2

The Natural Biology of Dietary Ethanol, and its Implications for Primate Evolution

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Introduction

Evolutionary perspectives can sometimes provide novel insights into questions of human health and behaviour, as exemplified by the field of Darwinian medicine (Williams & Nesse, 1994). Addictions in general pose substantial medical and sociological challenges, and arguably the most prominent, if not destructive of these addictions is the phenomenon of alcoholism. Evolutionary and even historical considerations have not usually been considered germane to our understanding of the behavioural attraction to and physiological dependence on ethanol, although clearly the modern phenomenon of substance dependence must derive, in part, from neural activation of ancient reward pathways (Nesse & Berridge, 1997; Nesse & Williams, 1999; Smith, 1999).

Here, I expand upon earlier arguments (Dudley, 2000, 2002, 2014) that evolutionary exposure of humans to dietary ethanol well precedes crop domestication and the origin of *Homo sapiens*, and is in fact characteristic of all fruit-eating (i.e. frugivorous) animals, including many primates and the hominid lineage leading to modern humans. Yeast-based fermentation within ripe fruit and concomitant production of ethanol indicate sustained historical exposure of all animal frugivores to this psychoactive and potentially addictive compound. As a consequence, an ancestral sensory bias linking ethanol consumption to nutritional gain and ultimately to selective advantage characterizes a broad diversity of animal taxa, ranging from fruit flies and fruit bats to the great apes and modern humans. The evolutionary consequences of regular dietary ingestion of ethanol are substantial, and in particular may underlie recent epidemiological evidence demonstrating the health benefits of low-level consumption. Modern-day patterns of alcohol consumption, metabolism, and abuse may thus be deeply rooted in evolutionary time.

Fruits and Natural Fermentation

Alcoholic fermentation of sugars by yeasts has been universally recognized since the mid-nineteenth century work of Pasteur. Sugars suitable for such fermentation occur naturally within ripe fruit pulp and serve as the primary caloric motivation for consumption by animals, typically mammals and birds, that consume the fruit and subsequently disperse seeds. Ripe fruits must be attractive to consumers (e.g. meeting the sensory criteria of colour, texture, and odour), and must simultaneously present sufficient nutritional reward to merit searching behaviour and consumption. An ecological definition of fruit ripeness, in fact,

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is suitability for consumption by a vertebrate frugivore. Sugar concentrations within ripe fruits range from trace quantities to levels as high as 61% of fruit mass, although typical values range from 5 to 15% (Tucker, 1993; Baker et al., 1998). Sugar-rich fruits thus provide ample nutritional substrate for the fermentative metabolism of yeasts.

Unripe fruits, by contrast, contain primarily starches that, during the ripening process, are converted to simple sugars. Because the maturing seeds of unripe fruits are not suitable for dispersal, developing fruits tend to be green, tough, and otherwise unpleasant to consume. As ripening proceeds, colour changes typically render the fruit more obvious against foliage (e.g. red, yellow, purple), the fruit softens, aromatic volatiles are expressed, and the likelihood of consumption increases (Brady, 1987; Dudley, 2004). Both microbes and vertebrates are, of course, possible consumers of developing fruits. Although both unripe and ripe fruits are chemically defended against microbial pathogens (Herrera, 1982; Janzen, 1983; Cipollini & Stiles, 1992; Cipollini & Stiles, 1993), the ubiquity of yeasts in natural environments indicates the possibility of fermentation and decay for all fruits prior to their localization and consumption by vertebrates (Last & Price, 1969; Spencer & Spencer, 1997). Fruit decomposition can thus be viewed as a race in time between microbe and dispersal agent to gain nutritional advantage. The suggestion that ethanol is toxic and renders fruit unpalatable to vertebrate consumers (Janzen, 1977) has recently been falsified empirically for mammalian dispersers (Peris et al., 2017).

