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Green tea is a source of compounds known as catechins, including epigallocatechin gallate (EGCG).

ONCOLOGY

Tea for tumours

Decades of research exploring the potential anticancer effects of green tea are yet to translate into clinical benefits.

BY MICHAEL EISENSTEIN

A reviving cup of tea is one of life's pleasures — a tonic for the problems of daily life. But some people think that this refreshing beverage could have much greater restorative properties: there is evidence that tea, or some of its chemical components, can guard against cancer. The prospect is tantalizing, but after decades of population-based health studies, and even clinical trials in cancer patients, the scientific community is still far from a clear-cut answer.

Early hints of the potential of tea — green tea in particular — as a means of cancer prevention come from observations of geographical differences in cancer incidence, and efforts to identify lifestyle factors associated with these differences. "Population studies clearly show that the rates of clinically evident prostate cancer are much lower in Asian countries — especially in Japan and China, where 35% of the world's tea is consumed," says Nagi Kumar, a cancer-prevention researcher at the Moffitt Cancer Center in Tampa, Florida. "Those were the initial studies that got us started."

Early epidemiological investigations from the 1980s and 1990s proved messy to interpret and offered conflicting results, but experiments exploring the pharmacological effects of tea's constituent molecules on cancer cells were encouraging. "These compounds work beautifully in many experimental models and many cell culture systems," says Hasan Mukhtar, a cancer researcher at the University of Wisconsin–Madison.

However, the enthusiasm of many working in this area of chemoprevention has been worn down by clinical trials that have proved inconclusive or shown only modest benefit. "When people ask me if tea prevents cancer, I say 'Yes, no and perhaps,'" says Chung Yang at Rutgers University in Piscataway, New Jersey, who has studied the pharmacology of tea's constituents for more than 30 years. "The animal studies are very strong, but there are no clear conclusions in humans."

READING THE LEAVES

Green tea's medicinal properties are primarily linked to a family of compounds known as catechins. The most important of these is epigallocatechin gallate (EGCG), which typically comprises 60–65% of the catechin content in a cup of green tea, and can be present at concentrations up to ten times higher than that of caffeine. EGCG has potent pharmacological effects both on cultured cancer cells and in mouse tumour models (see 'Steeped with potential'). "This has turned out to be the most active compound in animal studies," says Yang. However, in many cases the effective dose in animals might be impractical for use in humans; in some studies, the animals were given nothing but green tea or catechin-containing solutions to drink for the duration of the experiment.

Yang notes that EGCG is remarkable for its strong affinity for a wide range of different biomolecules. This promiscuity means that EGCG "affects many hallmarks of carcinogenesis", Kumar says. One common finding is that the compound causes tumour cells to self-destruct — a process known as apoptosis — while sparing adjacent healthy tissue. Kumar thinks that EGCG might do this by inhibiting an enzyme complex known as the proteasome, which cancer cells exploit to break down biomolecules that would otherwise promote apoptosis. EGCG and other catechins can also prevent formation of toxic reactive oxygen species (ROS), which can inflict severe cellular damage and promote cancerous growth.

How these various mechanisms contribute to EGCG's overall anticancer effect is difficult for researchers to unpick, but numerous preclinical studies have clearly demonstrated potential therapeutic benefits. A 2009 review by Yang found that 133 out of 147 published animal studies involving tea or tea extracts demonstrated effective prevention or growth inhibition of a wide variety of cancers[1]. This is not just down to EGCG, however: the compound exerts a potent solo effect in cell culture, but it seems unable to deliver a medical benefit in the body on its own. "Just EGCG doesn't work in an *in vivo* setting," says Kumar. "You have to give it as a mixture of all the catechins together."

Unfortunately, the medicinal benefits of tea in humans have been extraordinarily difficult to prove. Most early epidemiological work entailed case-control studies, which look at the medical history, lifestyle and history of environmental exposures to potential aetiological agents of people with cancer compared with healthy individuals from a selected population. On the basis of these studies, many researchers proposed that drinking green tea conferred some protection against cancer, but Piet van den Brandt, an epidemiologist at Maastricht University in the Netherlands, advises caution. "These case-control studies were done throughout the 70s, 80s and 90s, and there was a lot of suspicion that they could be prone to recall bias or selection bias," he says. One weakness of such studies is that they rely on self-reporting of past behaviour. Moreover, the results might have been clouded by lifestyle changes that cancer patients adopted at the time of diagnosis, such as a change in diet. For this reason, van den Brandt and others prefer cohort studies, which are forward-looking and prospectively track outcomes in large populations over the course of many years.

Conclusions from epidemiological studies looking at the effects of tea can also be muddied by lifestyle factors with more powerful effects on health, such as smoking. In 1994, a highly cited case-control study from Shanghai, China, suggested that green tea conferred a gender-specific protective effect against oesophageal cancer[2]. But Yang, who was not involved in the study, explains that this protection was seen only in women because, at the time of the study, 75%

of the men were smokers compared with only a small minority of the women. When this confounding effect was taken into account, the data indicated that tea drinking was associated with a 60% reduction in cancer risk — but only in non-smokers.

