

Effects of Active Compounds and Their Metabolites Associated with Coffee Consumption on Neurodegenerative Diseases

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Short notes

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A shortened version of the title

Effect of coffee consumption on ND

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Abstract

Coffee is one of the most known and consumed beverages worldwide. Only three species are used in commercial coffee production, i.e., *Coffea arabica* L. (Arabica coffee), *Coffea canephora* Pierre ex A. Froehner (Robusta coffee), and *Coffea liberica* Hiern (Excelsa coffee). The world population consumes approximately two billion cups of coffee per day, making it an important commercial resource of bioactive compounds in world markets. High interest in coffee consumption described in the literature is not only due to its organoleptic properties (for example desirable bitterness, amount of flavours, and aromas) but also for its ability to stimulate the central nervous system.

It is now known that there are more than 1000 compounds in coffee beverages, several of which have a bioactive activity. Recent studies show that consuming three to four cups of coffee per day, i.e. moderate consumption according to the European Food Safety Authority, may be beneficial for health.

The main objective of the proposed review is to provide a comprehensive overview of bioactive compounds in coffee and other caffeine-containing beverages and their effects on neurodegenerative proteinopathies.

Keywords: coffee, caffeine, neurodegenerative diseases, bioactive compounds

1. Introduction

Coffee typically contains more caffeine than most other beverages. Because it is widely consumed, it contributes significantly to the total caffeine intake of the general population, especially adults. However, its benefits and risks remain controversial. Several studies have shown an association between coffee consumption and improved health, reporting that coffee consumption is associated with a lower risk of several chronic diseases related to inflammatory processes, including neurodegenerative diseases (NDs). The health benefits of coffee are largely attributed to its rich phytochemicals. This has been linked to its potent antioxidant, anti-inflammatory, and anti-apoptotic effects against several types of NDs, including Alzheimer's disease (AD) and Parkinson's disease (PD) ⁽¹⁾. Neurotrophic factors, poly-(ADP-ribose)-polymerase, vascular endothelial growth factor, inflammatory processes, and antioxidant defences have been described as the main mechanisms involved in the specific effects of caffeine. In the last two decades, several studies have been conducted to demonstrate various modulatory effects of coffee/caffeine in experimentally induced ND conditions, especially in animal models ⁽²⁾. As caffeine is a water and fat-soluble substance, it can easily cross the blood-brain barrier and once in the brain, it can act on different molecular targets, modulating several pharmacological effects, such as adenosine receptor antagonism, phosphodiesterase inhibition, and calcium release blockade, without altering the physiology and homeostasis of the brain parenchyma. Coffee consumption is therefore associated with a lower risk of several chronic pathological conditions related to inflammatory processes, including NDs. Research suggests that regular coffee consumption in moderate amounts (e.g. 3-5 cups/300 mg of coffee) should be able to reduce the overall risk of cognitive impairment by playing a potential protective role in preventing and delaying the onset of NDs (e.g. reducing the risk of PD by 24% and AD by 64%) ⁽³⁾. These results support the hypothesis that coffee consumption is a highly protective factor, possibly acting on neurotoxicity associated with oxidative stress, amyloid-mediated neurotoxicity, and inflammatory processes. Caffeine is thought to exert neuroprotective and behavioural effects by blocking adenosine A2A and monoamine oxidase B (MAO-B) receptors while inducing tolerance to the impact of the adenosine 1A receptor blockade. The result is higher levels of serotonin and acetylcholine in the central nervous system (CNS). Caffeine may reduce lipid peroxidation by decreasing the production of reactive oxygen species (ROS) such as hydroxyl radicals and hydrogen. It may also act as an antioxidant by increasing glutathione S-transferase activity. In addition, it appears that caffeine may also protect dopaminergic neurons by activating some antioxidant

signalling molecules and promoting the activation of transcription factors involved in mitochondrial biogenesis as well as antioxidant and anti-inflammatory pathways ^(1,3). However, it is currently difficult to detect and determine its mode of action. Therefore, strong evidence supports the use of caffeine not as a substitute for conventional pharmacological treatments, but rather as an adjunct to suppress and manage the neuroinflammatory processes involved in NDs ⁽³⁾.