Ethanol itself may similarly serve to inhibit the growth of microbial competitors to yeasts, whereas yeast metabolism in laboratory and oenological contexts is itself substantially inhibited at ethanol concentrations greater than 10–12%. Anaerobic fermentation and concomitant production of ethanol first appeared in yeasts near the time of origin of fleshy fruits in the Cretaceous (Benner et al., 2002), and may specifically have evolved to inhibit activity of bacterial competitors within ripe fruit (Ingram & Buttke, 1984). Unfortunately, the role of ethanol inhibition for wild yeast strains and bacterial competitors growing on natural substrates appears never to have been investigated. Microbial decay generally can interfere with the plant's evolutionary goal of consumption and dispersal by vertebrates (Janzen, 1977; Borowicz, 1988; Cipollini & Stiles, 1992). Microbes, invertebrate fruit consumers (especially insect larvae), and vertebrate dispersers thus compete for access to a rich but transient nutritional substrate. Sensory mechanisms that facilitate rapid identification of ripe fruit will therefore be of advantage to vertebrate frugivores that must acquire and consume these transient and often spatially distant nutritional resources.

What then is the typical ethanol content of ripe fruits in natural ecological habitats? Few data are available that are relevant to this important question. Ethanol concentrations in decomposing agricultural fruits in the temperate zone (e.g. grapes) range from trace quantities to values as high as 12% (Gibson et al., 1981; McKechnie & Morgan, 1982; Oakeshott et al., 1982). However, the relevance of these measurements to decomposition of wild fruit crops is not entirely clear, given the effects of artificial selection on fruit biochemical composition. Ethanol concentrations for small bird-dispersed fruits of two shrub species in Finland reached maxima of 0.3%, although average values were much lower (Eriksson & Nummi, 1982). Temperate-zone fruits are unlikely, for reasons of low ambient temperatures alone, to be characterized by particularly high ethanol concentrations. Fermentation of fruit crops is instead more pronounced in warm and humid environments that promote both yeast growth and rapid decomposition. Tropical rain forests are of particular interest in this regard, given the ecological associations of most frugivorous primates.

Field work on Barro Colorado Island in the Republic of Panama has established the presence of substantial ethanol concentrations within tropical fruit. The palm *Astrocaryum standleyanum* is a common species in lowland Panamanian rainforest, and bears heavy crops of large orange fruits that are consumed by white-faced monkeys, red-tailed squirrels, Central American agoutis, and collared peccaries. Fruit of this palm species can therefore be considered as representative of mammal-dispersed fruits in the tropics. Sugar and ethanol measurements were made for homogenized fruit pulp excluding both the skin and the large seed, given that the carbohydrate rewards for dispersers are located primarily, if not exclusively, within the pulp. Sugar concentrations (weight/weight) were determined using a hand-held refractometer; ethanol concentrations within pulp (w/w) were estimated from equilibrium vapour pressure measurements made using an electrochemical ethanol sensor (PAS Systems, Fredericksburg, VA) calibrated against ethanol solutions of known concentration.

These measurements found that ripe palms fruits contained on average 0.6% ethanol within the pulp, but that over-ripe fruits (as categorized by a human observer), had much higher levels, averaging 4.5% (Dudley, 2002). By contrast, unripe green fruits contained no measurable ethanol. For ripe and over-ripe fruits combined, ethanol content also varied inversely with sugar concentration of the pulp. The obvious inference is that yeast metabolism converts sugars to ethanol in a substantial fraction of the fruit crop, and that human perception of an over-ripe condition corresponds to fermentative microbial activity. Variance in yeast presence and associated ethanol production was high, and discrete characterization of the over-ripe condition may encompass a wide range of fungal decomposition according to fruit age, composition of the microbial community, and climatic conditions. A continuum of fermentative activity likely results in variable ethanol production throughout the pulp (and particularly in large fruits), but the important message is that animals consuming these fruits will necessarily ingest low-concentration ethanol. Ethanol may thus be a widespread component of sugar-rich fruits growing in humid tropical environments. Data to date suggest the utility of widespread screening of tropical fruits consumed by vertebrate taxa (and particularly primates), relying on quantitative assays of ripeness, sugar, and ethanol content. Substantial levels of ethanol within pulp also characterize fruits in Southeast Asia over a range of ripening stages (Dominy, 2004). Critically, the consequences of ripeness and ethanol content for detection and dietary choice by frugivores are unstudied. It is clear, however, that the warm and wet climates most conducive to fermentative yeast metabolism are those tropical habitats within which our fruit-eating ancestors first evolved.

