GREEN TEA

Camellia sinensis L. (Kuntze)

Family

Theaceae. Synonyms *Thea sinensis* L. and *Camellia viridis* Sweet among others.[1]

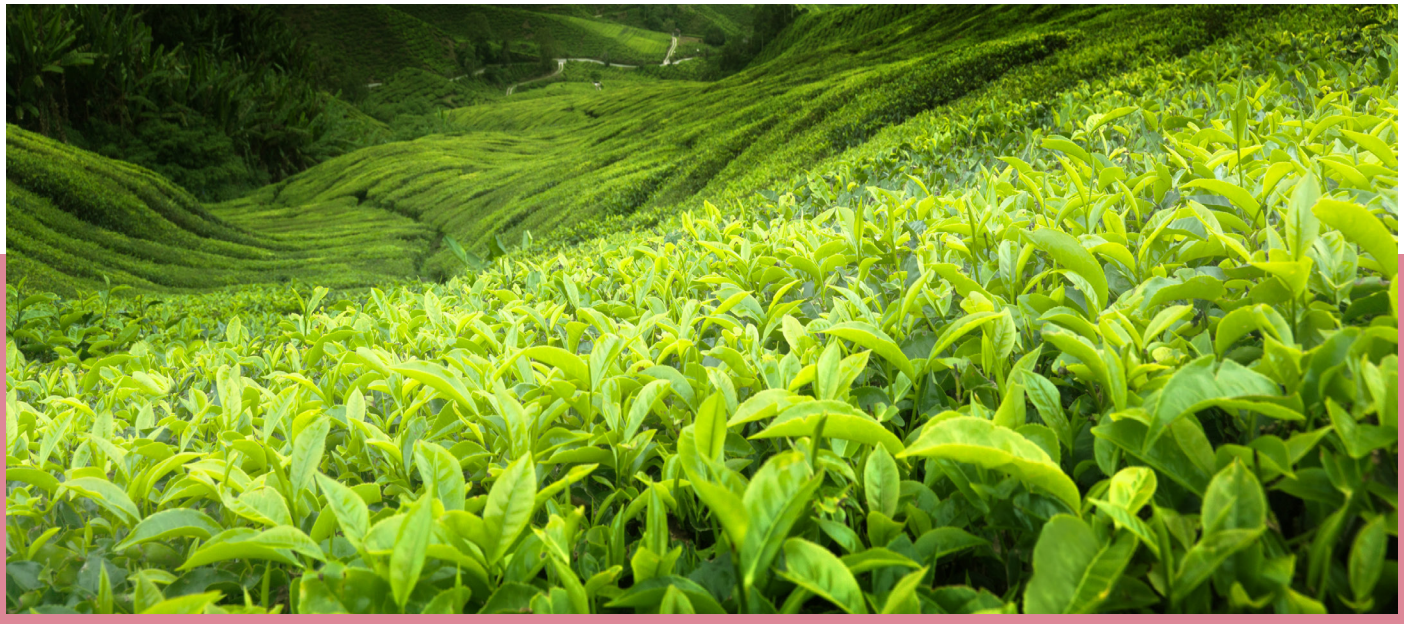
Parts Used

Leaf.

Description

The tropical and temperate regions of Asia, Africa and South America are considered the main origins of the tea plant, an evergreen shrub. The majority of members of the Theaceae family are obtained from India, Sri Lanka, China and Japan. The physiological properties and colour e.g. black, white, green or oolong tea strongly depends upon the degree of fermentation and processing conditions.[2] White tea is produced from very young leaves and buds that have not yet turned green, and the only processing is drying.[3] To produce green tea, freshly harvested leaves are immediately steamed to prevent fermentation yielding a dry, stable product. This steaming process destroys the enzymes responsible for breaking down the colour pigments in the leaves and allows the tea to maintain its green colour during the subsequent rolling and drying processes.

These processes preserve natural polyphenols with respect to the health-promoting properties. As green tea is fermented to oolong and then to black tea, polyphenol compounds (catechins) in green tea combine to form a variety of theaflavins with the result that these teas have different biological activities. Black tea contains up to three times the amount of caffeine as green tea.[4] The highest-quality leaves are the first spring leaf buds called the 'first flush'. The next set of leaf buds produced is called the 'second flush' and considered to be of



poorer quality. Tea varieties also reflect the area they are grown in (e.g. Darjeeling in India), the form produced (e.g. pekoe is cut, gunpowder is rolled) and processing method (black, oolong or green).[5]

Traditional Use

"Tea is a miraculous medicine for the maintenance of health. Tea has an extraordinary power to prolong life." Eisai ('Father of Tea' in Japan), *Maintaining Health by Drinking Tea*, 1211.[6]

Tea is the most consumed beverage in the world after water, drunk in the United Kingdom for 350 years and in Asia for more than 4000 years.[7] Since tea drinking has such a long history there have been many scientific research papers on the nature of its components. Some publications are based on strong evidence while others appear to be superficial. Many of the beneficial effects found in the laboratory have been carelessly extrapolated to human health and reported in the media.[8]

Green tea, which makes up around 20% of tea production worldwide, is consumed most often in China, Korea and Japan. Oolong tea is consumed most in China and Taiwan. Black tea (around 78% of tea production) is mostly consumed in the United States and the United Kingdom. However the consumption of green tea is now increasing in Western countries because of increasingly new investigations on its health benefits and anticarcinogenic activities in various organs.[9,10]

