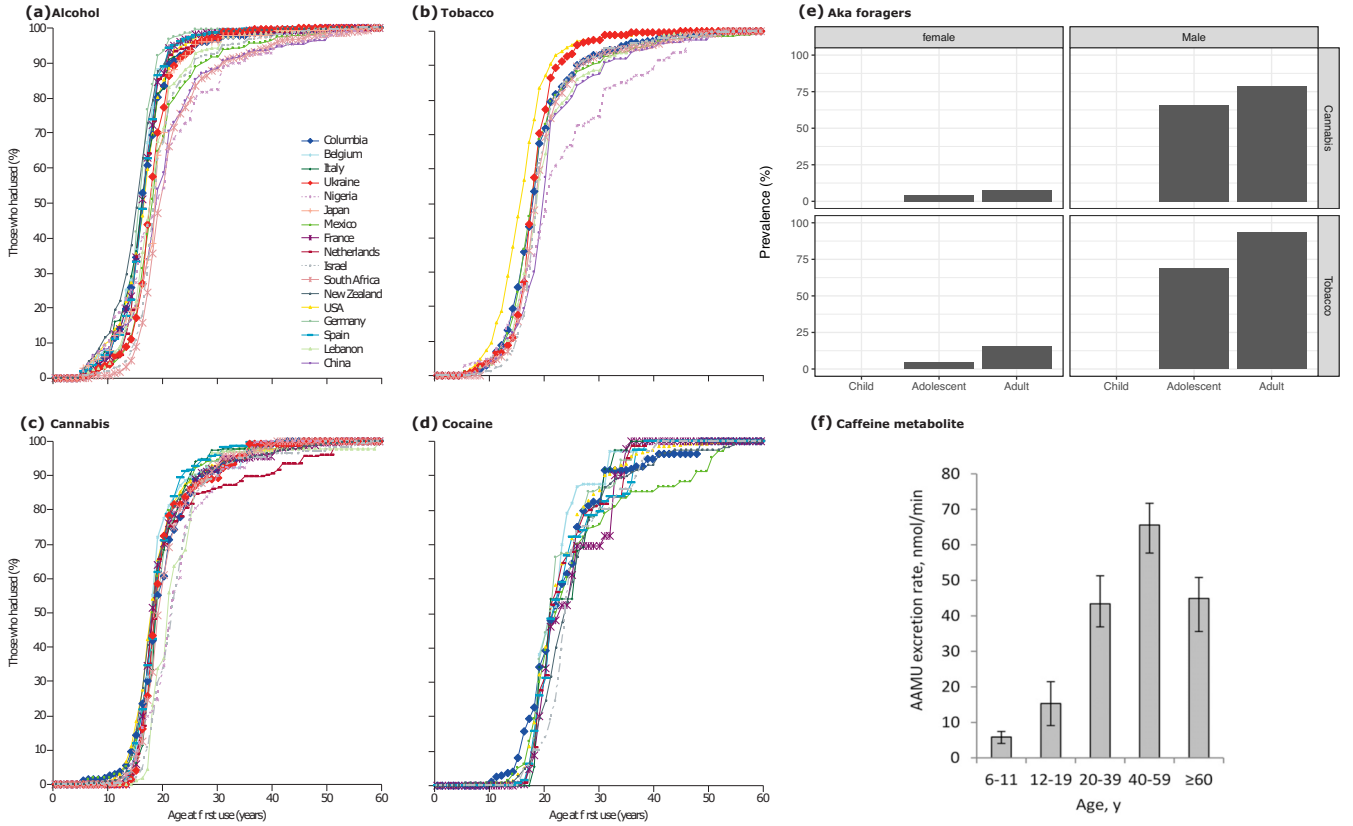

FIGURE 7 (a–d) The universal transition to psychoactive druge use in adolescence. Cumulative distribution of self-reported age of first use of alcohol, tobacco, cannabis, and cocaine in a large ($N = 85{,}052$) cross-national sample of users of these substances. Figure from Degenhardt et al. (2016). (e) Prevalence of tobacco and cannabis use among Aka forager children, adolescents, and adults, by sex (no children reported use). Data from Roulette, Hagen, et al. (2016). (f) Urinary caffeine metabolite (AAMU: 5-acetylamino-6-amino-3-methyluracil) excretion rate in a nationally representative US sample ($N = 2714$); 97.5% had detectable AAMU. Self-reported caffeine intake in this sample exhibited the same age dependence, as did concentrations of urinary caffeine and other caffeine metabolites. Figure and data from Rybak et al. (2015). These patterns suggest the existence of a developmental "switch" to psychoactive drug use during adolescence.

costs, humans, and perhaps other animals, have an evolved propensity to seek out and regularly consume psychoactive plant defensive chemicals, that is, those that cross the BBB and interfere with neural signaling, so as to deter, control, and eliminate pathogen invasions of the immune privileged CNS parenchyma.