Human Origins and the Comparative Biology of Ethanol Consumption

Many primates, including modern humans, derive ancestrally from frugivorous precursors. The earliest known euprimate (modern aspect) fossils date from the Eocene (~56 Ma). Based on dentitional evidence, these animals were fruit-eaters (Bloch & Boyer, 2002). Frugivory by primates diversified throughout the Eocene (Kay et al., 1997), and characterized the first hominoids (i.e. human-like apes) around 24 Ma (Andrews, 1996). Of the extant hominoid taxa (gibbons, orangutans, chimpanzees, and gorillas), only the highland gorillas are characterized by diets containing less than 50% fruit, with all other taxa

being strongly frugivorous (Andrews & Martin, 1991; Rowe, 1996; Morgan, 2017) (see Figure 2.1). Arguments based on fossil evidence also suggest fruit-eating by a variety of now extinct hominoid lineages (e.g. Afropithecinae, Dryopithecinae, Kenyapithecinae: see Teaford, 1988; Kay et al., 1997). Evolutionary reconstruction of dietary habits in hominoids strongly supports ancestral frugivory in our immediate hominin (i.e. bipedal hominid) as well as distant ancestors (Figure 2.1).

Humans and chimpanzees diverged at ~5 Ma. Modern chimpanzees eat ripe fruits most of the time (McGrew et al., 1988; Malenky & Wrangham, 1994), and a similar diet is thought to have pertained to early humans (Grine & Kay, 1988). Hominins over the last two million years have progressively supplemented a fruit-based diet with more animal fat and protein (Eaton et al., 1997; Sponheimer & Lee-Thorp, 1999), but fruit consumption would have remained a stalwart dietary feature, particularly in tropical forests (Roberts et al., 2016). Overall, this historical perspective suggests that, until very recent times, humans and their hominoid precursors were regularly exposed to low-concentration ethanol in the course of frugivory. The vast majority of our close relatives, as well as the primate lineage from which hominoids were derived in evolutionary time, are strongly frugivorous. Ethanol consumption via frugivory would, in turn, have resulted in physiological and sensory adaptations that link nutritional reward with dietary exposure to this molecule.

One of the strongest selective forces acting relative to frugivory is localization of ripe fruit crops within forests. Particularly in the tropics, ripe fruit is a highly transient and spatially

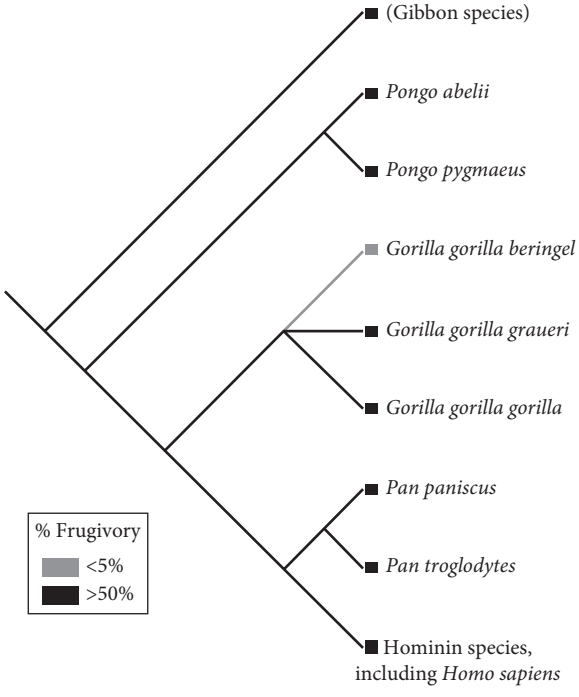

Figure 2.1 Phylogeny and extent of frugivory for extant hominoid taxa. Extent of frugivory (%) refers to the approximate proportion of fruit that contributes to total dietary intake. Taxonomic identifications are as follows: *Pongo*, orangutans; *Gorilla*, gorillas; *Pan*, chimpanzees; hominins, human taxa subsequent to divergence from ape precursors.