There are many legends surrounding green tea. According to one account, tea was discovered quite accidentally by the Chinese emperor Shen Nung in 2737 B.C. The 'Divine Healer', as the emperor was called, routinely boiled his drinking water before consuming it and one day some leaves from a nearby tree fell into the pot producing an excellent tasting and fragrant beverage. The emperor, upon drinking the concoction, proclaimed the beverage as "heaven sent", and as a result tea was discovered. Another legend tells of a Buddhist monk named Bodhidharma who struggled to remain awake during a prolonged meditation. Legend has it that the monk cut off his eyelids and flung them to the ground in desperation so that he would not sleep. Such heroic devotion won the favour of the gods who instantly turned his eyelids into the first tea plants. Bodhidharma managed to stay awake for the next seven years by chewing nothing but tea leaves, and tea became forever mystically linked with Buddhism and meditation. Used first during the Song Dynasty (960 to 1279) the fine powder of green tea leaves, called 'tea mud' is no longer popular in China but it is still widely used in Japan. The cultivation of tea in Japan was initiated in the 11th century by the Zen Buddhist monks who also developed methods for processing and preparing the powdered green tea known as 'matcha'. In Japanese 'cha' means tea, and 'ma' means powder. The Buddhist monk Eisai acclaimed tea as a 'divine remedy and supreme gift of heaven' for preserving human life.[11] Historically green tea was a luxury beverage in Japan available only to court nobles, Buddhist monks and other select members of society. It was also used for medicinal purposes. Today green tea is an integral part of the Japanese diet drunk together with meals. Along with matcha they also drink high grade gyokuro, Sencha, genmaicha which is green tea mixed with roasted brown rice and houjicha which is roasted Sencha.[12] Green tea is an important part of Chinese culture and is regarded as a key element in health maintenance. It is used in Traditional Chinese Medicine as an astringent, cardiotonic, central nervous system stimulant and diuretic. It may be

used for treating flatulence, for regulating body temperature, promoting digestion and improving mental processes. In India green tea has additionally been used to treat fungal infections. Green tea bags have also traditionally been used topically to soothe sunburn, headache, tired eyes and to stop bleeding of the gums or tooth sockets.[13]

Tea was introduced in Europe as a beverage by the Dutch East India Company around 1610. The tea initially imported into Europe was green tea. *Camellia viridis* was included in Culpeper's Complete Herbal (1880) as diuretic, stomachic and useful in headache. The stimulant action on the nervous system is mentioned as a side effect. Among all teas consumed in the world green tea is the most studied for its health benefits including cancer prevention and degenerative diseases like cardiovascular diseases, arthritis and diabetes. The question is can these observations sustain the scrutiny of modern scientific research? The modern experimental results below provide a scientific basis for some of the beneficial health effects of green tea described in the classical literature.[14]

Constituents

The chemical composition of green tea is complex. It contains polyphenols, which include flavanols, flavandiols, flavonoids and phenolic acids. These compounds may account for up to 30% of the dry weight. Most of the green tea polyphenols are flavonols, commonly known as catechins, which are found in greater amounts in green tea than in black or Oolong tea. There are four kinds of catechins mainly found in green tea: epicatechin (EC), epigallocatechin, epicatechin-3-gallate and epigallocatechin-3-gallate (EGCG). The amount of catechins in green tea varies depending on the location of cultivation of the tea plant, variety of the plant, season of harvest, manufacturing process, which leaves are harvested, how the leaves are processed and how the tea is prepared. Comparison of ingested doses in animal studies is not possible because the catechin quantification before administration is often not known.[15,16]

Green tea also contains proteins (15 to 20% dry weight), whose enzymes constitute an important fraction; amino acids (1 to 4% dry weight) such as theanine or 5-N-ethylglutamine, glutamic acid, tryptophan, glycine, serine, aspartic acid, tyrosine, valine, leucine, threonine, arginine and lysine; carbohydrates (5 to 7% dry weight) such as cellulose, pectins, glucose, fructose and sucrose; minerals and trace elements (5% dry weight) such as calcium, magnesium, chromium, manganese, iron, copper, zinc, molybdenum, selenium, sodium, phosphorus, cobalt, strontium, nickel, potassium, fluorine and aluminium; and trace amounts of lipids (linoleic and α-linolenic acids), sterols (stigmasterol), vitamins (B, C, E), xanthic bases (caffeine, theophylline), pigments (chlorophyll, carotenoids) and volatile compounds (aldehydes, alcohols, esters, lactones, hydrocarbons). Because brewing techniques vary according to cultural customs around the world it is very difficult to estimate the caffeine intake from tea or coffee for that matter.[17] Variables that have a significant influence on caffeine extraction include temperature of the water, time brewed, type of tea, leaf structure and whether a tea bag was used.[18]

Green tea extracts are more stable than pure EGCG because of the presence of other antioxidant constituents in the extract. In general, herbal medicines are complex mixtures of different compounds that often act in a synergistic fashion to exert their full beneficial effect. However relatively few herbal medicines have been well characterised and their efficacy demonstrated in systematic clinical trials as compared to Western drugs.[19]

There is significant evidence that whole green tea is a more reasonable mixture of tea polyphenols for cancer prevention in humans than EGCG alone and that it is even more effective when it is used in combination with other cancer preventives. Scientists first reported that combinations with the active catechins and inactive EC induced synergistic effects on induction of apoptosis and inhibition of cell growth of a human lung cancer cell line, and inhibition of TNF-α release from cells treated with okadaic acid, a tumour promoter. This suggests that whole green tea, which is a mixture of green tea catechins, is a more effective and practical cancer preventive than green tea catechins alone.[20]

This monograph will focus on whole green tea studies and not isolated constituents.

Actions

Antioxidant, anti-inflammatory, anticarcinogenic, antimutagenic, chemoprotective, antiproliferative, antifibrotic, cardioprotective, antihyperlipidaemic, hypocholesterolaemic, antiarteriosclerotic, antiplatelet, thermogenic, antimicrobial, antibacterial, antifungal, antiviral, hypoglycaemic, neuroprotective, hepatoprotective.

