

# COFFEE CONSUMERS ARE LESS LIKELY THAN OTHERS TO BE DEPRESSED

## A REVIEW OF CURRENT RESEARCH ON COFFEE, DEPRESSION, AND DEPRESSIVE SYMPTOMS

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### **Coffee drinkers are less likely to be depressed than people who do not drink coffee.**

Meta-analyses that included more than 300,000 individuals, of whom more than 8,000 were depressed, found that people who consumed higher levels of coffee were at lower risk of depression than people who consumed less or no coffee. [1][2] The peak protective effect appeared to be among those who consumed 400 mL/day (i.e., 13 ounces). Since then, additional studies have found that coffee drinkers are at lower risk of depression than people who do not drink coffee. For example, of more than 14,000 graduates of the University of Navarra in Pamplona, Spain who continue to be followed, those who drank at least four cups of coffee per day showed a significantly lower risk than others of physician-diagnosed depression worthy of antidepressant medication. [3] In addition, among almost 10,000 adults in the Korean National Health and Nutrition Examination Survey, coffee drinkers ( $\geq 2$  cups/day) had a 32% lower prevalence of self-

reported depression than people who did not drink coffee. [4]

### **Why should coffee drinkers be at reduced risk of depression?**

At least five explanations seem likely. Three explanations are based on what is readily available in the cup or mug. The fourth explanation requires modification (by the gut microbiome) of what is in the cup or mug. The fifth explanation invokes changes in the gut microbiome to facilitate the modifications that characterize the third explanation.

#### **1. Anti-oxidant effects**

Blood levels of oxidative-stress indicators are raised in people who have a major depressive disorder. [5-8] Women who had high scores on an assessment of depression symptoms tended to have diets with lower total antioxidant capacity (attributed, in part, to lower coffee consumption) than otherwise similar

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women with lower scores. [9] Indeed, polyphenol flavonoids (components of brewed coffee) possess anti-oxidant and anti-depressant activities. [10-14]

## 2. Inflammation and depression

Depressed people tend to have higher blood levels of inflammation-related proteins than people who are not depressed. [15-17] Suicidal ideas have also been associated with inflammation. [18][19] The observation that selective serotonin reuptake inhibitors (SSRIs) lower the blood concentrations of some inflammation indicators has raised the possibility that the therapeutic effects of these drugs might, in part, reflect their anti-inflammatory properties. [20] Coffee has anti-inflammatory properties, [12-14][21] some of which are associated with anti-depressive properties. [22]

## 3. Caffeine, adenosine and depression

In most large scale prospective studies, most people consume their caffeine in coffee. Not enough people in each of these studies get their caffeine exclusively from sources other than coffee to help identify the contribution of caffeine to preventing depression. In mice, however, caffeine reduces the occurrence of helpless-like and motivational behaviors that are characteristic of mouse models of depression, [23] [24] and can enhance the beneficial effects of antidepressants. [25]

Caffeine functions as an adenosine receptor antagonist, [26] which may explain why in humans, the higher the caffeine consumption, the higher the plasma adenosine concentration. [27] Serum adenosine levels are lower in bipolar disorder patients than in people who do not have

bipolar disorder. [28] In addition, among bipolar disorder patients, the higher their depression scale scores, the lower their serum adenosine levels.

While most of the benefits of adenosine are receptor-mediated, [29] some can be attributed to anti-inflammation properties. [30]

## 4. Some benefits modification of what is in the brew

Brewed coffee also contains substances that need to be metabolized by the gut microbiome before they can possess anti-depression properties. Some of these have anti-oxidative properties, others have anti-inflammatory properties, while others are neurotransmitters. A discussion of these metabolites and the role they play in diminishing depression follows the discussion about the gut microbiome.

### The gut microbiome

Probiotics have been defined as 'Live microorganisms which when administered in adequate amounts confer a health benefit on the host.' [31] Prebiotics, on the other hand are food and beverage components that are "selectively utilized by host microorganisms conferring a health benefit," [32] while postbiotics are "molecules that are secreted, modulated, or degraded by the microbiome" [33] and benefit the host. [34] In essence, prebiotics, such as phenols and melanoidins in brewed coffee, are not readily metabolized by humans, but are metabolized by gut organisms into digestible short chain fatty acids and other metabolites (including neurotransmitters) that confer health benefits. [35] When probiotics and prebiotics confer mental health benefits they are called psychobiotics. [36]

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Psychobiotics offer the promise of diminishing depressive symptoms, thereby justifying the claim that probiotics and prebiotics are capable of modulating depression and depressive mood. [37] [38] Support for this claim also comes from the observation that by metabolizing polyphenols (including those in brewed coffee), gut bacteria have the ability “to enhance the bioavailability of gut-derived, brain-penetrating, bioactive polyphenol metabolites that ultimately influence mechanisms associated with the promotion of resilience against psychological and cognitive impairment in response to stress.” [39] Some of the brain-penetrating metabolites of the gut microbiome are the very neurotransmitters (e.g., serotonin, norepinephrine, GABA, dopamine) that are deficient in people who are depressed. [40][41][42-45]

### Neurotransmitters

When a nerve impulse arrives at the end of a nerve fiber, the chemicals released that can stimulate the next nerve in the sequence are called neurotransmitters. Almost all the explanations for what happens in the brain of a depressed person invoke a relative deficiency of specific neurotransmitters in specific areas of the brain.