heterogeneous resource. Rapid localization and consumption will be essential in the face of unrelenting competition from the aforementioned range of microbial and metazoan frugivores. Foraging behaviours under such circumstances must be efficient, and possibly were associated with the initial elaboration of spatial memory in arboreal primates (Milton, 1993). Unfortunately, we know little about the behavioural and physiological mechanisms of fruit localization by wild primates across large spatial scales. An obvious candidate, however, is the olfactory plume of ethanol emanating from ripe fruit. Low molecular weight and substantial concentrations within fruit pulp render this molecule highly suitable for long-distance signalling of availability to appropriate dispersers. Moreover, the obligate association of ethanol with nutritional reward suggests a possible physiological role as an appetitive stimulant.

If preceding arguments concerning the role of ethanol in fruit-eating are correct, then diverse animal taxa should exhibit natural behavioural responses to ethanol. However, the influence of ethanol on animal frugivores in the wild has never been systematically investigated. Overall, the ethanol concentrations measured to date in fruit suggest regular low-level consumption by frugivores, but not exposure to levels typically associated with inebriation and overt behavioural consequences. The zoological literature nonetheless contains numerous anecdotal accounts of fruit-derived drunkenness in such taxa as diverse as fruit flies, butterflies, numerous bird species, warthogs, elephants, and even baboons (Dennis, 1987; Siegel, 1989; Miller, 1997; Dudley, 2014). The natural occurrence of ethanol ingestion is, however, undocumented in any quantitative sense, although diagnosed ethanol toxicosis in cedar waxwings that had been feeding on fermenting hawthorn fruits has been recorded (Fitzgerald et al., 1990; Kinde et al., 2012). Moreover, wild tree shrews and slow lorises feed on the fermenting nectar of certain palm flowers in Malaysia, and, although they never are overtly inebriated, their hairs contain high secondary metabolites of ethanol, indicating substantial chronic exposure (Wiens et al., 2008).

Blood-ethanol concentrations have never been measured in free-ranging animal frugivores, but represent a logical experimental goal for investigation in parallel with characterization of fruit ethanol profiles. Eriksson and Nummi (1982) fed naturally fermenting fruits to three captive bird taxa, and found that the most specialized frugivore among the three also exhibited the fastest rates of ethanol clearance and the most active alcohol dehydrogenase (ADH) isozyme in the liver. Similarly, Prinzinger and Hakimi (1996) found the fastest activity of blood ADH in a frugivorous species among the three sampled bird species. In laboratory contexts, non-human models of human alcohol consumption have also been developed, particularly to elicit genetically based addictive behaviours and withdrawal symptoms (Ervin et al., 1990; Crabbe et al., 1994; Li, 2000). The success of many such non-human models has been mixed, perhaps in part because the predominant rodent model used in such studies (i.e. laboratory rats) is not ancestrally a tropical frugivorous species. Such research has also explicitly decoupled nutritional substrate from liquid ethanol solutions in an attempt to simulate modern human drinking behaviour, whereas the evolutionary perspective presented here suggests that ethanol and other nutrients are inextricably mingled within natural fruit substrates.

Among invertebrates, the best studied system for natural exposure to dietary ethanol is the fly genus *Drosophila*. Intra- and interspecific variation in ADH and aldehyde dehydrogenase (ALDH) activity of fruit flies is pronounced, and is correlated with the extent to which ethanol occurs within oviposition substrates (Merçot et al., 1994; Ashburner, 1998;

Fry, 2001). Adult fruit flies also use ethanol plumes to locate suitable oviposition sites. The study of ethanol responses in *Drosophila* fruit flies is potentially useful for understanding molecular pathways of inebriation in humans (Devineni & Heberlein, 2013). Interestingly, behavioural preference by fruit flies for ethanol-containing substrates is correlated with the ability to metabolize ethanol, suggesting a direct link between metabolic capacity and sensory motivation (Cadieu et al., 1999). Modulation of fly behaviour by ethanol at natural concentrations is a potentially powerful phenomenon for studying not just the proximate molecular mechanisms of inebriation, but also for interpreting evolutionary consequences of chronic exposure.