This review is based on a systematic, bibliographic literature search of PubMed, Web of Science, Scopus, and Google Scholar, covering articles published from the databases' inception to 2024. The search strategy included combinations of the terms “coffee”, “caffeine”, “neurodegenerative disease”, “Parkinson’s disease”, “Alzheimer's disease”, and “parkinsonism”. In addition, relevant publications were identified and included from the reference lists of the articles.

2. Bioactive compounds and their composition in Coffee

Roasted coffee beans contain more than 1000 bioactive compounds with various physiological effects as well as health benefits ^(4,5). Active compounds and their derivatives contained in coffee have several neuroprotective properties that reduce the risk of cognitive decline and neurodegenerative diseases. A growing body of evidence suggests that regular consumption of coffee, as well as tea and dark chocolate (cocoa), may support a reduction in the risk of age-related neurodegenerative disorders. However, the complex array of phytochemicals in these components hinders a clear understanding of the components that influence neuronal plasticity and resilience ⁽⁶⁾. Anti-inflammatory (inhibition of the expression of cytokines genes, modulation of nuclear factor kappa-light chain enhancer of activated B cells, regeneration of neurons, neuroplasticity), antioxidant (elimination of free radicals, reduction of oxidative stress), antifibrotic (reduction of oxidative DNA damage, elimination of free radicals), antimicrobial (antimicrobial activity against a range of Gram-positive and Gram-negative bacteria), and anticancer (prevention of initiation of carcinogenesis, antitumoral activity) properties have also been described, leading to reduced mortality and improvements in endocrine, hepatic, gastrointestinal, cardiovascular, and cancer diseases ^(7,8,9,10).

The optimal benefits obtained from coffee in pathologies depend on higher daily doses. Existing research believes that coffee has great therapeutic potential in the future, but there is

still a need to elucidate the mechanisms of true causal relationships in certain neuropathologies in further studies.

Coffee is a complex blend of many compounds and nutrients that work synergistically together. However, its multidirectional effects and mechanism of action are still poorly understood. The composition of elements in coffee beans varies with the type of coffee, country of origin, growing conditions, roasting conditions, temperature, time, speed, brewing conditions, and grind size of coffee beans ⁽¹¹⁾. Caffeine (CAF) is one of the most important and discussed compounds not only in coffee but also in tea, cola, and chocolate of different types and brands. The different abundances and contents of CAF are studied because of its many effects on the organism (genetic polymorphism, sex, and metabolic heterogeneity) ⁽¹²⁾.

The most important compounds of coffee beans are:

- 1) caffeine (0.5-2.6%): differences between Arabica (0.7-1.4%), Robusta (2.2-2.4%), and Excelsa (0.86-1.13%)
- 2) theobromine, theophylline (1%)
- 3) caffeic acid, quinic acid (10%)
- 4) chlorogenic acid (4-6%)
- 5) polysaccharides (25-30%)
- 6) proteins (13%)
- 7) fats and waxes (0.1-0.8%)
- 8) water (10-13%)
- 9) minerals (4%)
- 10) vitamin B3 (trace amount) ⁽¹³⁾.

Among the most important, physiologically effective compounds are:

- 1) purine alkaloids- methylxanthines (CAF, theobromine, theophylline, nicotinic acid);
- 2) polyphenols (chlorogenic acids (CGA) and their derivatives such as CAF, quinic acids, phenylindanes, ferulic acid, quercetin, hydroxyhydroquinone, and pyrocatechol);
- 3) fatty acids (eicosanoyl-5-hydroxytryptamine);
- 4) diterpenoids (cafestol and kahweol);
- 5) flavonoids (anthocyanins and catechins);
- 6) lactones;
- 7) and many other micronutrients such as potassium and magnesium ^(7,14,15).