Pharmacological Activity

Almost 6000 publications have been cited in PubMed discussing epidemiological and experimental data on the health effects of green tea.[21] Many laboratory studies strongly suggest the beneficial health effects of green tea consumption in the prevention of chronic diseases. However the results from epidemiological studies have not been consistent. Large cohort studies have shown beneficial effects in reducing the risk of deaths from all causes (combined) and cardiovascular disease, but that from cancer is inconsistent, and the protective effects are generally strong among non-smokers. Regarding human intervention studies there are many successful examples that demonstrated the beneficial effects of tea constituents in weight reduction and metabolic syndrome alleviation even though there are still some inconsistencies. Intervention trials for cancer prevention have not yielded convincing results possibly due to the difficulties in conducting long-term studies in the appropriate populations.[22]

Antioxidant Activity

Antioxidant effects come from the ability of green tea to limit the amount of free radicals by binding to reactive oxygen species (ROS).[23]

A recent review found that regular consumption of green tea in amounts of at least 0.6 to 1.5 litres a day may increase plasma antioxidant capacity and reduce lipid peroxidation (especially oxidation of LDL). This may contribute to the protection against cardiovascular diseases and different types of cancer.[24]

A human study found that two cups of green tea has the ability to improve the overall antioxidant status and to protect against oxidative damage when consumed within a balanced controlled diet. In the study 24 healthy women consumed green tea for 42 days.[25]

A significant genoprotective effect was found with an *in vitro* study and a small human trial using a biomarker of oxidative stress.[26]

Anti-inflammatory Activity

The anti-inflammatory effects of green tea may be a result of increased production of IL-10, an anti-inflammatory cytokine. Inflammation is involved in, among other conditions, arthritis, cardiovascular disease, aging, and cancer.[27]

Epidemiological evidence has shown an association between tea consumption and the prevention of age-related bone loss in elderly women and men. Ingestion of green tea and green tea bioactive compounds may be beneficial in mitigating bone loss of this population and decreasing their risk of osteoporotic fractures. A recent review found tea and its bioactive components might decrease the risk of fracture by improving bone mineral density and supporting osteoblastic activities while suppressing osteoclastic activities.[28]

Anticancer Activity

While it is still unclear if green tea reduces the incidence of all cancers or has any effect on mortality it has been linked to the prevention of many types of cancer including lung, colon, oesophagus, mouth, stomach, small intestine, kidney, pancreas and mammary glands. A recent overview of the clinical evidence found there is some positive evidence for risk reduction of breast, prostate, ovarian and endometrial cancers. The anticarcinogenic mechanisms may include inhibiting angiogenesis and cell growth and inducing apoptosis in cancer cells. Evidence is largely based on epidemiological (the study of how often diseases occur in different groups of people and why) studies with few clinical studies available. The conflicting results from different studies and reviewers may be due to confounding factors in different populations, dosages and differences in the EGCG content of green teas.[29,30,31]

The current evidence does not support the use of green tea as a cancer treatment however there are some exceptions which suggest an adjunctive role for ovarian, cervical, colorectal, prostate, leukaemia

and breast cancers. Studies have been conducted with various doses of green tea in different cancers producing mixed results.[32]

The results of epidemiologic studies investigating the association between green tea consumption and cancer risk have not been consistent. Many studies have found no association and some have found a favourable effect. The quality of studies varies and the dosage is often quite high and occurs over long periods. The concentration of the tea infusion is also a factor. In one of the earliest studies reported the daily consumption of at least 10 Japanese-size cups of green tea resulted in delayed onset of cancer.[33] Several more recent epidemiologic studies from China provide possible dosage information: just over 8g per day of dry leaf is equivalent to two cups per day.[34,35]

A 2017 review found that evidence for the protective role of green tea is often claimed based on data from animal experiments and cell culture data. Epidemiological correlation of green tea with a variety of different tumour types has been published. All reviews of epidemiological data about the connection between green tea intake and cancer prevention have judged the epidemiological evidence as ambiguous at best, whereas *in vitro* studies and their reviews usually emphasise the positive green tea effects.[36]

A recent review on clinical studies critically assessed the association between green tea consumption and the risk of cancer incidence and mortality. Reports indicate that 51 prospective controlled interventional and observational studies of 1.6 million participants conducted assessed either the associations between green tea consumption and risk of cancer incidence or cancer mortality. These results assessed associations between green tea and risk of digestive tract cancer incidence which was inconclusive and conflicting. Although there was evidence, albeit limited, that green tea could reduce the incidence of liver cancer, the evidence for oesophageal, gastric, colon, rectum and pancreatic cancers were contradictory. Observational studies and one randomised controlled trial on prostate cancer suggested a decreased risk in men consuming higher quantities of green tea or green tea extracts. There was limited to moderate evidence that the consumption of green tea reduced the risk of lung cancer, especially in men. There was also evidence that green tea consumption could increase the risk of bladder cancer.[37]

An earlier review concluded that green tea was associated with a reduced risk of upper gastrointestinal tract cancers and had a beneficial role in breast cancer. However they suggested results on overall cancer prevention were inconclusive. The researchers said that while experimental studies have consistently shown the inhibitory activities of tea extracts on tumorigenesis in multiple model systems epidemiological studies have produced inconclusive results in humans.[38]

The results of an *in vitro* study strongly indicate that green tea itself is a more effective and practical cancer preventive than EGCG alone and that drinking green tea enhances the cancer-preventive activity of sulindac (a non-steroidal anti-inflammatory drug) and tamoxifen (hormone therapy drug), resulting in smaller doses of these drugs and fewer adverse effects.[39]

Breast Cancer

Breast cancer is the most common cancer among women. In recent years many *in vitro* and *in vivo* studies indicate that green tea possesses anti-cancer effects however the epidemiological studies have produced inconclusive results in humans. Likewise, results from animal models about the preventive or therapeutic effects of green tea components are inconclusive. The mechanisms by which green tea intake may influence the risk of breast cancer in humans remain elusive. As early as 1997 there was an epidemiological study which showed that increased consumption of green tea had a potentially preventive effect on breast cancer in a Japanese population, especially among females drinking more than 10 cups a day. Since then, the association between green tea consumption and breast cancer risk has been extensively investigated. To date, three meta-analyses have been published on the association between green tea and breast cancer risk and/or recurrence although they did not find a significant effect of green tea on breast cancer prevention. However in some studies there appears to be a benefit of green tea drinking of three or more cups daily with

reduction in the risk of breast cancer. Some recent studies are suggesting the aromatase-inhibiting action may be more effective for women drinking green tea premenopause, which may delay onset of breast cancer.[40,41,42]