9 | IMPLICATIONS FOR THE EVOLUTION OF HUMAN COGNITION

We propose that pathogens were an ecological selection pressure for increased cognitive capacity in the human lineage. Increased selection to co-opt anti-infective plant secondary compounds would have selected for the cognitive abilities necessary to identify a large variety of plant parts rich in various pharmaceutical compounds and then to determine which compounds best treated which illnesses. To illustrate: in order to evaluate the effects of each of 20 plant substances on 10 illnesses would require 200 "tests". Moreover, combinations of drugs can often outperform single drugs. Traditional Chinese medicine specifies treating *Taenia* with a combination of areca and pumpkin seeds, for instance, and this combination has been shown to outperform either plant substance alone (Li et al., 2012). There are 190 combinations of two plant substances chosen from 20; testing each combination against 10 illnesses would require 1900 tests. In addition, different pathogens can cause similar symptoms, further complicating diagnosis and treatment. We are not proposing that humans evolved to systematically test every combination of plant substances against every illness; we are simply illustrating the complexity of discovering effective plant-based treatments of infectious diseases. Successful prevention and treatment of infections, in turn, especially zoonotic infections, would have enabled a heavier reliance on energy-rich meat and reduced the lifetime energetic cost of immune responses, thereby making more energy available to, among other things, support the evolution of a larger brain.

10 | ALTERNATIVE HYPOTHESES, CAVEATS, AND COMPLICATIONS

The hypotheses we have developed here are speculative and must be rigorously tested against plausible alternatives. We sketch some of