Despite these challenges, several large-scale cohort studies have also shown some beneficial effects of green tea on cancer prevention. A 2016 study tracking the health of more than 164,000 Chinese men between 1990 and 2006 linked regular consumption of green tea with an 8–21% reduction in the risk of dying from cancer[3]. And in Europe, van den Brandt and colleagues have been tracking the effects of tea and other dietary factors on the long-term health of 120,000 middle-aged men and women since 1986 as part of the Netherlands Cohort Study (see go.nature.com/2b8uhql). Van den Brandt has found that, in men, as tea drinking goes up, cancer mortality, cardiovascular mortality and overall mortality all go down[4]. "But the relationship seems to be non-linear — there is an optimum intake," he says, with peak benefit observed at three cups of tea per day. Interestingly, the greatest improvements in mortality were observed in men who drink roughly equivalent quantities of tea and coffee, highlighting potential health benefits from the latter beverage as well. In contrast to the Shanghai study, van den Brandt observed no meaningful health benefit for female tea drinkers.

EXTRACTING ANSWERS

A number of groups have explored green tea's effect on cancer through clinical trials in which EGCG and other constituents are administered as either therapeutic or preventive agents. Because tea can be prepared in numerous ways that affect the strength and quantity of a given cup, which might alter its physiological impact, clinical researchers often work instead with defined extracts that replicate the catechin composition of a strong cup of brewed green tea, and that can be given in capsule form.

Many trials have focused on the safety and bioavailability of these extracts — the latter being a prominent concern because EGCG quickly passes through the body. But the oral administration of green tea extracts has also showed some promise in containing the progression of prostate and colorectal cancer[5,6]. In 2006, a small Italian study suggested that such extracts might prevent precancerous prostate growths from turning cancerous[6]. Only one malignancy was observed after a year in a 30-patient treatment arm, against 9 in the equivalent placebo arm. A 2015 trial of green tea extract by Kumar and colleagues failed to demonstrate a statistically significant effect in terms of preventing prostate cancer, although the team did observe a decrease in the formation of certain precancerous lesions in those who received the extract, relative to the placebo group[7]. "For a disease of such a long latency period, I think that's a remarkable finding."

Extracts are more reproducible than brewed tea, but also have potential safety concerns. The adverse events in clinical trials so far have been largely minor and manageable — in some cases, resulting more from the effects of caffeine than of catechins. But Yang cautions that high doses of EGCG carry a risk of liver toxicity, a problem that has emerged in people who consume high doses of over-the-counter tea-derived supplements, commonly taken for weight loss. "I haven't seen liver toxicity due to tea drinking," he says, "but when you put it all together into a capsule, there are more than 30 clinical reports of toxicity from tea-based supplements." European authorities recently recommended further investigation of the safety of these supplements, possibly as a prelude to tighter regulation.

This is problematic because the modest anticancer effects in trials up to now suggest that cancer prevention might require a stiffer dose of EGCG than would be delivered by a cup of tea. Several groups are exploring nanotechnology-inspired strategies that might use this catechin's effects in a more targeted way. Mukhtar and colleagues have developed an encapsulated EGCG formulation that can home in on prostate tissue and inhibit tumour growth in preclinical models. Motoichi Kurisawa and colleagues at the A*STAR Institute of Bioengineering and Nanotechnology in Singapore have even found that EGCG itself can be modified into a drug-delivery vehicle that not only shepherds other anticancer agents through the body but also amplifies their effects[7]. Kurisawa's team has demonstrated the effectiveness of these EGCG nanocarriers in mouse models, including a formulation of the kidney cancer drug sunitinib that could greatly alleviate the toxicity associated with the normal drug regimen. Kurisawa notes that sunitinib is typically administered at a dose of 40 milligrams per kilogram of body weight. "But we observe very strong tumour-growth inhibition effects when we use just 5 milligrams of drug per kilogram with our nanocomplexes," he says.

A BITTER BREW

With only modest evidence of clinical efficacy at hand, tea is an increasingly tough sell to those setting budget priorities for cancer research. "You can't get anything funded these days if you're working on green tea," says Mukhtar.

In Yang's view, this is a general problem for chemoprevention research — intervention studies in people are expensive, and have generally borne little fruit. One high-profile example is the Selenium and Vitamin E Cancer Prevention (SELECT) trial of a decade ago, which cost US$114 million and demonstrated no meaningful benefit. Kumar's perspective as a clinical researcher at a major cancer centre is somewhat sunnier, but she also acknowledges that natural products and chemoprevention face stiff competition from more powerful new therapies, such as immunotherapy, that are starting to show impressive results. "We are always in line behind the others," she says. Exacerbating the problem is the lack of a strong business model: drug companies have little incentive to invest in trials of a product that is cheap and widely available.

The limited success in demonstrating a direct anticancer effect of tea has been deeply disappointing, and highlights the inherent difficulties in studying the medical benefits of foods and natural products. But Yang sees other avenues of research where the evidence for tea's health effects is stronger, and which might also contribute to reducing long-term cancer risk — for example, by preventing the onset of metabolic syndrome. "If tea can reduce body weight and reduce the risk of cardiovascular disease, that would decrease cancer risk," he says. "We're counting on large cohort studies to give us more informative answers." ■

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STEEPED WITH POTENTIAL

Tea is rich in epigallocatechin gallate (EGCG), a compound with anticancer properties. Although researchers have proposed several mechanisms of action for EGCG, it remains unclear whether any has clinical potential.