Findings of a recent study suggest that green tea may modify oestrogen metabolism or conjugation and in this way may influence breast cancer risk. As a rich source of phytochemicals that can interact with and regulate xenobiotic metabolising enzymes, green tea may modify metabolism or conjugation of oestrogens and may thereby impact breast cancer risk. Scientists examined the associations of green tea intake (less than once a week, 1 to 6 times weekly, or 7 plus times weekly) with urinary estrogens and oestrogen metabolites (jointly EM) in a cross-sectional sample of healthy Japanese American women, including 119 premenopausal women in luteal phase and 72 postmenopausal women. Dietary intake of black tea, coffee, decaffeinated coffee and caffeinated soda was also queried. In premenopausal women intake of green tea was associated with lower luteal total EM and lower urinary 16-pathway EM. In postmenopausal women, urinary oestrone and oestradiol were approximately 20% and 40% lower in women drinking green tea daily compared to those drinking less than once a week. Caffeine was calculated assuming standard serving sizes and the following estimates of caffeine content, based on food composition databases and measures in the literature: 81mg caffeine per serving of coffee, 2mg caffeine per serving of decaffeinated coffee, 20mg caffeine per serving of green tea, 30mg per serving of black tea and 29mg per serving of caffeinated soda.[43]

Colorectal Cancer

A recent meta-analysis of 13 case controlled studies indicated a weak lower tendency for colorectal cancer development with green tea consumption.[44]

Gastric Cancer

Green tea has been reported to have a protective effect against stomach cancer prompting the review of 17 epidemiologic studies in 2013. Ten case-control studies and seven cohort studies were included. This review concluded that the evidence was insufficient to suggest that green tea reduces the risk of gastric cancer. They found seven studies with no association, eight with an inverse association and one study showing a positive association. However they did suggest that Helicobacter pylori infection may be a confounding factor and that future research should include this subgroup.[45]

Kidney and Bladder Cancer

Results based on a 2017 meta-analysis indicate there is no significant association between tea consumption and risk of bladder cancer. Controversial results of the association between tea (black tea, green tea, mate, and oolong tea) consumption and risk of bladder cancer have been reported among epidemiological studies. One meta-analysis indicated that green tea reduced bladder cancer risk in Asians and the other suggested that high level of tea consumption in smokers was related to an elevated risk of bladder cancer. Twenty five case control studies (15,643 cases and 30,795 controls) and seven prospective cohort studies (1,807 cases and 443,076 participants) were included. The researchers said caution is needed in interpreting the results with further studies needed.[46]

Leukaemia

Several studies on Asian and North American populations suggest that drinking green tea can help reduce the risk of leukaemia. Clinical trials also show that green tea extracts can help treat some forms of leukaemia. A study published in the British Journal of Cancer examined the link between green tea consumption and the risk of leukaemia among 107 adults with leukaemia and 110 orthopaedic controls in China. This case control study found that a higher intake of green tea was linked with a reduced risk of adult leukaemia and with significant dose response relationships. A reduced risk was found with longer duration, higher quantity, and frequency of green tea intake, for acute lymphocytic leukaemia and chronic myeloid leukaemia/chronic lymphocytic leukaemia combined.[47]

A Taiwanese study concluded that drinking sufficient amounts of green tea may reduce the risk of leukaemia. The protective effect was significant in the 16 to 29 year age range with higher amounts of green tea consumption.[48]

Liver Cancer

The results of a 2017 meta-analysis showed that increasing green tea intake may have a preventive effect against liver cancer. The downward trend was most obvious when the consumption of green tea increased up to about four cups per day. A trend was also found with the increasing years of green tea intake, with 20 plus years showing a significant decrease in liver cancer risk.[49]

A total of 13 epidemiological studies, consisting of six case-control and seven prospective cohort studies, found borderline significance between tea consumption and primary liver cancer.[50] Green tea consumption may protect against development of primary hepatocellular carcinoma (HCC). A recent case-control study of 204 HCC patients found that drinking large quantities of green tea (more than 250g of green tea per month or about two or more cups a day) for a longer duration resulted in a protective effect, with those drinking green tea for over 30 years having the lowest risk. In the subgroup of patients with chronic hepatitis infection, the risk of HCC in non-green tea drinkers was twice that of those consuming green tea.[51]

Lung Cancer

A recent systemic review found that although some evidence suggests that chemopreventative benefits can be accrued from green tea there is currently insufficient evidence to support green tea as a treatment or preventative agent for lung cancer. However human studies indicate that four cups of green tea daily decreased DNA damage in smokers.[52]

Results from an earlier meta-analysis suggested a favourable effect of green tea consumption and risk of lung cancer. Results suggest the dose response relationship is nonlinear (does not vary with the dose) between green tea consumption and risk of lung cancer.[53]

Oesophageal Cancer

Regularly drinking very hot tea, when combined with tobacco or alcohol use, is associated with an increased risk for oesophageal cancer, according to a 2018 study with more than 450,000 participants. The risk for oesophageal cancer was five times higher in individuals who drank very hot tea and drank more than 15g of alcohol every day compared to those who drank tea less than once a week and consumed fewer than 15g of alcohol daily. In addition the risk for oesophageal cancer was doubled in those who drank piping hot tea each day and smoked tobacco compared to non-smokers who drank tea only occasionally. Although the study showed no increased risk for oesophageal cancer in participants who drank only tea every day, scalding or not, the study authors emphasised that chronic thermal injury to the oesophageal mucosa may initiate carcinogenesis.[54]

An earlier 2013 meta-analysis found that consumption of green tea might reduce the risk of oesophageal cancer in female subjects however the results are based on limited research.[55]

Ovarian and Endometrial Cancer

A 2017 study found that tea consumption had a significant protective effect against ovarian cancer. A large number of epidemiological studies have provided conflicting results about the relationship between tea consumption and ovarian cancer so the researchers aimed to clarify this. A total of 18 (11 case-control and 7 cohort) studies, representing data for 701,857 female subjects including 8683 ovarian cancer cases, were included in the meta-analysis. Although different types of tea (green, red and black tea) may have different effects on the risk of ovarian cancer they did not perform a detailed meta-analysis to determine these differences due to the lack of available studies.[56]