The overall message of comparative biology to studies of ethanol addiction in modern humans is that behavioural responses to low-concentration ethanol may be ancestral and apparently advantageous in many animal taxa. Such responses may have been the direct target of natural selection in evolutionary time for many primate species, including human ancestors. Ethanol plumes can be used to localize ripe fruit, whereas consumption of ethanol within fruit pulp may then act as a feeding stimulant. Natural consumption rates of ethanol via frugivory and associated blood-ethanol levels are unfortunately not known for any animal taxon. Choice trials with two basal species of nectar-feeding primates indicate increasing preference for higher-concentration ethanol solutions (Gochman et al., 2016).

Quantitative assays of fruit ripeness, ethanol content, and palatability are essential for any such analysis. As in *Drosophila*, intra- and interspecific variation in ADH and ALDH activity among extant frugivorous primates would be predicted to follow the relative dietary inclusion of ethanol. For example, frugivorous lowland gorillas should be more capable of metabolizing ethanol than the more folivorous montane gorillas. Overall, any tendency of specific animal taxa towards ethanol preference and even addiction would be predicted to parallel naturally occurring patterns of genetic variation in the efficacy of ethanol and acetaldehyde degradation.

Nonetheless, the wide-reaching frugivorous heritage of *Homo sapiens* (Figure 2.1) suggests a sustained evolutionary exposure to ethanol. Recent paleogenetic reconstruction of alcohol dehydrogenase genes across the hominid phylogeny confirms a dramatically enhanced catabolic capacity of these enzymes starting about 10 million years ago, congruent with terrestrialization by bipedal apes and perhaps greater access to fermenting fruit crops on the ground (Carrigan et al., 2015; also Chapter 3). Moreover, wild chimpanzees readily consume anthropogenically sourced fermentations of palm sap within the tree canopy (Hockings et al., 2015; also Chapter 4), clearly indicating that ethanol at low concentrations is not aversive to these primates.

The Use and Abuse of Alcohol by Modern Humans

Relative to the age of our species (~200 000 years), anthropogenic production of ethanol is very recent (Table 2.1). Crop domestication was well-established by 8000 BC in southwest Asia. Tartaric acid residue of grapes characterizes Chinese pottery from 7000 BC, and is the earliest evidence for intentional fermentation by humans (McGovern, 2009; also Chapter 6; see also Dietrich & Dietrich, Chapter 7). For most of human history (see Table 2.1), alcoholic beverages were therefore limited to the low ethanol concentrations enabled by the fermentation process alone (i.e. <10%). Tangentially, it is important to realize that even

Table 2.1 Evolutionary timeline and historical exposure of humans to ethanol (dates are approximate Ma, thousands of years ago)

Date	Event
650 AD	Intentional distillation of high-concentration ethanol
7000 BC	Intentional fruit fermentation in Yellow River Valley, China
9000 BC	Crop domestication in the Near East
0.2 Ma	Origin of Homo sapiens
2 Ma	Origin of genus Homo
12 Ma	Origin of hominids
55 Ma	Origin of primates

concentrations of more than 5% are unlikely to be realized within the natural fruit substrates, as most yeast strains used by modern humans have been selected over many generations for enhanced ethanol resistance.

