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A cup of coffee for a brain long life

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Coffee is one of the world's favorite and most popular beverages, the third most popular beverage after water and tea. For many people, it is an indispensable habit before going to work and a socialization tool for the rest of the day. In general, the average consumption varies from 2 to 6 cups per day. What are the health implications? Given this consumption, the benefits are actually greater than the risks. This is the conclusion of a careful study published in the New England Journal of Medicine (van Dam et al., 2020).

The beneficial pharmacological effects of coffee, as demonstrated by numerous scientific studies, are related to its anti-inflammatory, antioxidant, antiangiogenic, anticancer, chemoprotective and hepatoprotective properties (Doepker et al., 2022; Ruggiero et al., 2022). Coffee contains more than a thousand compounds, many of which have yet to be discovered. Several phytochemicals have been described as coffee components, including alkaloids (caffeine, trigonelline, adenine-7-glucosyl, theobromine, and 7-methylxanthine), flavonoids (anthocyanins, quercetin glucoside, quercetin, isoquercitrine, rutin, and kaempferol), terpenoids (kahweol, cafestol, and 16-O-methyl cafestol), amino acids (histidine and pipecolic acid), sucrose, tannins, xanthonoids (mangiferin and isomangiferin), phenolic acids (caffeic, chlorogenic, p-coumaric, ferulic, and sinapic acids), and catechins (catechin and epicatechin).

Many authors have studied the effects of caffeine and its major constituents in clinical and cellular experiments (Doepker et al., 2022; Ruggiero et al., 2022; Teramoto et al., 2023). However, the published results are controversial regarding its effects on different types of pathologies. Moderate coffee consumption in good health, with the exception of some phases of a woman's life (pregnancy and lactation), can have beneficial effects, significantly reducing various chronic diseases. A recent study reports that coffee consumption is associated with a lower risk of head and neck cancer; in this regard, meta-analyses consistently report a beneficial relationship between coffee consumption and all-cause mortality, concluding that approximately 6% of years of healthy life lost would be prevented if all consumers drank three cups of coffee per day (Doepker et al., 2022).

Coffee consumption is associated with a lower risk of developing chronic liver disease (Kolb et al., 2020). The beneficial effect would be independent of the type of coffee: it is good whether it is instant, ground or decaffeinated and is associated with a reduced risk of chronic liver disease, including hepatitis (Kennedy et al., 2021). In addition, there are studies reporting that increased coffee consumption is associated with lower circulating hepatitis B virus DNA and hepatitis B surface antigen levels and reduces the development of hepatitis B virus-associated hepatocellular cancer (Kakiyama et al., 2022).

It is reported that regular and moderate consumption of coffee can reduce the risk of death and the risk of death from cardiovascular causes. In fact, a study conducted by Simon et al. (2022), focuses that regular coffee consumption plays a role in protecting against cardiovascular disease. From the results of this analysis, which included 468,629 participants who had no signs of these pathologies at the time of recruitment, it appears that people with light to moderate coffee consumption have a 12% lower risk of dying from the disease than those who do not drink coffee. For cardiovascular disease, the risk of death is reduced by as much as 17%, and for stroke it is reduced by as much as 21%. Among other findings, it should be emphasized that people who consume up to three cups of coffee a day have a healthier heart in terms of size and function, in line with a lower effect of aging on the organ.

In contrast, heavy coffee consumption appears to be associated with an increased risk of cardiovascular disease mortality in patients with severe hypertension, but not in subjects without hypertension and with grade 1 hypertension (Teramoto et al., 2023).

In addition to caffeine and chlorogenic acids, many other minor components of coffee have been identified and studied, including polyphenols, diterpenes, melanoidins, and trigonelline. Researchers attribute these beneficial effects to the combined action of molecules in coffee, including kahweol and cafestol. In fact, coffee alone does not work miracles, since cardiovascular diseases are associated with other determining parameters of lifestyle, in particular diet (too much fat, too much sugar). It is possible, however, that coffee can make a difference with the same behavior. The beneficial effects of regular coffee consumption on the cardiovascular system could be explained by its antihypertensive, antidiabetic, antiarrhythmic and anti-atherosclerotic effects (Surma et al., 2023).