A recent meta-analysis on the correlation between drinking green tea and the risk of female ovarian tumours, with a total of 9,113 people, reported that green tea drinking can significantly decrease the risk of ovarian cancer. More research is suggested to assess different teas and dosages, and how different subgroups are affected.[57]

A recent systematic review of *in vivo* and *in vitro* studies examined the effects of green tea or green tea components on the prevention and progression of epithelial ovarian cancer. The researchers concluded that it was difficult to extrapolate data as the catechins in the green tea varied, there were different cup sizes and various definitions of high tea intake. In epithelial ovarian cancer cell lines, green tea and green tea components have been shown to downregulate the expression of

proteins involved in inflammation, cell signalization, cell motility and angiogenesis. Green tea and green tea components would induce apoptosis and could potentiate the effects of cisplatin, a chemotherapeutic agent. In human observational studies, significant associations between green tea intake and both decreased ovarian cancer occurrence and better prognosis were reported.[58]

A literature review found four case-control studies of green tea and ovarian cancer and a meta-analysis of these studies found evidence of a combined inverse association between green tea drinking and ovarian cancer, with a 32% reduction in risk for green tea drinkers. The same authors performed a review and meta-analysis of six observational studies which confirmed a dose-dependent protective role of green tea drinking and endometrial cancer risk, suggesting a 23% reduction in risk for regular green tea drinkers. The authors suggest caution in interpreting the results because of the differences in green teas and the amount of tea consumed.[59]

An Australian case-control study conducted over 3.5 years (1,368 patients and 1,416 controls) reported a significant inverse association between green tea drinking (four or more cups) and ovarian cancer. The same authors conducted a meta-analysis (which included 17 studies) and found a trend towards green tea drinking and ovarian cancer prevention.[60]

Pancreatic Cancer

Emerging laboratory and animal studies indicate that green tea inhibits development and progression of pancreatic cancer but evidence from epidemiologic studies appears inconsistent and inconclusive. A 2014 meta-analysis summarising published case control and cohort studies was performed to evaluate the association of green tea consumption with risk of pancreatic cancer. A total of three case-control studies and five prospective studies were included, comprising 2,317 incident cases and 288,209 subjects. The researchers said cumulative epidemiologic evidence suggests that green tea consumption is not associated with pancreatic cancer.[61]

A recent large scale population-based case-control study (including 908 patients with pancreatic cancer) found that regular drinking of green tea, increased consumption, longer duration of tea drinking and lower temperature of tea were associated with 30 to 40% reductions in pancreatic cancer risk in women. No associations were found between most tea drinking habits and pancreatic cancer risk in men, except for drinking lower temperatures which was related to a 40% reduction in pancreatic cancer risk. Drinking more than 150g of dry tea leaves per month (also lower-temperature tea) resulted in a reduction in risk by 43% for women compared with non-tea drinkers. With men there was only an association between pancreatic cancer risk and tea for regular tea drinkers consuming lukewarm and cool tea compared to hot tea.[62]

Prostate Cancer

A 2017 meta-analysis found there was a trend of reduced incidence of prostate cancer with each one cup per day increase of green tea. Higher green tea consumption was linearly associated with a reduced risk of prostate cancer with more than seven cups per day. Seven observational studies and three randomised controlled trials were included.[63]

Strong evidence from *in vitro* and *in vivo* animal studies supports the role of green tea in prostate cancer prevention. However, prior to assuming that these benefits translate to humans, several points need to be considered. First most of the *in vitro* studies do not take the pro-oxidant activity of EGCG at alkaline pH into consideration. With the elimination of the "hydrogen peroxide" effect, much higher concentrations of green tea polyphenols would be necessary to induce the same effects. Second it appears that mouse tissue bioavailability of green tea polyphenols is considerably different from human tissue. Therefore the bioavailability in human tissue may be more limited and the potential of green tea polyphenols more limited. Nonetheless, human population studies provide some supportive evidence for a decrease in risk of prostate cancer associated with increased consumption of tea. The evidence from human clinical trials demonstrating a decrease in the rate of tumour progression from prostate intraepithelial neoplasia to adenocarcinoma, together with evidence of a decrease in serum markers of tumour progression, provide strong support for the preventive actions of green tea in localised prostate cancer. Overall, epidemiological and human clinical studies, as well as animal and basic mechanistic studies on green

tea support a chemopreventive role in prostate cancer but more research efforts at many levels is needed.[64]

Cardiovascular and Hyperlipidaemic Activity

Cardiovascular effects include the antioxidant and anti-inflammatory effects, and consumption of green tea has been shown to inhibit atherosclerosis, reduce lipid levels overall and improve the ratio of LDL to HDL.[65]

Randomised controlled trials of green tea and cardiovascular risk factors suggest that green tea may reduce low-density lipoproteins and total cholesterol, although studies are of short duration.[66]

Results from two 2017 cohort studies found that green tea consumption may be inversely associated with risk of all cause and cardiovascular disease mortality in middle-aged and elderly Chinese adults, especially among people who have never smoked. While a possible protective role of green tea consumption in risk of specific chronic disease mortality in humans has been suggested in epidemiological studies these findings remain controversial. Recently several cohort studies have suggested that the consumption of green tea may lower the risk of all-cause mortality by reducing the number of deaths due to cardiovascular disease. However inconsistent results have been observed in different populations and studies. Meta-analysis of five cohort studies indicated that green tea consumption was associated with a lower risk of total and cardiovascular disease and mortality however the evidence was mainly based on Japanese populations.[67,68]

Higher green tea consumption (more than four cups a day) was inversely associated with risk of cardiovascular disease and stroke (especially intracerebral haemorrhage) in the general population a recent prospective study found. The cohort consisted of 82,369 Japanese people. The participants completed self-administered food frequency questionnaires over a 13-year period.[69]

A recent Cochrane review reported on 11 randomised controlled trials with seven of these on green tea alone (five studies with 375 to 600mg daily of green tea extract and two studies on green tea beverages). The authors concluded that total cholesterol, LDL-cholesterol, with a trend towards a reduction in triglycerides, and blood pressure were significantly reduced with green tea consumption. On analysis of three trials which measured blood pressure they found a statistically significant reduction in both systolic and diastolic blood pressure. They suggested the results should be treated with some caution due to the small number of trials contributing to each analysis.[70]

