Clinical Commentary

Biological Psychiatry

Dancing Goats, Civet Cats, and the Case of Coffee

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Legend tells us that coffee's story began with a single goat herd. Kaldi, a 9th-century Arab goat herder, noticed his flock behaved strangely after eating a particular fruit. The goats were "abandoning themselves to the most extravagant prancings." Curious and melancholic, Kaldi tried the berries himself. "He forgot his troubles and became the happiest herder in happy Arabia." One day, a man of prayer passing by noticed the "saltatorial madness" of "a score of goats executing lively pirouettes." The scene was so striking that he confided in Kaldi his shame from falling asleep during his prayers and inquired how he had so much energy. The man "reasoned that Mohammed without doubt was revealing this marvelous fruit to him to overcome his sleepiness" (1).

This energizing concoction traveled across deserts and seas, fueling the rise of trade empires. One astonishing story came from Indonesia, where much of the coffee crops were grown on plantations run by Dutch colonists. The local farmers were forbidden from taking any of the precious beans they cultivated. Nevertheless, they knew their value. So, they gathered and cleaned minimally digested beans in civet feces. This method of processing now produces one of the modern world's rarest and highly coveted coffees, kopi luwak (Indonesian for *civet coffee*).

Over the ensuing centuries, coffee became infused as a daily ritual in most cultures across the world. It became a staple of high intellectual society in 18th century England. Many great thinkers of the time went to coffee houses to chat with colleagues and neighbors. The discourse was so rich, coffee houses became known as "penny universities" because you could get an evening education for the price of a coffee. It fueled innovations and revolutions. But no one stopped to wonder if the jolt of energy might come at a cost.

Then, in 1981 the civet poop hit the fan. A team of researchers led by Brian MacMahon were searching for environmental causes of pancreatic cancer. They surveyed 369 cases (and 644 controls) about their use of various substances including cigarettes, cigars, pipe tobacco, alcohol, tea, and (you guessed it) coffee. Astonishingly, they found the relative risk of pancreatic cancer was 3.2 in individuals who drink 5 or more cups of coffee per day (2).

A *New York Times* headline on March 12, 1981, read, "Study Links Coffee Use to Pancreas Cancer" (3). The coffee pendulum had swung from a mark of society's upper echelon to a carcinogen. Now, a global morning ritual suddenly carried a weight of guilt. A beverage that fueled science, art, and spirituality was now condemned as a toxin.

In the ensuing years, scientists handled the surprising result in a surprisingly responsible way: they attempted to replicate it. But they failed—over and over again. Epidemiologists soon sorted it out. Heavy coffee drinkers were also overwhelmingly heavy smokers[a]. Years later, a team of researchers were able to accurately control for the complex interaction between smoking and caffeine consumption (4). The result flipped the narrative yet again: not only did coffee drinkers not get pancreatic cancer, they actually lived longer!

So where does coffee stand? To make any sense of the data—including the possibility that it prolongs life—we have to start with how it works. What is the active ingredient?

The intuitive candidate is caffeine. Caffeine's primary neural effects occur through the adenosine system, where it antagonizes two functionally distinct receptors: A_1 and A_{2A}. A_1 antagonism produces the familiar, immediate effects: heightened vigilance and subtle nudges toward movement, social engagement, and productivity. A_{2A} receptors, on the other hand, intersect with dopaminergic motivation circuits in the striatum. In the absence of caffeine, A_{2A} receptors in these circuits normally act as a "brake" that resists effortful actions; when A_{2A} receptors are blocked with caffeine, this "brake" is released and individuals feel a reduction of perceived effort (5). But the *sustained* effects might be more notable. Remarkably, chronic antagonism of A_{2A} receptors has been described to lower the risk of Parkinson's disease by nearly 40% (6) and to confer benefits in inflammation, fibrosis, and cellular energy efficiency (7).

These more chronic effects are best understood through one of the new frontiers in psychiatric neuroscience. *Allostasis* is the term that describes the brain's capacity to shift set points in response to sustained stress (8). With aging, we know this capacity decreases, meaning your brain and body tend to lose the ability to adapt to novel stressors. Chronic A_{2A} antagonism appears to counteract this age-related change. It preserves people's ability to adapt to novel stresses largely by interrupting inflammatory signaling cascades. These findings seemed to offer the mechanism by which coffee prolongs health (9). But new evidence soon emerged from the brew.

Marilyn Cornelis is a prominent genetics researcher out of Northwestern University whose work focuses on coffee consumption (though she doesn't even like the taste of it). Cornelis and her team approached the question from a population angle that clinicians rarely consider. They realized that a

[a]A shared metabolic mechanism suggests a causal link between these two behaviors: smoking increases caffeine metabolism by inducing CYP1A2; thus, increased coffee consumption may reflect a compensatory response.