Even more recent than intentional fermentation is the chemical process of distillation and exposure to ethanol concentrations higher than those attainable by yeast metabolism alone (see Table 2.1). The technology of distillation was developed in central Eurasia in the early centuries of the first millennium (Needham, 1980; Huang, 2000), and then became widespread in China during the Tang dynasty (700–900 AD), diffusing concurrently into the Near East. In Europe, distillation of alcoholic beverages became common only in medieval times. The antiquity of intentional fermentation and distillation therefore corresponds to but a miniscule fraction of the age of humans themselves. The intentional consumption of ethanol in solution is also a strongly culturally transmitted trait, as anthropological surveys of drinking patterns worldwide show that responses to ethanol are context-dependent and are conditioned socially (Marshall, 1979; Douglas, 1987; Gefou-Madianou, 1992; Heath, 1995; Hunt & Barker, 2001). Relatively recent exposure to high ethanol concentrations, ad libitum availability facilitated by industrialization, and the vast fabric of human culture all contribute to patterns of alcohol consumption that differ dramatically from those of our frugivorous ancestors.

As an extreme of ethanol consumption, the biomedical and sociocultural phenomenon of alcoholism poses particular challenges. Biologically, alcoholism is known to be both partially heritable and polygenic in character (Cook & Gurling, 1990; Goldman & Enoch, 1990). Genetically based variation in the physiological response to ethanol is substantial, and is correlated with enzymatic activity of ADH and ALDH alleles both among and within human populations (Shen et al., 1997; Osier et al., 2002). Such variation, in turn, has been correlated with the propensity towards alcoholism for certain populations. Rates of alcoholism, however defined, tend to be much lower among East Asians than in West European and North American populations, consistent with deterrent effects on ethanol consumption associated from slow-acting ALDH and corresponding accumulation of toxic acetaldehyde (Agarwal & Goedde, 1990; Helzer & Canino, 1992).

Even more suggestive of genetic influences on ethanol consumption are studies within particular East Asian populations. Japanese and Taiwanese alcoholics, for example, exhibit reduced frequencies of catalytically more effective ADH alleles as well as higher frequencies

of faster-acting ALDH alleles (Tanaka et al., 1997; Harada et al., 1999; Reich et al., 1999). Although genotype-by-environment interactions are likely to be pronounced in the clinical emergence of alcoholism, these studies clearly implicate aversive acetaldehyde accumulation, derived from the interacting dynamics of ADH and ALDH activities, as being protective against excessive alcohol consumption (Li, 2000). In sum, the capacity to metabolize ethanol, as derived in evolutionary time from frugivorous ancestors, now influences the drinking behaviour of modern humans.

An Evolutionary Perspective on Human Alcohol Consumption

If ethanol is routinely found within ripe fruits, and given that *Homo sapiens* is descended from a predominantly frugivorous lineage of primates, what then might have been the evolutionary consequences for modern humans of such historical exposure to ethanol? By definition, phenotypic traits evolve when selection acts on heritable variation. If regular exposure to low concentrations of ethanol is an inevitable consequence of frugivory, then selection will favour the evolution of metabolic adaptations that maximize physiological benefits associated with ethanol ingestion while concomitantly minimizing any related costs. Exposure to higher concentrations of ethanol that are not naturally encountered may, by contrast, be stressful and cause harm. Such a non-linear dose-response curve is termed hormesis, and is a general evolutionary outcome that maximizes organismal fitness and reduces costs of exposure to substances that occur at low concentration (Gerber & Williams, 1999; Calabrese & Baldwin, 2003). Because evolutionary fitness necessarily invokes lifetime reproductive capacity, the possibility of trade-offs between short-term physiological benefits, life history traits, and overall fecundity must also be considered (Forbes, 2000).

Hormetic effects of ethanol have been experimentally determined only for the fruit fly genus *Drosophila*. As predicted from aforementioned evolutionary considerations, longevity of *Drosophila* species that naturally encounter fermenting nutritional substrates is enhanced at very low concentrations of ethanol, but decreases at zero exposure and at higher concentrations (Parsons, 1983; Parsons, 1989) (see Figure 2.2A). Most importantly, lifetime fecundity of *Drosophila* is also enhanced by the presence of low-concentration ethanol vapour (Etges & Klassen, 1989). These results are consistent with evolved metabolic responses that maximize physiological and overall fitness benefits of chronic environmental exposure to ethanol. Similarly, in modern humans, numerous epidemiological studies demonstrate a reduction in cardiovascular risk and overall mortality at low levels of ethanol consumption relative either to abstinence or to higher levels of intake (Vahtera et al., 2002; Klatsky, 2003) (Figure 2.2B). Greater residence time of ethanol within the body because of slow-acting ADH alleles is also associated with reduced risk of cardiovascular disease (Hines et al., 2001), providing further evidence of direct protective effects. The wide range of human behavioural responses to alcohol is consistent with evolutionary predictions, namely that exposure to novel concentrations of toxic compounds increases overall phenotypic variance (Holloway et al., 1997; Gerber & Williams, 1999). The aforementioned populational differences both in physiological reactions to ethanol and in susceptibility to alcoholism are also consistent with this latter prediction. The possible consequences of chronic ethanol ingestion for reproductive fitness have not, however, been systematically evaluated for modern humans.