Dyslipidaemia (an abnormal amount of lipids such as triglycerides, cholesterol and/or fat phospholipids in the blood) is a significant cardiovascular risk factor. A 2016 study investigated the beneficial effects of green tea on cardiovascular risk factors, specifically low-density lipoprotein (LDL) cholesterol levels. Serum LDL cholesterol levels were significantly lower in the green tea consuming participants.[71]

Daily supplementation with 379mg of green tea favourably influences blood pressure, insulin resistance, inflammation and oxidative stress, and lipid profile in patients with obesity-related hypertension. In a double-blind, placebo-controlled trial, 56 obese, hypertensive subjects were randomised to receive a daily supplement of one green tea capsule for three months. After three months of supplementation, both systolic and diastolic blood pressures had significantly decreased along with considerable reductions in fasting serum glucose and insulin levels and insulin resistance. Supplementation also contributed to significant decreases in the total and low-density lipoprotein cholesterol and triglycerides, but an increase in high-density lipoprotein cholesterol.[72]

A recent systematic review of 31 randomised controlled trials found there is limited evidence that regular consumption of green tea in amounts of at least 0.6 to 1.5 litres per day may increase plasma antioxidant capacity (AC) and reduce lipid peroxidation (especially oxidation of LDL). This may contribute to the protection against cardiovascular disease and different types of cancer. Beneficial effects seem to be more likely in participants exposed to oxidative challenge.[73]

Some animal studies suggest that green tea might protect against the development of coronary heart disease by reducing blood glucose levels and body weight. However all this data is based on middle-aged animal populations, not elderly populations, whose nutritional status tends to be more

adversely influenced by age-related biological and socioeconomic factors.[74,75]

Weight Loss, Diabetes and Metabolic Activity

In studies dealing with weight control, metabolic syndrome and diabetes beneficial effects have been observed in individuals consuming three to four cups of tea daily.[76]

Positive effects of green tea supplementation have been observed particularly in the prevention and control of type 2 diabetes and in recent years there are a considerable number of randomised controlled trials to suggest that green tea does reduce body weight in the short term and have favourable effects on body composition. There is also growing evidence for using green tea in the prevention and treatment of obesity and coexisting diseases. Clinical study observations have included moderate weight loss, reduction in waist circumference and improvement in metabolic parameters and it has been suggested that green tea may be helpful when combined with an exercise program. The wide disparity in green teas, green tea extracts and dosage protocols hampers the pooling of results, in meta-analyses, in a meaningful way.[77,78]

In 2018 matcha green tea drinking was found to enhance exercise-induced fat oxidation in females. Researchers examined the effect of matcha green tea drinks on metabolic, physiological and perceived intensity responses during brisk walking. Thirteen females consumed three drinks (each drink made with 1g of matcha) the day before, and one drink two hours before the 30 minute walk.[79]

A small intervention study of 45 elderly patients with metabolic syndrome found that drinking three cups of green tea (1g sachets) a day for 60 days significantly reduced weight, waist circumference and BMI compared to placebo.[80]

The results of recent randomised controlled trial with 46 obese participants confirm the beneficial effects of green tea extract supplementation on body mass index, lipid profile, and total antioxidant status in patients with obesity. Green tea extract (379mg a day) or placebo was given over three months and the supplemented group had a reduction in BMI, waist circumference, total and LDL-cholesterol, triglycerides and glucose. The green tea extract group also saw an increase in antioxidant levels and zinc, HDL-cholesterol and magnesium, although iron levels were lower than the placebo group.[81]

A recent double-blind, placebo-controlled trial with 36 overweight or obese women included dietary changes and resistance training over a four week period. They reported significant increases in resting metabolic rate, lean body mass and strength and significant reduction in waist circumference, body fat and triglycerides when combining green tea with resistance training compared with placebo and resistance training only.[82]

An inverse relationship among habitual green tea consumption, percent body fat, and body fat distribution was found in Taiwanese adults, especially for those who have maintained the habit of tea consumption for more than 10 years.[83]

Regular Chinese green tea consumption is protective for diabetic retinopathy a 2015 study found. A case-control study investigated the association between regular green tea consumption and the risk of diabetic retinopathy in type 2 diabetic patients in a tea-growing area of China. One hundred diabetic retinopathy patients were matched by age and sex to 100 diabetic controls. A regular green tea drinker was defined as someone who drank green tea every week for at least one year. Diabetic patients who had regularly drunk Chinese green tea every week for at least one year in their lives had a diabetic retinopathy risk reduction of about 50% compared with those who had not.[84]

A recent meta-analysis of 17 trials reported significant lowering of fasting glucose concentrations compared with controls. Subgroup analysis found that green tea lowered fasting glucose in those at risk of metabolic syndrome but not in healthy subjects. In further analysis the higher-quality trials also showed green tea significantly reduced fasting insulin.[85]

The conclusion that green tea, when consumed on a regular basis, is beneficial to health and could reduce the risks of major metabolic syndrome including obesity, diabetes and cardiovascular diseases seems to have been well established in a cohort study in Japan. A one-third risk reduction of developing type 2 diabetes mellitus was found in subjects consuming six or more cups of green tea on a daily basis compared with those consuming

only less than one cup per week.[86]

Nonalcoholic fatty liver disease (NAFLD) is a constellation of progressive liver disorders that are closely related to obesity, diabetes, and insulin resistance. A recent review presented the experimental evidence demonstrating the hepatoprotective properties of green tea and its catechins and the proposed mechanisms by which these targeted dietary agents protect against NAFLD.[87]

Immune Activity

Accumulating evidence has revealed green tea's immunomodulating effect. Several types of immune cells, in both the innate and adaptive immune systems, are known to be affected in varying degrees by green tea. Among them the dramatic effect on T cell functions has been repeatedly demonstrated, including T cell activation, proliferation, differentiation and production of cytokines. In particular dysregulated T cell function with respect to different subsets of CD4(+) T cells is a critical pathogenic factor in the development of autoimmune inflammatory diseases. Consistent with these findings studies using animal models of autoimmune diseases have reported disease improvement in animals treated with green tea.[88]

