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Review Article

Biological potential and mechanisms of Tea's bioactive compounds: An Updated review

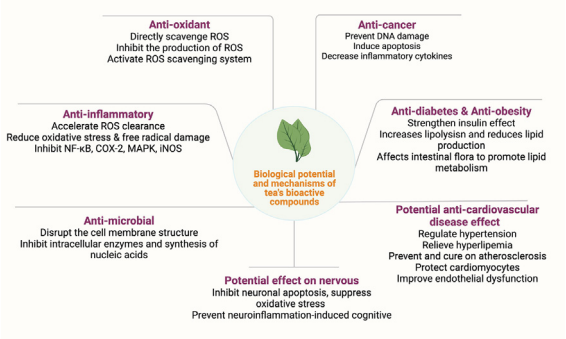
Qiaoxian Luo [a,1], Longbiao Luo [a,1], Jinmin Zhao [b], Yitao Wang [a,*], Hua Luo [a,b,*]

[a] Macau Centre for Research and Development in Chinese Medicine, State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao, 999078, PR China
[b] College of Pharmacy, Guangxi Medical University, Nanning, 530021, PR China

HIGHLIGHTS

- Updated the research progress of the tea's bioactivities and its health functions.
- Provided an overview of the main chemical substances of tea and the pharmacological action.
- Summarized the potential risk of tea and provide the suggestion of the future research and using direction.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Tea (Camellia sinensis) has a rich history and is widely consumed across many countries, and is categorized into green tea, white tea, oolong tea, yellow tea, black tea, and dark tea based on the level of fermentation. Based on a review of previous literature, the commonly recognized bioactive substances in tea include tea polyphenols, amino acids, polysaccharides, alkaloids, terpenoids, macro minerals, trace elements, and vitamins, which have been known to have various potential health benefits, such as anticancer, antioxidant, anti-inflammatory, anti-diabetes, and anti-obesity properties, cardiovascular protection, immune regulation, and control of the intestinal microbiota. Most studies have only pointed out the characteristics of tea's bioactivities, so a comprehensive summary of the pharmacological characteristics and mechanisms of tea's bioactivities and their use risks are vital.

Aim of Review: This paper aims to summarize tea's bioactive substances of tea and their pharmacological characteristics and mechanisms, providing a scientific basis for the application of bioactive substances in tea and outlining future research directions for the study of bioactive substances in tea.

Abbreviations: ACE, acetaminophen; AD, Alzheime's disease; AMPK, AMP-activated protein kinase; AngII, angiotensin II; Ara, arabinose; AS, atherosclerosis; CAT, catalase; COX-2, cyclooxygenase-2; CVB3, coxsackievirus B3; DW, dry weight; EC, (-)-epicatechin; ECG, (-)-epicatechin gallate; EGC, (-)-epigallocatechin; EGCG, (-)-epigallocatechin gallate; ERK1/2, extracellular signal-regulated kinase 1/2; Gal, galactose; GalA, galacturonic acid; Glc, glucose; GluA, glucuronic acid; GSH-Px, glutathione peroxidase; HNSCC, head and neck squamous cell carcinoma; HSPs, heat shock proteins; ICAM-1, intercellular adhesion molecule-1; IGFBP-3, IGF-binding protein-3; iNOS, inducible nitric oxide synthase; LOX, lipoxygenase; Man, mannose; MAPK, mitogen-activated protein kinase; NANO, nanoparticles; NMSC, Non-Melanoma Skin Cancer; PD, Parkinson's disease; Rha, rhamnose; Rib, Ribose; ROS, oxygen species; SOD, superoxide dismutase; TFDG, theaflavin-3,3′-digallate; TFs, theaflavins; TRF2, repeat-binding factor 2; TRs, thearubigins; VacA, vacuolating cytotoxin A; vitamin B1, thiamine; vitamin B11, folic acid; vitamin B2, riboflavin; vitamin B3, pantothenic acid; vitamin B5, niacin; vitamin C, ascorbic acid; vitamin P, catechin and flavonoids; Xyl, xylose; ε-PL, ε-poly.