Methylxanthines, of which **CAF** (1,3,7-trimethylxanthine) is best studied, have clear effects on neuronal network activity, protecting neurons from dysfunction and promoting sustained cognitive development. Since it is a purine alkaloid, it is described as an antioxidant, capable of protecting against oxidative damage, which is typical of most neurodegenerative diseases. Its mechanism of action is based on the antagonism of different subclasses of adenosine receptors, thereby mediating protection by dopamine receptors, stimulating the central nervous system, and enhancing mood and alertness. In addition, it is a phosphodiesterase inhibitor, with a consequent effect on metabolism. It is most commonly associated with neuroprotective effects, mediated by the inhibition of lipid peroxidation and reduction of reactive oxygen species production ⁽¹⁴⁾. CAF has been shown to reduce excitotoxicity, cellular apoptosis, and inflammation, as well as partially resolve memory problems. In Alzheimer's disease (AD), CAF has been shown to protect against blood-brain barrier disruption, reducing amyloid beta (A β) levels through inhibition of its secretory pathway specifically, demonstrating its anti-inflammatory, antioxidant, and mitochondrial activity, as well as neurological stimulation and neuroprotection. α -tocopherol has demonstrated neuroprotective activity through antioxidant activity and free radical scavenging activity, which has been associated with inhibition of some forms of neurotoxicity and improvement of memory impairment in Parkinson's disease (PD)⁽⁵⁾.

Other representatives of methylxanthines are **theobromine** (3,7-dimethylxanthine) and **theophylline** (1,3-dimethylxanthine), also found in tea or chocolate. They show high bioavailability and are associated with hypoglycemic and neuroprotective benefits. Moreover, theobromine levels inversely correlate with A β ₄₂ levels in AD patients ⁽⁶⁾.

CAF metabolites **paraxanthine** (1,7-dimethylxanthine) and **theophylline** (1,3-dimethylxanthine) provide neuroprotection against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which induces dopamine loss in the striatum and also shows inhibition of dopamine reduction ⁽⁶⁾. While paraxanthine is not present in plant extracts, in humans its blood concentrations reach levels comparable or higher than those of CAF. Therefore, it should be considered when investigating the physiological effects of CAF, especially under conditions of chronic intake.

Mancini *et al.* ⁽¹⁶⁾ investigated another group of coffee compounds - the **phenylindanes**. Using fluorescence assays to determine the level of inhibition of neurodegenerative protein accumulation, they found that the phenylindanes in dark-roasted coffee exhibited strong inhibitory activity, suggesting the importance of neuroprotection ⁽¹⁶⁾.

When coffee undergoes roasting, amino acids and carbohydrates react through a process called the Maillard reaction⁽¹⁷⁾. Through this, other compounds such as melanoidins and acrylamide are produced. Moreira *et al.*⁽¹⁸⁾ point to **melanoidins**, as having high antioxidant activity, especially in scavenging free radicals. These bioactive substances were studied in rats that were given approximately six cups of espresso (1 espresso = 30 ml of caffeine source/ 60 mg caffeine content in the product) (to give an idea, *Figure 1* summarizes the CAF content in caffeine-containing beverages). Melanoidins were able to decrease the concentration of pro-inflammatory cytokines (tumour necrosis factor-alpha (TNF- α), interferon-gamma (IFN- γ)) and increase the number of anti-inflammatory substances, such as interleukins (ILs).

β -carbolines harman and norharman, are two compounds present in roasted coffee with a known spectrum of physiological effects in the human body. This is a group of chemicals widely found in nature and structurally very similar to the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which has been linked to the development of PD. On the other hand, these compounds have recently been investigated for some neuroprotective effects. In particular, β -carbolines can reversibly inhibit monoamine oxidase (MAO) and increase the concentration of neurotransmitters such as dopamine, thus protecting against the neurodegenerative process. Indeed, MAO inhibition is increasingly being reported as an important mechanism for reducing the rate of PD, mainly by reducing the oxidative deamination of key neurotransmitters, including dopamine, the neurotransmitter most affected in this disease. While caffeine is reported to act as an antagonist for the adenosine A2 receptor, blocking the effect of adenosine on the suppression of dopaminergic transmission and thus reducing dopamine neurotoxicity, norharman and harman are potent competitive and reversible MAO inhibitors, both in rats and humans. The high levels of these β -carbolines in roasted coffee place them at the top of the list of suspected compounds likely to influence the course of Parkinson's disease^(5,18,19).

Chlorogenic acids (CGAs) share not only antioxidant properties but also anti-inflammatory effects by inhibiting the expression of cytokine genes and modulating the activation of inflammatory nuclear factor kappa B (NF κ B), which is associated with neuronal regeneration, thereby contributing to neuroplasticity. For this reason, together with CAF, they have attributes of neuroprotective properties⁽²⁰⁾.