Antimicrobial Activity

The precise antimicrobial spectrum of tea is difficult to define due to variation in the methods of testing that have been used. Antibacterial effects of tea have been demonstrated against a number of microorganisms including *Staphylococcus aureus, Vibrio cholerae, Escherichia coli, Shigella* spp., *Salmonella* spp., *Bacillus* spp., *Klebsiella* spp. and *Pseudomonas aeruginosa*. Teas and tea ingredients seem to have both bactericidal and bacteriostatic actions. Antiviral effects of green tea have been demonstrated against the influenza virus, as well as against the *Herpes simplex* virus, tobacco mosaic virus, enterovirus, rotavirus, Epstein Barr virus, HIV virus. Antifungal effects of tea have been reported against *Candida albicans, Trichophyton mentagrophytes* and *Trichophyton rubrum*.[89] Antimalarial properties have been shown *in vitro* with a crude extract of green tea strongly inhibiting Plasmodium falciparum growth.[90]

The first documented report of an antibacterial action of tea was made in 1906 when McNaught, a British Army surgeon, showed that tea killed the causal organisms of typhoid fever *(Salmonella typhi)* and brucellosis *(Brucella melitensis)*.[91]

Green tea has a direct antimicrobial effect *in vitro* on *Streptococcus mutans*, the main cause of dental caries. It also seems to inhibit the attachment of the bacteria to oral surfaces.[92] In a recent randomised controlled trial 66 healthy subjects rinsed with 40mL of a green tea extract for one minute three times a week, and at the end of four and seven days there was a significant reduction in *Streptococcus mutans* and *lactobacilli* in the green tea group.[93]

A recent observational study of 2,663 Japanese elementary students (aged between six and 12 years old) suggests that the consumption of one to five cups of green tea per day may prevent influenza infection. Green tea is known to contain antiviral components that prevent influenza infection. A limited number of adult clinical studies have been undertaken but there is a paucity of clinical evidence concerning children.[94]

The possibility that green tea may affect the gut microbiome has been studied in animal models and humans. For example *in vivo* green tea powder feeding affected gut microbiota and reduced the levels of body fat, hepatic triglyceride and hepatic cholesterol and the reduction was correlated with the amount of *Akkermansia* and/or the total amount of bacteria in the small intestine. The abundance of *Akkermansia muciniphila* has been shown previously to be increased in prebiotic treated mice. Changing gut microbiota, for example by the administration of *Saccharomyces boulardii*, has also been shown to reduce hepatic steatosis, low grade inflammation and fat mass in obese and type 2 diabetic mice. In humans green tea consumption has been reported to decrease the abundance of *Clostridium* species and increase the abundance of the *Bifidobacterium* species in fecal samples. Increase of intestinal *Bifidobacterium* by a prebiotic (oligofructose) has been shown previously to decrease biomarkers for diabetes in mice. These results suggest the possibility that tea may alleviate metabolic syndrome by enriching the probiotic population in the intestine. However a recent study in humans indicated that long-term green tea consumption did not change the gut microbiota. More studies in this

area with green tea preparations are needed.[95]

As mentioned above a great number of *in vitro* and *in vivo* studies showing the influence of dietary polyphenols on gut-inhabiting bacteria have been published in recent years. Although *in vitro* assays facilitate experimentation caution must be taken in extrapolating results to *in vivo* and human clinical situations as many factors are acting upon this process. In general, in both *in vitro* and *in vivo* studies, polyphenols or polyphenol-rich sources have been shown to influence the relative abundance of different bacterial groups within the gut microbiota, reducing numbers of potential pathogens, including *C. perfringens* and *C. histolyticum*, and certain Gram-negative *Bacteroides* spp. and enhancing mainly beneficial *Clostridia*, *bifidobacteria* and *lactobacilli*. A better understanding of the interaction between dietary polyphenols and gut microbiota through the emerging advances in high-throughput meta-genomic, transcriptomic, and proteomic approaches, would be essential in order to identify genes and micro-organisms involved in polyphenol (in) activation and conversion and thus, to elucidate the implications of diet on the modulation of microbiota for delivering health benefits.[96]

A small clinical study in Japan demonstrated that a green tea preparation was able to positively affect intestinal dysbiosis in nursing home patients by raising levels of *lactobacilli* and *bifidobacteria*, lowering levels of *Enterobacteriaceae*, *Bacteroidaceae* and *Eubacteria*, and decreasing odorous compounds. Levels of pathogenic bacterial metabolites were also decreased. A further study found that supplementation with tea catechins produced favourable improvements in the participant's bowel conditions, as evidenced by a reduction of faecal moisture, pH, ammonia, sulphide and oxidation-reduction potential. In both trials the dose was 300mg/day of tea catechins which is equivalent to about six cups of green tea.[97,98]

Green tea extracts were evaluated for their effect in inhibiting the growth of pathogenic bacteria isolated from farm animals, their effect on improving intestinal microflora balance and their effect in preventing digestive and respiratory organ diseases in calves. Green tea showed moderate and wide spectrum inhibitory effects on the growth of pathogenic bacteria, including seven strains of *Staphylococcus* spp., seven strains of *Streptococcus* spp., one strain of *Corynebacterium* suis, 19 strains of *Escherichia coli*, and 26 strains of *Salmonella* spp. Feed containing green tea maintained high faecal counts of *Bifidobacterium* spp. and *Lactobacillus* spp., and decreased *Clostridium perfringens*, which improved microflora balance and decreased the frequency of diarrhoea in transported calves. A decrease in the number of calf deaths was also observed, due to the effect of green tea in the prevention of digestive and respiratory organ diseases in calves while nursing.[99]

Cognition and Brain Function Activity

A 2017 review presented evidence that green tea influences psychopathological symptoms (e.g. reduction of anxiety), cognition (e.g. benefits in memory and attention) and brain function (e.g. activation of working memory seen in functional MRI). The effects of green tea cannot be attributed to a single constituent of the beverage. This is exemplified in the finding that beneficial green tea effects on cognition are observed under the combined influence of both caffeine and l-theanine, whereas separate administration of either substance was found to have a lesser impact. The researchers reviewed and assessed 21 studies, four of which were randomised controlled trials, 12 cross-over studies, four were cross-sectional studies and one was a cohort study.[100]