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fixed caffeine dose produces varied effects across individuals: some feel energized and focused; others feel jittery or anxious; many feel nothing at all (10). If caffeine's subjective effects vary so widely, can we assume that its long-term health effects vary as well? Cornelis *et al.* (11) put that assumption to the test by controlling for individuals' baseline rates of metabolism. Intriguingly, her team found that the reduction in all-cause mortality was comparable in both slow and fast caffeine metabolizers. Even more striking, when they looked at people who only drink decaffeinated coffee, the studies still demonstrated a mortality benefit–though this effect was more modest than fully caffeinated coffee (11). So, caffeine matters, but it cannot be the whole story. Something else must be contributing beneath the surface.

It turns out that coffee (like cannabis) is not a single drug, but a cocktail containing over 2000 potentially bioactive agents including polyphenols, melanoidins, and diterpenes (9, 12). These compounds have been found to prevent telomere shortening, reduce oxidative stress, improve insulin sensitivity, and promote gut microbiome health (13–15). Remarkably, chronic black coffee consumption has been shown to benefit nearly every organ system (Figure 1).

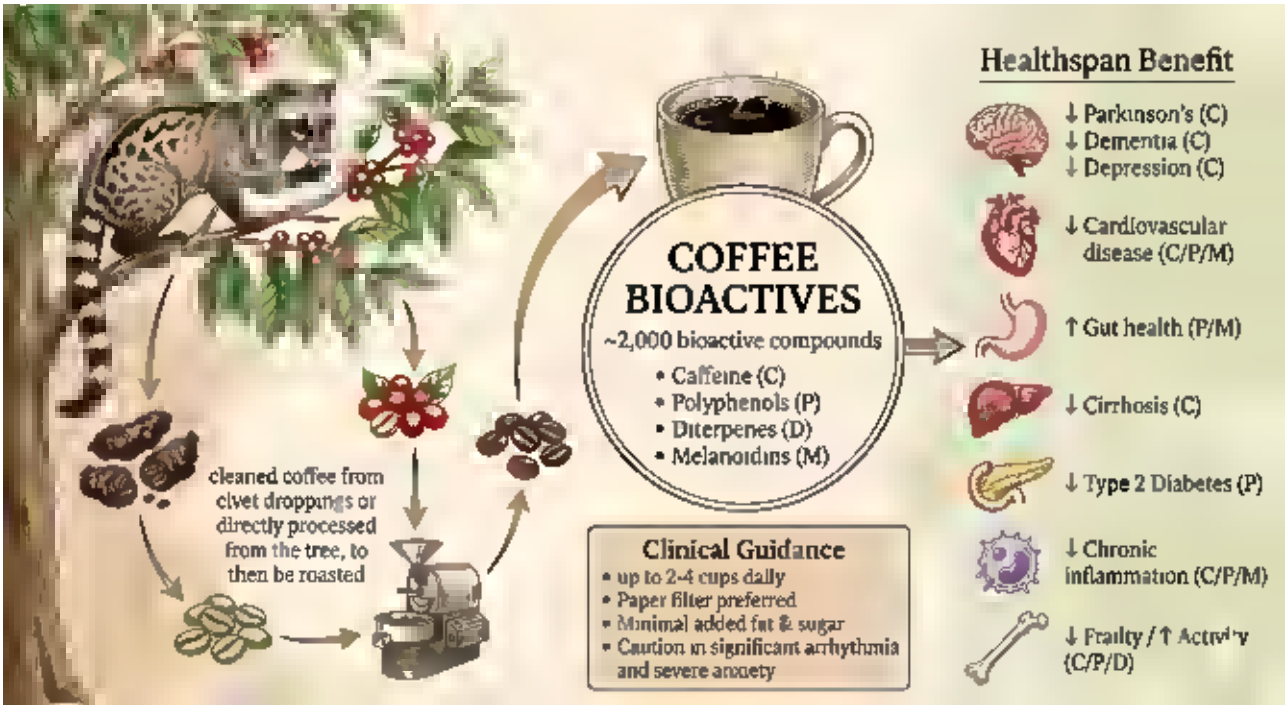

Figure 1. Proposed pathways linking coffee bioactive compounds to health span benefits. **Caffeine**, at A_1 receptors, reduces inhibitory tone on neuronal firing, increases dopaminergic and noradrenergic signaling, reduces sleep pressure and fatigue, and promotes alertness, psychomotor output, movement, and social/reward salience. These effects contribute not only to improved attention and executive function but also to greater physical activity and less sedentary behavior, which may indirectly support cardiometabolic health, improved cognitive aging, and lower depression risk. At A_{2A} receptors, caffeine appears to reduce neuroinflammation and microglial activation, preserve dopaminergic signaling, improve mitochondrial efficiency, and dampen fibrosis-related signaling. Caffeine metabolites also reduce collagen deposition in liver cells, lowering risk of hepatic fibrosis and cirrhosis. These mechanisms are especially relevant to basal ganglia function, neurodegeneration, chronic inflammation, and cardiovascular remodeling and may help explain epidemiologic associations between coffee intake and lower risk of Parkinson's disease, lower rates of dementia, slower functional decline, and greater cardiovascular resilience (5–7). **Polyphenols**—especially chlorogenic acids—support insulin sensitivity, glucose regulation, hepatic lipid and carbohydrate metabolism, and broader metabolic resilience. In biochemical terms, they activate antioxidant defense pathways such as Nrf2, suppress proinflammatory signaling through nuclear factor-κB, influence cellular differentiation through PI3K (phosphoinositide 3-kinase)/AKT/PTEN, and improve metabolic homeostasis through AMPK (adenosine monophosphate–activated protein kinase) activation. Polyphenols may also reduce oxidative stress, platelet aggregation, vascular remodeling, and endothelial dysfunction, offering plausible mechanistic links to the observed dose-dependent association between coffee consumption and the lower risk of type 2 diabetes, hypertension, atherosclerotic disease, heart failure, and myocardial infarction. In addition, polyphenols are metabolized by the gut microbiome into short-chain fatty acids such as acetate, propionate, and butyrate, which further support glucose homeostasis, lipid metabolism, immune regulation, and gut barrier integrity (12). **Melanoidins**, formed during roasting, contribute by acting as antioxidants and supplying prebiotic