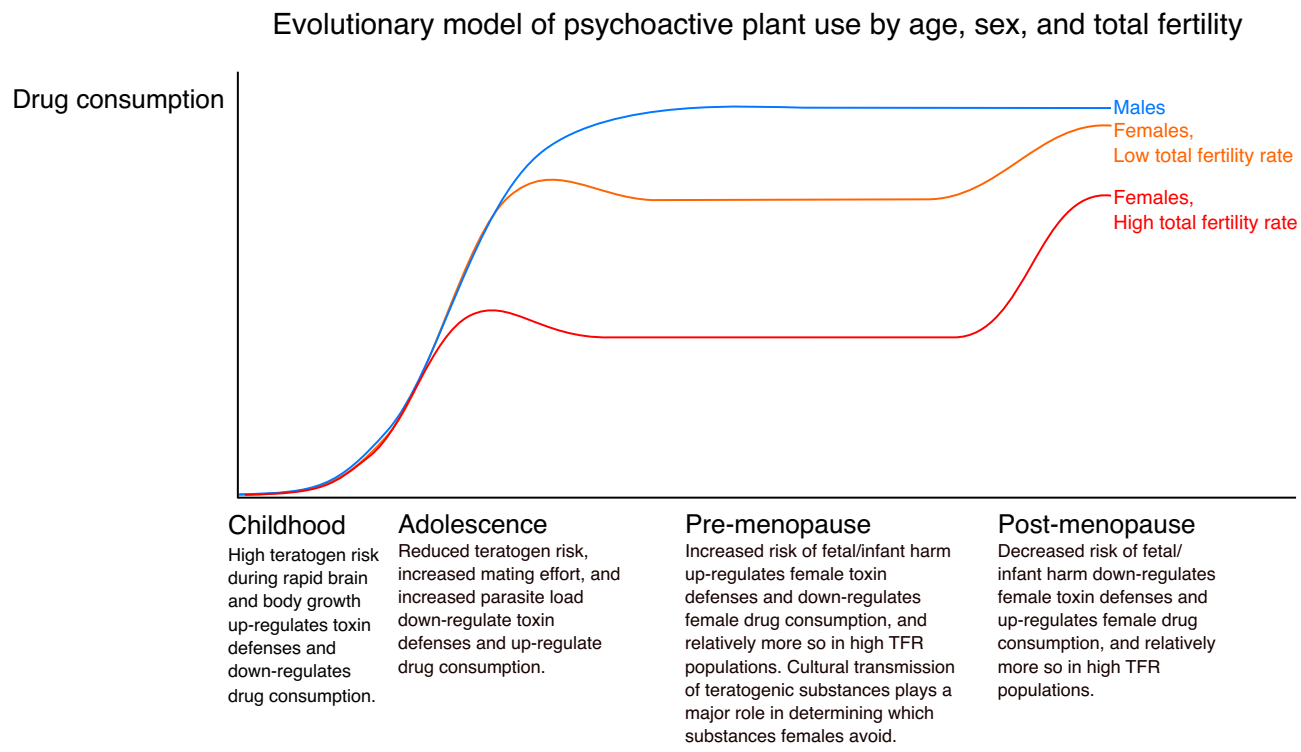

FIGURE 8 Theoretical model of recreational drug use as an evolved constitutive pathogen defense that varies by age, sex, reproductive status, total fertility rate (TFR), and cultural information about teratogenic substances. For details, see Hagen et al. (2016) and Hagen and Tushingham (2019).

those alternatives next, along with the types of evidence that could discriminate among them.

Human's intensified use of medicinal plants could simply be a byproduct of a capacity for cumulative culture that evolved for other reasons (e.g., foraging or sociality). The motivation to use such plants could be common to all primates or mammals, with only the cognitive ability to do so increasing in humans. In addition, modern global trade would facilitate this usage by providing access to a much greater variety of plants than are available to other species.

One test would be to determine the extent to which patterns of medicinal and psychotropic plant use by chimpanzees and other apes converge or diverge from human patterns of use. For example, do chimpanzees or other apes exhibit a developmental shift to regular consumption of psychotropic substances that resembles the switch-like transition seen in human adolescents (Figure 7)? Chimpanzees do consume ethanol and fermented fruit under natural conditions (Amato et al., 2021; Hockings et al., 2019). Unlike tobacco and other psychotropic plants favored by humans, however, ethanol contains substantial calories, which might explain its use by chimpanzees and other primates (Dudley, 2014).

The effectiveness of psychotropic drugs against CNS infections is largely hypothetical and the possibility remains that psychotropic effects are merely a byproduct of the shared features of human and parasite nervous systems, and that the use of these drugs has more to do with their effects elsewhere in the body, for example in the gut, as argued previously (Hagen et al., 2009; Hagen et al., 2013; Sullivan et al., 2008).

Possible tests include investigations of the prophylactic effects of typical serum levels of nicotine, arecoline, caffeine, and other psychoactive drugs against CNS infections of Taenia and other helminths or pathogens in model organisms; evidence that regular psychoactive drug use protects against helminth or other infections of the CNS in humans; evidence that CNS infections were a significant selection pressure, and more so in humans than other apes (e.g., genetic evidence of selection on CNS-specific immune genes and regulatory elements that diverge from other apes); and evidence that clearing Taenia or other infections of the CNS in humans reduces psychoactive drug use (similar to Roulette et al., 2014).

If humans evolved to seek out some substances as prophylactics, they may continue to seek these substances even in the absence of immune challenges. Similarly, humans might seek out substances which present cues similar to medicinal plants, that is, psychoactive effects, even if the particular plants chosen are not themselves medicinal. Both of these factors may make establishing the link between drug use and pathogen defense more challenging, particularly in modern, low-pathogen contexts.

If humans evolved a taste for plant secondary compounds for self-medication, this could have encouraged drug plant domestication and created runaway selection in which plants were selected for greater and greater amounts of these compounds (Alternately, this same process can also be seen as plants having been selected to manipulate humans by producing these compounds in order to encourage humans to spread and cultivate them, e.g., Pollan, 2002).