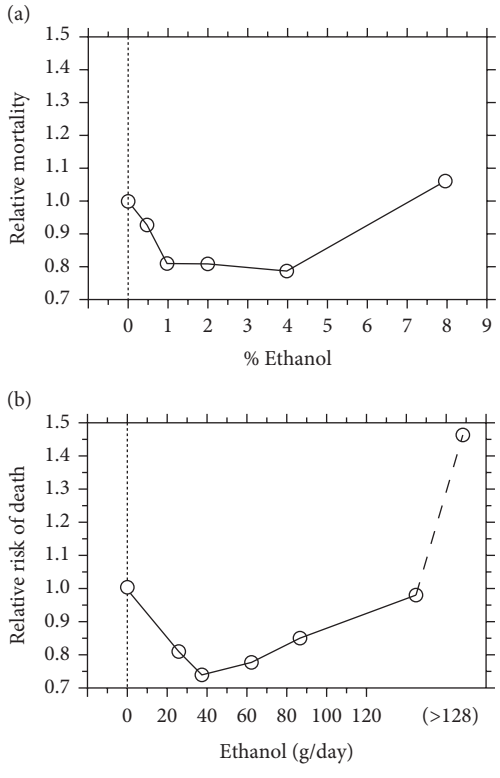

Figure 2.2 Hormetic effects of ethanol in (A) fruit flies (Starmer et al., 1977) and (B) modern humans (Renaud et al., 1998). Mortality (A) and death risk (B) are normalized relative to zero exposure or consumption, respectively. Data for ethanol consumption rates in the study of Renaud et al. (1998) are approximate and are presented here as the maximum value within any given category of consumption.

In common with fruit flies, therefore, humans exhibit several genetic, physiological, and behavioural responses to ethanol that are consistent with historical exposure of both taxa to low-concentration ethanol within nutritional substrate (Table 2.2). Natural selection may thus have acted on human ancestors to associate ethanol with nutritional reward, promoting rapid identification and consumption of ethanol-containing fruit resources. In turn, excessive consumption of ethanol by modern humans (e.g. alcoholism) may be viewed conceptually as a disease of nutritional excess. In this evolutionary perspective, genetically based behaviours adaptive in the ancestral environment become disadvantageous in a modern technological environment that provides *ad libitum* access to nutritional substrates. Such an interpretation of alcoholism is analogous to hypotheses linking high rates of obesity and diabetes in modern humans to the ready availability of fats and sugars in industrialized societies (O'Dea, 1992). As with variation in the capacity to metabolize ethanol, contemporary interpopulational variation in susceptibility to diabetes has similarly been attributed to historically variable selective regimes on the diet of early humans.

An evolutionary perspective on alcohol raises the possibility of novel interpretations for the motivational mechanisms underlying both ethanol consumption and actual addiction. One immediate prediction of the hypothesis linking alcohol consumption to frugivory is

Table 2.2 Physiological, behavioural, and evolutionary consequences of ethanol exposure that are common to *Drosophila* fruit flies and modern humans