3. Caffeine and Parkinson's disease

While there are CAF intake doses determined to be not to be associated with adverse effects by Health Canada (400 mg/day for adults [10 g for lethality], 300 mg/day for pregnant women, and 2.5 mg/kg/day for children and adolescents), 2.5 mg CAF/kg body weight/day remains an appropriate recommendation ⁽²¹⁾. Because CAF is water and lipid-soluble, it readily crosses the blood-brain barrier. It produces complex pharmacological effects in the brain, ranging from adenosine receptor antagonism to phosphodiesterase inhibition, to GABA receptor blockade and calcium release ⁽²²⁾.

CAF levels and their metabolism can be analysed from blood or saliva. Deciphering the molecular networks distinguishing PD from healthy individuals and patients with other, unrelated PD diseases may lead to new insights into pathogenesis and identification of crucial biomarkers. Previous studies have confirmed the involvement of oxidative stress and dyshomeostasis in catecholamine, tryptophan, and CAF metabolism in PD ⁽²³⁾. In the moderate/ advanced PD group, patients with motor complications had significantly reduced basal salivary CAF concentrations, significantly longer disease duration, and an increase in the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) compared to those without motor complications, whereas patients with early PD or *de novo* patients did not. There was a negative association with antiparkinsonian medication, supporting the hypothesis that CAF levels in PD are a marker of disease progression ^(24,25). Similarly, a protective effect of coffee has also been reported in dementia and AD, with CAF reversing cognitive impairment and reducing amyloid burden. The results of the study by Hong *et al.* ⁽¹²⁾ suggests that coffee consumption among healthy individuals and PD patients was significantly associated with a lower hazard ratio for the risk or progression of PD leading to a favourable causal relationship between CAF consumption and the risk of PD. A potential neuroprotective effect of CAF consumption has also been reported in epidemiological case-control studies. Although another constituent in coffee, eicosanoyl-5-hydroxytryptamide, is thought to protect against neurodegeneration. A similar effect is also thought to occur with tea consumption. Instead of psychostimulation, CAF antagonizes the adenosine A2A receptor. In the CNS, A2A is expressed exclusively in dopaminergic neurons, and activation of the adenosine A2A receptor triggers cAMP-proteinase A, which is dependent on an increase in intracellular calcium and release of glutamate. This suggests that excessive intracellular calcium and glutamate concentrations are responsible for excitotoxicity in neurodegeneration ⁽¹²⁾.

4. Mechanism of action of caffeine

Clinically, CAF appears to improve motor symptoms by non-selective antagonism at the adenosine A2A receptor ⁽²⁶⁾. A2A receptors are predominantly distributed in the *putamen*, *nucleus caudatus*, *nucleus accumbens*, and *globulus pallidus*, while indirectly interacting with dopamine D2 receptors of the basal ganglia. In the study by Ishibashi *et al.* ⁽²⁷⁾, they report that CAF binds to striatal A2A receptors in a dose-dependent manner, with sufficiently occupied receptors obtainable by drinking at least one cup of coffee, equivalent to approximately 100 mg of CAF ⁽²⁷⁾.

Eicosanoyl-5-hydroxytryptamine (EHT) is a derivative of serotonin, whereas C₂₀ is a saturated eicosanoic fatty acid linked to the serotonin amino group. EHT purified from coffee serves as an agent leading to enhancement of the enzymatic activity of the specific phosphatase, **protein phosphatase 2A (PPA2)**, which dephosphorylates pathogenic α -synuclein while working synergistically with CAF in PD and dementia with Lewy bodies (DLB). In the case of coffee, PPA2 thus inhibits the methylesterase and remains in a highly active methylated state. This synergy is through the enhancement of PPA2, which is dysregulated in the brains of patients with synucleinopathies. EHT is also an inhibitor of PME-1 methylesterase, thereby contributing to an increase in brain PPA2 methylation and phosphatase activity, which reduces the amount of phosphorylated α -synuclein (p- α -syn), improving neuronal integrity, suppressing neuroinflammation, and preserving the behavioural phenotype. It also exhibits antioxidant and anti-inflammatory effects.