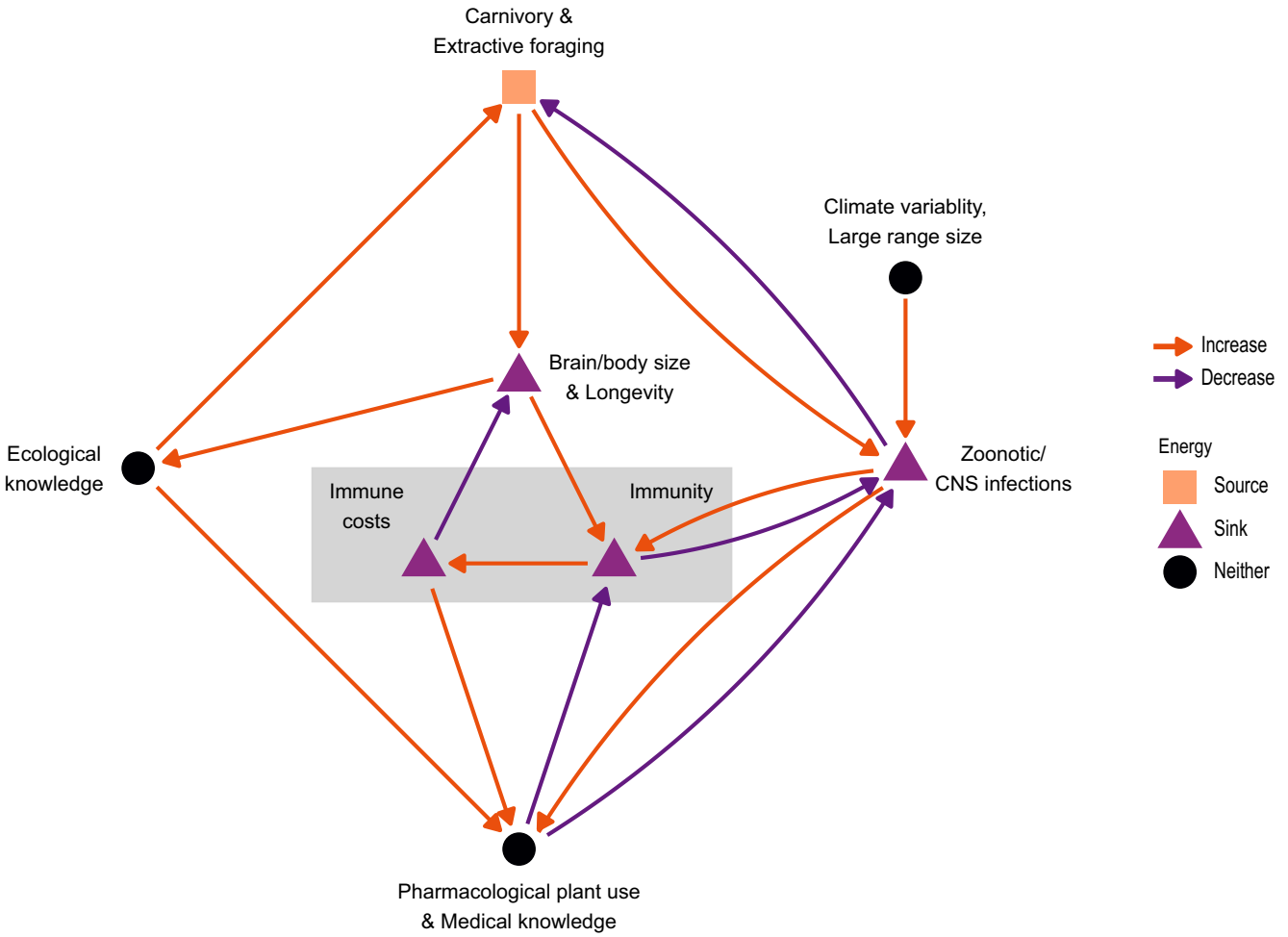

FIGURE 9 *Homo medicus*: Hominin entry into a more carnivorous niche provided the caloric density necessary to evolve a larger brain and body size, enabling a greater reliance on learned ecological knowledge in a long-lived animal. It also increased exposure to novel zoonotic diseases, some of which may have been more likely to infect the CNS. Pleistocene climate variability and increased range size in Homo also increased zoonotic pathogen pressure. Defending the larger, longer-lived body and brain from increased pathogen pressure selected for increased investment in immunity, which has energetic and other costs, constraining the evolution of a larger body and brain. Ecological knowledge would have been useful in acquiring knowledge of pharmacological plants that provided constitutive and inducible defenses against pathogens. Selection would have particularly favored hominins who sought out compounds able to cross the BBB to supplement defense of the immune-priviledged CNS. The evolution of drug use, spice use, and healthcare would have further reduced mortality risk and increased energy availability by reducing immune costs and increasing the safety of carnivory. These effects caused further positive feedback on selection for bigger brains, extended juvenile periods and longevity, allowing for even more acquisition of ecological knowledge and even greater payoffs from pharmacological plant use.