Higher consumption of green tea may confer protection against depression. In a cross-sectional study in two workplaces in north-eastern Kyushu, Japan a total of 537 men and women aged 20 to 68 years were questioned. Higher green tea consumption was associated with a lower prevalence of depressive symptoms. Compared with participants consuming less than one cup a day, those consuming more than four cups of green tea a day had a 51% significantly lower prevalence odds of having depressive symptoms.[101]

Long-term green tea ingestion improves antioxidant systems and activates cyclic AMP response element-binding (CREB) *in vivo* leading to neuroprotection. The same researchers previously found that prolonged consumption of green tea protected proteins and lipids against oxidation as

well as improving spatial memory during aging *in vivo*.[102]

Green tea is effective in enhancing learning and memory *in vivo* indicating that it may serve useful in reversing age-related deficits.[103]

Chelating Activity

Green tea may be useful in management of risk factors in patients with β–thalassemia major, an inherited chronic haemolytic (abnormal breakdown of red blood cells) anaemia. A 2017 study found that green tea consumption had favourable effects on iron status and oxidative stress which are the main factors in the development of β–thalassemia major. The researchers said green tea's metal binding activity suggests that it could be used as a protective agent in pathological disorders caused by oxidative stress in iron overload conditions. They also said the standard chelating drugs have noticeable side effects whereas green tea could be used with a high degree of safety. The objectives of this study were to examine the effects of green tea consumption on serum iron, ferritin and transferrin saturation and antioxidant status in β–thalassemia patients. 52 people with β–thalassemia major drank green tea (2.5g tea bag infused for 12 minutes in 150mL hot water) three times per day, immediately after meals, for eight weeks. Green tea significantly decreased serum levels of iron, ferritin and malondialdehyde and increased total antioxidant capacity.[104]

A 2017 *in vivo* study showed that green tea improves iron overload induced hepatotoxicity, apoptosis and oxidative stress. It does this via inhibition of hepatic iron accumulation, improving the liver's antioxidant capacity and down regulating serum hepcidin as well as reducing the release of apoptotic related proteins. Iron overload toxicity is associated with chronic liver diseases which leads to hepatic fibrosis and subsequently cancer through oxidative stress and apoptotic pathways.[105]

Dermatological Activity

There have been an increasing number of studies and trials investigating green tea and its extracts in the treatment of various dermatological diseases. Many studies are promising and suggest the use of green tea as an effective therapeutic option in chronic, infectious, inflammatory and hair disorders as well as a preventive tool not only against skin aging but also skin cancer. However, to date there are only a few studies on the use of green tea extracts with double-blind, randomised approaches and large patient numbers. More studies are required in order to be able to determine the true efficacy of green tea derived treatment approaches in most dermatological diseases as well as their long-term safety and tolerability. The epidemiologically and experimentally observed antioxidant, anticarcinogenic and anti-inflammatory effects of green tea have led to the implementation of green tea extracts in multiple therapeutic applications both in dermatological and cosmeceutical preparations. For external genital warts a topical ointment with green tea extracts was licensed in the USA in 2010, and recently also in Europe. Although oxidation reactions are essential for life they can also be damaging. In the skin, oxidative stress has been linked to inflammation, photo damage, cancer and skin aging. As a logical consequence all living organisms maintain complex systems of multiple types of antioxidants to protect their cells from oxidative damage which have been increasingly discovered as potential targets in the development of new treatments.[106]

Indications

- Cancer prevention and prevention of recurrence, cancer therapy adjuvant
- Cardiovascular protection, hypertension, hyperlipidaemia, hypercholesterolemia, reducing atherosclerosis and thrombosis
- General antioxidant therapy
- Weight loss, Small Intestinal Bacterial Overgrowth (SIBO), Irritable Bowel Syndrome (IBS), intestinal dysbiosis, ulcerative colitis
- General anti-inflammatory therapy for arthritis, osteoporosis and other inflammatory diseases
- Liver disease, renal disease, fibrosis of pancreas and liver, diabetes
- Chelation therapy adjuvant especially iron
- Infections, influenza, allergic rhinitis
- Dementia, cognitive impairment, depression
- Topically used for genital warts, gingivitis, sunburn protection, skin aging, bags under the eyes, athlete's foot

Energetics

Sweet and bitter with cooling properties.

Use in Pregnancy

While dietary intakes appear safe, excessive use is not recommended due to caffeine content.

Contraindications

Considered safe and nontoxic as a tea in moderate amounts.

Drug Interactions

Avoid with bortezomib (an anticancer medication), ephedrine and nadolol (used to treat high blood pressure). Caution with amphetamines, anticoagulant/antiplatelet (such as warfarin) drugs, clozapine (psychiatric medication), hepatotoxic drugs, lithium, monoamine oxidase inhibitors (MAOIs, antidepressants), phenylpropanolamine (used as a decongestant), theophylline (used to manage the symptoms of asthma and other lung conditions) and verapamil (used to treat high blood pressure). Monitor with alcohol, antidiabetic drugs, antifungal agents, cimetidine (used to treat heartburn), central nervous system depressants, central nervous system stimulants, disulfiram (used to treat alcoholism), fluvoxamine (a selective serotonin reuptake inhibitor (SSRI) antidepressant), iron, oral contraceptives and quinoline antibiotics. There is a theoretical beneficial interaction with doxorubicin (a chemotherapy medication).

Administration and Dosage

Liquid Extract:	1:2
Alcohol:	55%
Weekly Dosage:[107]	20 to 60mL

When considering green tea beverage the desirable intake is three to five cups per day (up to 1200mL per day).[115] However the dose varies depending on the indication it is being used for. Some research suggests eight to 10 cups of green tea per day are required for effects. It is likely that the dose also depends on the quality of the green tea. For reduced risk of cancers: five or more cups daily. For cardiovascular disease protection: 3 to 10 cups daily.[108]

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