The catalytic subunit of a specific phosphatase, PP2A, which dephosphorylates α -synuclein, is hypomethylated in the brain of a PD patient, preventing the assembly of an active trimeric holoenzyme and leading to a decrease in phosphatase activity. This phosphatase deficiency contributes to the accumulation of hyperphosphorylated α -synuclein, which tends to fibrillate more than unmodified α -synuclein.

CAF is primarily metabolized by cytochrome P450 (CYP), specifically the CYP1A2 and CYP2E1 subunits, and protects against the dopaminergic neurotoxin MPTP, and acts as an adenosine A2A receptor antagonist. However, in early-onset PD patients, CAF consumption has no effect on the rate of disease progression, nor have any associations between gene polymorphism and frequency of disease onset been confirmed ⁽²⁶⁾. Co-treatment of CAF with EHT reduces p- α -syn and protects against neuronal damage and neuroinflammation, as such treatment combination significantly reduces the number of p- α -syn immunoreactive cells in

the brain and restores neuritic integrity. These results suggest that this treatment has a synergistic effect in protecting neuronal integrity and preventing inflammatory response ⁽²⁸⁾.

A 4-year prospective study by Moccia *et al.* ⁽²⁹⁾ examined the clinical correlates of CAF consumption in a *de novo* patient population, where they described that greater CAF consumption was associated with reduced deterioration in both motor and non-motor impairment. Concerning motor symptoms, higher CAF product use was associated with lower motor impairments throughout the study period, suggesting that CAF may have a symptomatic effect, possibly delaying an individual's motor impairment. Pathophysiologically, the motor effect of CAF in PD is likely mediated by the inhibition of adenosine A2A receptors in striatopallidal neurons, which determines the improvement of parkinsonian symptoms. Consistent with this, there is another hypothesis that the motor function of PD patients can be improved by a targeted strategy of incorporating CAF into the development of novel antiparkinsonian drugs. Since antiparkinsonian drugs can competitively affect CAF metabolism, significant improvement in PD patients with antiparkinsonian treatment has been observed ⁽²⁶⁾. Also, study results show that PD patients with higher CAF use presented a reduced need for dopaminergic treatment ⁽²⁹⁾.

Findings studied in mouse models suggest that subtherapeutic doses of CAF and EHT may synergistically act on biochemical and molecular changes in the mouse brain, leading to brain protection in synucleinopathies. This also preserves neuronal integrity and dampens the inflammatory response in phosphatase activity, which is associated with reduced p- α -syn accumulation. Similar biochemical changes are described in a cellular model where there is a significant increase in PPA2 methylation, cytoprotection, and a decrease in p- α -syn ⁽²⁸⁾. Additionally, antagonism of A2A receptors with selective inhibitors or genetic knock-out mimicked CAF protection in various experimental models of PD. In animal models of PD, caffeine treatment improved oxidative stress, restored striatal and midbrain dopamine depletion, prevented decline in motor activity and muscle strength, and improved norepinephrine levels ⁽³⁰⁾.

5. Caffeine change modelling tools

Liquid chromatography coupled with mass spectrometry (LC-MS), along with gas chromatography, is a powerful tool for profiling metabolite changes, using four CAF metabolites that have been confirmed as biomarkers of *de novo* PD progression ⁽²⁶⁾.