More than 60 years ago, recognition that mood-altering compounds increased the concentration of monoamine neurotransmitters (e.g., serotonin, dopamine, and norepinephrine) led to the hypothesis that depression is caused, in part, by a deficiency of monoamines. [46] Various called the monoamine hypothesis, [47] the catecholamine hypothesis, [48] and the serotonin hypothesis of depression, [49] this explanation for depression has proved rewarding and disappointing. Selective

serotonin-uptake inhibitors (SSRIs), which drugs of choice for treating depression, provide help to two-thirds of the people who take them. That also means that approximately one-third of clinically-depressed patients do not experience satisfactory therapeutic benefits. [50]

Although conceptual models of monoamine deficiency have guided research efforts for decades, they have not generated a compelling and conclusive model either for depression neurobiology or for antidepressant drugs' actions. As a consequence, other theories have emerged that invoke other deficiencies. These have included the neurotrophic hypothesis of depression, [51] the GABAergic deficit hypothesis, [52] an excitatory synapse hypothesis of depression, [53] and the glutamate signaling deficit hypothesis. [54] These diverse hypotheses, each of which has some support, has led to attempts to create an integrated view of the neurobiology of depression, [55] and a unified hypothesis of the neurobiology of depression. [56] Neither of these has yet received enthusiastic support, leading to the inference that many scientists working in this field view depression as a heterogeneous collection of brain disorders. [57]

### **4. Some benefits modification of what is in the bowel**

Although, the composition of the gut microbiota can be influenced by stress and other experiences, [58-61] characteristics of the gut microbiome also seem capable of influencing human behavior.<sup>62</sup> Indeed, a considerable body of circumstantial evidence supports the view that gut microbiota influence the occurrence of depression. [62-66]

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For example, the profiles of the fecal microbiome among patients with major depression [67-72] and those with bipolar disease, [73-77] tend to differ from those of people who are not depressed.

The prebiotics contained in brewed coffee are not only converted to highly beneficial metabolites, but they are also capable of enhancing the proliferation of gut microbiota that have characteristics of a “healthy” gut microbiome, [78-83] such as diversity, [78] and “intestinal balance.” [79-84] Support for the hypothesis that a “healthy microbiome” reduces the occurrence of depression comes from randomized, controlled trials of probiotics given to depressed patients. [85]

### **Summary**

Coffee drinkers are at reduced risk of depression, in part because coffee has anti-inflammatory and anti-oxidative properties, provides the gut microbiome with nutrients to metabolize coffee constituents into beneficial substances, and promotes a healthy microbiome.

### **Notes of caution**

The following comments are intended to raise awareness of the obstacles that it make it difficult to study how coffee consumption reduces the risk of depression and suicide.

#### **a. Misclassification of diagnosis/outcome**

Some who seek the mechanisms leading to depression acknowledge how complicated is the study of depression. They point out that some studies use fairly clear cut (but limited) criteria as

assessed by a professional, for example as set forth in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), [86] while others accept self-reported clinical diagnoses, while still others use self-reported symptom/questionnaire data. Nevertheless, some question if studies might be improved by adding biomarker criteria (blood levels of selected proteins?, imaging?) [87] or classifying psychiatric diagnoses by severity. [88]

#### **b. Heterogeneity and complexity in depression**

Depression is probably much more than just a few separate disorders with the single common feature of depression.” [57] These multiple disorders are often preceded and accompanied by changes in the brain. [55] The complexity of these changes prompted the National Institute of Mental Health to set up Research Domain Criteria (RDoC), constructs, and definitions, of all these changes and an accompanying matrix. [89]

Then there is the issue of heritability, which accounts for some of the heterogeneity and complexity. How much of the risk of depression can be attributed to genetic propensity? The heritability estimate for major depressive disorder (MDD) is around 40%, [90] while common single nucleotide polymorphism variants together probably account for about 25% of the heritability of bipolar disease (the tendency to both mania and depression). [91] Patterns of single nucleotide polymorphism associations and genetic correlations across nine symptoms of depression suggest that current depressive symptoms are genetically heterogeneous. [92] In addition, exposure characteristics can be associated with differences in estimated heritability. [93]

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Thus, identification of exposures that might protect are best studied with methods that assess gene-environment interactions. [94] Unfortunately, much of the literature evaluating exposures that might influence the occurrence/risk of depression have not assessed gene-environment interactions.

### **c. Confusion/controversy about what happens in the brain when a person is depressed**

The range of brain dysfunctions that appear to account for depression in humans and the varied responses to similar anti-depressant medications [95] has led to the view that “depressive disorders are heterogeneous diseases.” [57]

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