Trait	Drosophila	Homo sapiens
Genetic variation in ADH and ALDH	Taxonomic variation correlated with environmental exposure to ethanol	Geographical and ethnic variation in isozyme expression
Ethanol-associated search behaviour	Positive anemotaxis in ethanol plumes	Exploratory appetitive stimulant
Behavioural effects of low-dosage exposure	Locomotor stimulation	Disinhibition, euphoria
Behavioural effects of high-dosage exposure	Loss of postural control, immobility	Discoordination, sedation
Hormetic effects of chronic ethanol exposure	Adult lifespan prolongation at low-level exposure relative to control and higher-concentration exposures	Health benefits and reduction in cardiovascular mortality at intermediate levels of consumption

that hominids in the wild preferentially select and consume ripe fruits containing ethanol. Olfactory mechanisms by which frugivorous taxa locate ripe fruit over long distances (e.g. anemotaxis within odour plumes) are amenable to field and laboratory investigation. Olfactory sensitivity of primates to various alcohols is well-developed (Simmen, 1994; Laska & Seibt, 2002), but specific responses to ethanol have, remarkably, never been established in our nearest primate relatives. Ethanol evokes neural hyperactivity in the brain-feeding circuits of rodents, supporting the notion that this molecule is an appetitive stimulant in mammals (Cains et al., 2017).

The use of non-human vertebrate models would also provide for direct experimental tests of the potentially hormetic effects of ethanol, as predicted by evolutionary theory. Studies of captive colonies of omnivorous (e.g. baboons) and frugivorous (e.g. chimpanzee) primate taxa would be particularly informative in this regard, given the possibilities for measuring overall reproductive fitness as well as lifespan of known individuals. The potentially confounding caloric contributions of ethanol are well-known in the use of such non-human models of alcoholism, but in general the experimental solution to provide aqueous ethanol has simply compounded the problem of interpretation. By fully decoupling liquid ethanol from its natural substrate and instead linking ethanol to water in emulation of human drinking patterns, the range of induced behavioural and addictive responses may deviate substantially from those experienced historically. In particular, ethanol ingestion via frugivory may contribute to feeding responses and ultimately to satiation.

One of the most pressing experimental needs relative to evolutionary hypotheses of alcoholism is to determine both the natural occurrence of ethanol within fruits and the typical levels of ingestion and intoxication experienced by mammalian frugivores, including primates. Fermentation of non-domesticated fruit in natural ecosystems is virtually unstudied. The wide taxonomic range of microbial, invertebrate, and vertebrate consumers of ripe fruit also suggests similar variation in the sensory and behavioural responses of animal frugivores to ethanol under natural conditions. It would be of great interest to determine if

the particular sensory mechanisms that mediate ethanol ingestion via frugivory also predispose certain taxa to excessive consumption under artificial conditions of availability. Addictions in general, and alcoholism in particular, have generally been viewed as novel afflictions devoid of evolutionary context. However, the arguments presented here suggest that ethanol ingestion via frugivory is ancestral and may influence contemporary behavioural responses by humans. The study of natural exposure to ethanol in contemporary frugivorous animal taxa may therefore contribute to our understanding of modern patterns of alcohol consumption and abuse.

Conclusions

Most historical reviews of humans and ethanol consider their interaction to have begun in the Palaeolithic with the domestication of crops and the intentional production of beer and wine. By contrast, dietary consumption of ethanol by humans, their hominoid ancestors, primates, and indeed all frugivorous and nectarivorous animals is ancient and persistent across millions of years of evolution. The forces of natural selection associating ethanol with nutritional gain have been substantial, yielding as a consequence strong patterns of intra- and interspecific variation in the ability to metabolize ethanol. For fruit flies and humans, an impressive commonality of behavioural and physiological responses to ethanol suggests shared evolutionary outcomes for all frugivores and nectarivores that have been exposed to this molecule via dietary ingestion. Typical ethanol concentrations within consumed fruit, naturally occurring blood-alcohol levels within animal frugivores and nectarivores, and the hormetic effects of ethanol on extant hominids represent fruitful future areas for comparative research. Ultimately, the recognition that 'history' includes evolutionary time, as well as more recent human events may facilitate deeper understanding of both the natural occurrence of ethanol ingestion, and of the extreme events associated with excessive consumption in modern times.

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