compounds. They can bind and transport polyphenols, reduce the formation and absorption of proatherogenic lipid oxidation products during digestion, and promote the growth of beneficial gut bacteria such as bifidobacteria. These compounds have also been linked to anti-inflammatory, antimicrobial, and antihypertensive effects (15). **Diterpenes**, particularly cafestol and kahweol, produce a more mixed risk/benefit profile. These have beneficial effects on bone metabolism by promoting osteoblast function and inhibiting osteoclast function. However, they also increase low density lipoprotein (LDL) cholesterol by suppressing bile acid synthesis through downregulation of cholesterol 7α-hydroxylase and sterol 27-hydroxylase, leading to decreased LDL receptor expression. Importantly, these diterpenes are largely removed by paper filtration (17,18). (Figure created with assistance from Google Gemini's free-tier image generation tool. The authors reviewed, edited, and approved the final figure and take full responsibility for its content, accuracy, and interpretation.)

Still, details are important. What you add to your coffee and how you filter the grounds both matter. Later research, building on Cornelis's work, found that adding too much sugar and dairy negates several of coffee's health benefits, blunting improvements in insulin sensitivity and increasing inflammatory markers (16). In addition, unfiltered coffee contains a substance called cafestol that raises low density lipoprotein cholesterol (14). Cafestol is entirely removed by a paper filter (17,18), but not by the metal meshes used in making French press or some other types of coffee (much to the dismay of the espresso-loving authors of this commentary). At this point, the data show the clearest mortality benefit for paper-filtered black coffee.

But are we actually ready to prescribe this health behavior to our patients? The history of medicine is full of unhealthy or harmful practices that we thought were healing. You might remember that population-based studies once wrongly predicted that coffee causes pancreatic cancer. So, how do we know if we are right now? To be confident, we would need prospective data over many years with high-fidelity nutrition data. Such studies often contain inherent bias due to self-reporting and high individual variability in consumption (brew method, add-ins, coffee product, etc.). But that doesn't mean we can't act on the data we have now.

The first thing we can do is demonstrate a bit of restraint. We should stop reflexively warning patients away from black coffee. Without contraindications (uncontrolled arrhythmias, severe anxiety, or significant reflux), the benefits are clear. The mortality signal is remarkably consistent across demographics, comorbidities, and genetic metabolizer status. Consuming roughly 2 to 4 cups of filtered, black coffee is safe for most adults and is modestly protective, with an estimated gain of 1.84 years of life (9). But context matters. A sedentary smoker drinking 6 sugar-loaded lattes is not the same as someone drinking a big mug of black coffee before a morning walk. In other words, coffee nudges systems toward longevity but is not a driving force.

Despite millennia of enmeshment in human culture, over the past 50 years the medical community has treated coffee with caution. As with many other topics in the history of medicine, we were wrong. Now, when a patient asks, "I love coffee, is my habit hurting me?" we can answer with intellectual honesty: if prepared properly and consumed in moderation, it is likely helping more than harming. And that subtle reframing, from guilt to guidance, may be one of the most practical interventions we can offer our patients before they even start their day.

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