Coffee consumption has been shown to reduce the risk of developing type 2 diabetes mellitus in humans. In this context, N-caffeoyltryptophan, a component of coffee, enhances adipogenic differentiation and promotes glucose uptake into adipocytes, involving mitogen-activated protein kinase kinase/extracellular signal-regulated kinase signaling and Sirtuin 1, ultimately leading to a reduction in postprandial glycemia (Sawamoto et al., 2023).

However, contraindications to coffee consumption have also been reported; in fact, coffee can significantly interfere with the absorption of alendronate (a drug used to treat osteoporosis) and can reduce the effectiveness of iron supplements. Quinolone antibiotics can even increase the absorption of caffeine: in all these cases, it is advisable to limit the consumption of this drink. Coffee is also contraindicated if you suffer from hyperthyroidism and glaucoma or diseases of the intestines, stomach, liver, heart, kidneys, pancreas, nervous system (Garcia-Villanueva et al., 2022).

What are the considerations regarding the use of decaffeinated coffee? Decaffeinated coffee is not completely caffeine-free: it contains a maximum of 0.1%, as opposed to 1.5–2% before decaffeination. It is therefore a coffee that has lost about 97% of its caffeine through processes. According to current legislation, a coffee can only be considered decaffeinated if the amount of caffeine is less than 0.1% of the dry product (Huamaní-Meléndez and Darros-Barbosa, 2018).

The main methods of caffeine extraction are: 1) removal by chemical solvents: mainly ethyl acetate and diclomethane; 2) the triglyceride method; 3) removal of caffeine by carbon dioxide; 4) the system through a water extractor.

Decaffeinated coffee exists in nature and comes from a plant called Coffea charrieriana. However, its use is not widespread due to the rarity of this plant. The use of decaffeinated coffee is controversial for two main reasons. The first is that many manufacturers use a chemical process to remove the caffeine from the coffee beans. The result is less caffeine, but more chemicals. Second, it is the caffeine in coffee that provides the health and energy benefits. Without it, there are few benefits other than maintaining the coffee ritual.

The role of oxidative stress and inflammation in the pathogenesis and complications of several chronic diseases, including cancer, diabetes, neurodegenerative disorders, and cardiovascular disease, is well established. The anti-inflammatory and antioxidant properties of coffee have been investigated in numerous studies. There are more than 1000 chemical compounds in coffee. The compounds most known for their anti-inflammatory properties include caffeine, chlorogenic acid, trigonelline, melanoidins, caffeic acid, kahweol, and cafestol (Castaldo et al., 2021).

Inflammatory bowel disease cannot be controlled by diet alone. Certainly, some dietary indications can be very useful, especially during periods of disease activity. In particular, patients with ulcerative colitis often wonder whether coffee, one of the most popular drinks among Italians, should be strictly avoided. The answer is not unequivocal: at the moment, in fact, there is no certain evidence of the harmful effect of coffee and caffeine on the intestines of patients with this pathology, so no specific correlation has been found between the consumption of this drink and the progression of the disease (Campmans-Kuijpers and Dijkstra, 2021).

Moreover, broad *in vitro* and *in vivo* studies have illustrated that coffee and its bioactive compounds show neuroprotective impacts suggesting their preventive and/or helpful potential for several neurodegenerative conditions (Di Meo et al., 2020; Ruggiero et al., 2022). Caffeine, in fact, lowers the risk of neurodegeneration in humans. In the short term, coffee may improve mood, alertness, learning and reaction time, and in the long term, it may protect against brain conditions such as Alzheimer's and Parkinson's diseases. Alzheimer's disease causes memory loss, as well as cognitive and behavioural problems. Diet-related factors can influence the risk of developing Alzheimer's disease and other forms of dementia. Observational studies have associated regular and moderate coffee consumption with up to a 65% lower risk of developing Alzheimer's disease, although the correlation is still being studied in depth (Ruggiero et al., 2022).

Parkinson's disease is a chronic disease of the central nervous system. It is characterized by the death of nerve cells in the brain that secrete dopamine and are important for muscle movement. Parkinson's primarily affects movement and often includes tremors. Some studies show that coffee may help reduce the risk of Parkinson's disease, with a 29% lower risk of developing the disease (Ruggiero et al., 2022). The caffeine contained in coffee appears to be the active ingredient capable of exerting these protective effects. Despite this, it is well known that neuroprotective effect of coffee is not due to caffeine alone, but to other bioactive components, such as polyphenols, including phenolic acid, i.e., caffeic acid, ferulic acid, p-coumaric acid, chlorogenic acid, and quinin acid. These bioactive polyphenols are described to improve motor and cognitive performance both in aging and depression (Di Meo et al., 2020).