* Corresponding authors.
E-mail addresses: ytwang@um.edu.mo (Y. Wang), hualuo@um.edu.mo (H. Luo).
[1] These authors contributed equally to this work.

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Key Scientific Concepts of Review: This review summarizes the main biologically active substances, pharmacological effects, and mechanisms and discusses the potential risks. It may help researchers grasp more comprehensive progress in the study of tea bioactive substances to further promote the application of tea as a natural bioactive substance in the medical field.

Contents

Introduction

Tea (Camellia sinensis) has been a part of human culture for thousands of years and remains a staple drink in many countries today[1]. In addition to being enjoyed as a beverage, tea has also been used in traditional Chinese medicine due to its beneficial active components. The statistical data show that regular drinking of tea can stimulate people's minds. Nearly 3 billion people in more than 160 countries around the world have the habit of drinking tea. According to records, tea as an herbal medicine can be traced back to the Tang and Song Dynasties in China. Tea infusion was used to brew herbs to produce Chinese medicine decoction, which became a tea-based treatment method. This article categorizes tea into six groups based on their processing methods and sensory qualities: green tea, white tea, yellow tea, oolong tea, black tea and dark tea [2,3] (Fig. 1A). As a natural herb, tea's primary components are tea polyphenols, amino acids, alkaloids, sugars, proteins, pectin, aromatic substances, enzymes, and organic acids. Previous research has reported that tea contains beneficial active components with various medical benefits, including anticancer, antioxidant, anti-inflammatory, antibacterial, cardiovascular protection, anti-sugar, and antiobesity properties[4–8]. To date, the health advantages of tea have been the subject of much study, but the previous studies have focused on a single aspect and many practical difficulties are met in the research process. Thus, this paper aims to provide a comprehensive review of the main bioactivities and their pharmacological mechanisms of tea, focusing on exploring the mechanisms of its healthful properties.

Bioactive substances of tea

After the production process, the six types of tea can be classified by their different component contents. Generally, according to the degree of oxidation of polyphenols, green tea is nonfermented tea and its color is green. White tea is a slightly fermented tea, yellow tea is a lightly fermented tea, oolong tea is semifermented, and black tea and dark tea are fully fermented[9]. Although black tea and dark tea are both called full fermentation tea for the high degree of oxidation of polyphenols, black tea generally has a golden yellow surface, while dark tea has a black color (Fig. 1A). To be precise, black tea is produced through endogenous enzymatic fermentation, using buds and leaves as raw materials, while dark tea is fermented by extraneous microorganisms with a strong aroma and can break down fat-cell stores and eliminate cellulite. This results in the representative catechin oxidation products, theaflavins, and thearubigins, which cannot be detected in dark tea[3,9–11]. Through literature review and data search, it is known that tea contains more than 500 chemical compounds and more than 450 organic compounds, including polyphenols, alkaloids, terpenoids, flavonoids, amino acids, vitamins, etc. [12]. Among these compounds, polyphenols, amino acids, polysaccharides, alkaloids,