6. Conclusion

Coffee consumption is associated with a reduced risk of PD, with CAF generally considered to be a protective agent. Coffee not only reduces the risk of PD, improving overall akinesia for a limited number of months, as shown in a prospective study ⁽²⁰⁾ but also exerts a beneficial antagonistic effect on the adenosine receptor in dopamine-rich areas of the brain, increasing its release and enhancing neurotransmission. This suggests that balanced coffee consumption was associated with slowdown executive dysfunction, as well as a reduced risk of progression to moderate cognitive impairment ⁽¹⁾. Regarding the beneficial effect of coffee, a large multicentre study from three European countries (the Netherlands, Finland, and Italy)⁽³⁾ and associated epidemiological and clinical studies consistently report that coffee/CAF consumption, could slow the progression of dementia or reduce the risk of PD, according to a confirmed dose-response pattern of observed disease improvement. Additionally, CAF improves the metabolism of amino acids and long-chain polyunsaturated fatty acids, which play an important role in disease development ⁽²³⁾ and improves the oxidative system by destroying free radicals on neurons as a consequence of the effect of polyphenols on the body ⁽³⁾. Another possible explanation for the beneficial effects of coffee may be the increase in the number of bifidobacteria, which are associated with a mitigation of the inflammatory response thereby reducing α -synuclein misfolding in the enteric nervous system, which reduces the risk of PD by limiting the spread of the protein to the brain ^(31,7). Although several studies have confirmed the beneficial effects of coffee (reduced need for dopaminergic treatment in patients with higher caffeine consumption) associated with neurodegenerative diseases, further research is needed as it is difficult to detect and determine the exact factor of its effect. If the action of CAF and its beneficial metabolites could be translated into drugs, it would represent a shift towards new therapeutic options/development of new antiparkinsonian drugs ⁽²⁹⁾.

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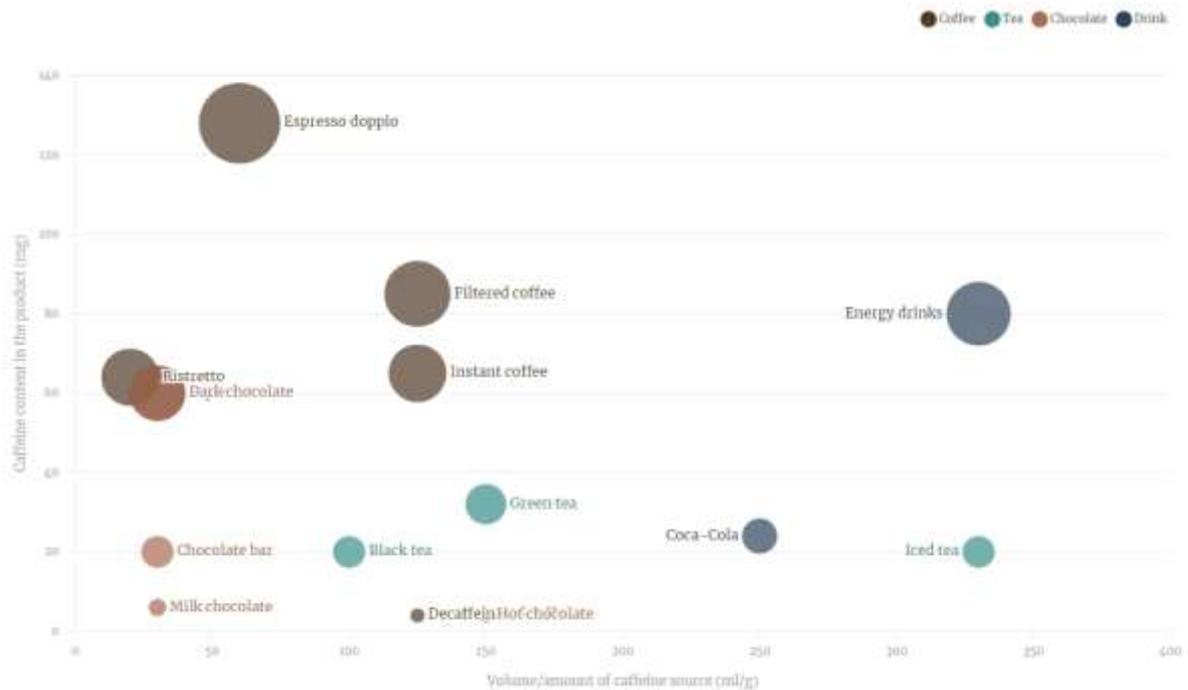


Figure 1 summarizes the ratio of the volume/ quantity of the caffeine source to the amount of CAF contained in the product. The amount of CAF (mg) is recorded in individual coffee and other soft drinks, as well as in different types of chocolate.

The size of the bubbles represents the amount of CAF in the product. Colour indicates product diversity: dark brown represents coffee drinks; light brown represents chocolate products; green represents tea drinks; and blue represents soft drinks.

An interactive version is available at <https://public.flourish.studio/visualisation/13411728/>.