In this respect, chlorogenic acid, a polyphenol derived from coffee determined neuroprotection against rotenone-induced Parkinson's disease by glucagon-like peptide-1 secretion (Sharma et al., 2022). Prospective studies are needed to gain further insight into the precise molecular mechanisms and signaling network implicated in the neuroprotective anti-inflammatory action of compounds present in coffee, other than caffeine, using *in vivo* models of Parkinson's disease as well as in the treatment of symptoms of Parkinson's disease in a clinical setting.

In addition, there is evidence that suggest that habitual coffee consumption can potentially have positive impact on the course of autoimmune diseases such as multiple sclerosis (Wasim et al., 2020).

Among coffee compounds, caffeine surely has been the most extensively investigated in terms of neuroprotective effects, but the beneficial effects of coffee consumption can attributable not only to caffeine. Aside from caffeine, as already above mentioned, there are several other compounds in coffee that may independently determine particularly interesting protective effects in neurodegenerative conditions consequently paying attention to the possible use of decaffeinated coffee as a preventive and neuroprotective treatment. In this respect, other that polyphenolic acids, which include cholinergic acids and caffeic acid, the compound known as trigonelline looks the most promising one in terms of neuroprotection both in Alzheimer's disease and in Parkinson's disease (Mirzaie et al., 2016; Fahanik-Babaei et al., 2019). Unfortunately, unlike caffeine, there are still no epidemiological or clinical studies on the protective value of the other coffee compounds in case of neurodegenerative disorders. Only preliminary data are present. For that reason, in-depth studies aimed at obtaining new information about the neuroprotective effect of coffee and its most promising bioactive compounds, represented by caffeine, coffee polyphenols, and trigonelline, are needed.

Therefore, coffee consumption seems to be associated with a reduced risk of inflammatory diseases, whose mechanisms of action appear to be multidirectional. It should be noted that in many circumstances the beneficial effects associated with coffee intake are not always clear, as the same subjective inflammatory/oxidative profile can constitute a variable. The beneficial effects associated with coffee consumption are illustrated in **Figure 1**.

An interesting aspect of these studies is to provide information on possible nutraceutical treatments, assuming that the coffee constituents may have pharmacological effects, acting synergistically or antagonistically, used alone or in combination with other compounds to reduce drug intake and encourage the consumption of natural ingredients in adequate doses to promote health and fight disease by reducing unwanted risks and side effects of conventional drug therapies. Coffee is cheap and the favourite drink all over the world, thus the coffee consumption may provide a cost-effective and alluring preventive measure against chronic disease.

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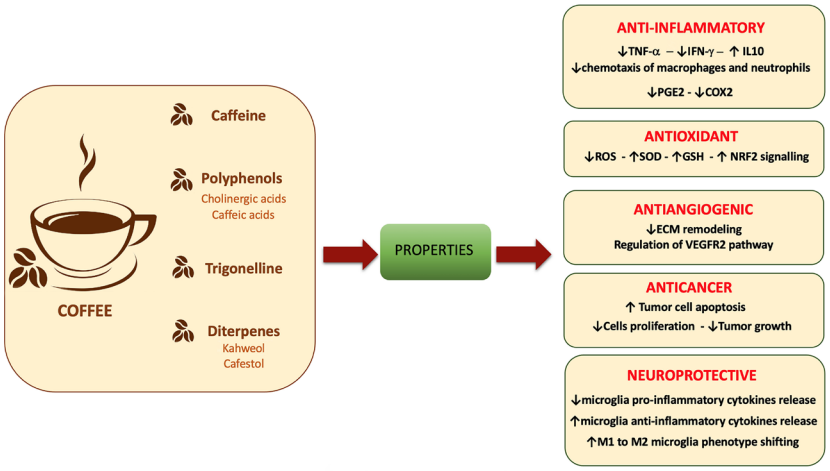

Figure 1 | **Health effect of coffee.**
Created with PowerPoint. ECM: Extracellular matrix; GSH: glutathione; IFN: interferon; IL: interleukin; NRF2: nuclear factor erythroid 2-related factor 2; PGE: prostaglandin E; SOD: superoxide dismutase; TNF: tumor necrosis factor.

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