Such a process could lead to selection for compounds with the strongest psychotropic effects, even if these are not the compounds with the greatest medicinal value.

Similarly, once humans began regularly consuming and using these compounds, their use might have taken on social, ritual, and recreational significance. Medical specialists are often religious leaders, for instance (Lightner et al., 2021b). Such seeking out of drugs for reasons unrelated to parasite defense may have further selected for drug seeking in humans and psychotropic compounds in plants, further divorcing the cue from the original parasite defense function.

Alternatively, religious leaders such as shamans might have emerged through the use of deceptive, subjectively appealing practices (Buckner, 2022; Hong, 2022). That is, shamans could gain prestige by professionalizing "plausible-seeming magical practices" that convince others of their superhuman qualities, independent of their ability to actually apply useful medicinal knowledge (Singh, 2018, p. 5). This hypothesized origin of shamanism would reflect a more exploitative account than ours offers, but the two are not mutually exclusive: Deceptive practices might coexist with beneficial medicinal services (Blackwell & Purzycki, 2018), and cross-culturally, shamans might only partially overlap with the traditional medicinal specialists we described here. Future research could test the social aspects of our proposal by investigating the efficacy of shamans' healing practices and comparing it to the efficacy of widespread folk alternatives. Consistent with alternative hypotheses, shamans'

healing practices might also be integrated into a broader set of religious practices that serve separate functions that have little-to-no relevance to medicine.

11 | CONCLUDING REMARKS

The human lineage entered a more carnivorous dietary niche c. 2.6 mya. Hunting provided the high-quality meat-based diet necessary to support the evolution of a large brain while at the same time posing formidable cognitive challenges, thereby selecting for increased cognitive abilities (Kaplan et al., 2000). It also increased the risk of zoonotic spillover. We propose that selection intensified for the self-medication strategies already in place in apes and other primates (Huffman, 2003) for three major reasons. The first was a shift and perhaps increase in zoonotic pathogen pressure from increased carnivory, climate variability, and range size. The second was the challenges of defending a large body from pathogens across what would eventually become one of the longest lifespans of any mammal. And the third was the increasingly negative consequences of CNS infections in a lineage that was rapidly evolving a larger brain, an organ in which immune defenses are highly constrained.

Local florae were continually evolving thousands of compounds to combat the same broad classes of continually evolving pathogens that infected human ancestors. The human lineage, entering a knowledge-based niche, began to evolve the cognitive mechanisms needed to determine which plant substances best prevented, reduced, or eliminated which illnesses. This resulted in an inducible defense system – treating specific illnesses with specific plants, that is, medicine and medical specialization, and two constitutive defense strategies: routinely adding plants high in pharmacological compounds—spices—to foods, and habitually consuming psychoactive plant substances that entered systemic circulation and crossed the BBB, suppressing pathogens in multiple tissues, including the CNS. Along with cooking, as emphasized by others (Smith et al., 2015; Wrangham, 2009), these medical behaviors would have permitted a heavier reliance on energy-rich animal foods and reduced the need for energetically expensive immune responses, supporting the evolution of a larger, energy intensive brain. See Figure 9. In the story of human evolution, which has long featured hunting, healing had an equal role to play.

AUTHOR CONTRIBUTIONS

Edward H. Hagen: Conceptualization (lead); project administration (lead); writing – original draft (lead); writing – review and editing (equal). **Aaron D. Blackwell:** Conceptualization (supporting); writing – original draft (supporting); writing – review and editing (equal). **Aaron D. Lightner:** Investigation (supporting); writing – original draft (supporting); writing – review and editing (equal). **Roger Sullivan:** Conceptualization (supporting); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated; the article describes entirely theoretical research; all data are in the cited sources.

ORCID

Edward H. Hagen https://orcid.org/0000-0002-5758-9093
Aaron D. Blackwell https://orcid.org/0000-0002-5871-9865

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