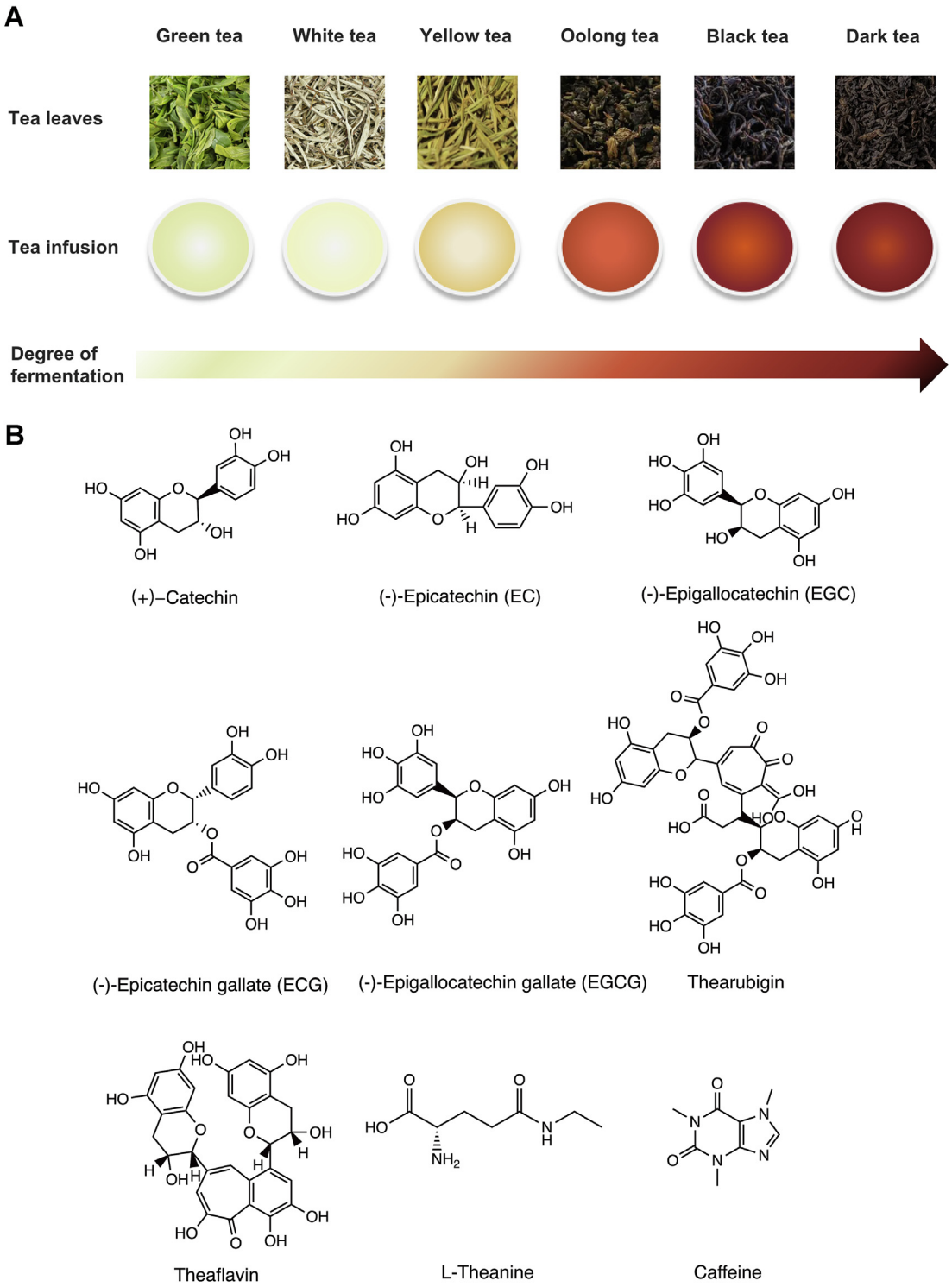

Fig. 1. (A) The general tea colors and fermentation situation of six types of tea; (B) The chemical compounds of tea's main bioactive substances.

macro minerals, trace elements and vitamins are common bioactive substances (Fig. 1B) [13–15].

Polyphenols

The common term for polyphenols in tea is tea polyphenols. Polyphenols comprise catechins, flavonoids, anthocyanins, and phenolic acids and make up approximately 15 % to 35 % of the dry weight of tea. It is the most significant bioactive component in tea. Catechins account for 70 % of tea polyphenols and are the central active part of tea[16]. The flavonoid compounds distributed in tea mainly exist in the form of flavonols, flavanols and anthocyanins[17]. Additionally, various phenolic acids are present in fresh tea, which can exist alone or combine with a molecule of sugar to form hydrolyzable tannins [18].

Tea polyphenols can be divided into (-)-epigallocatechin gallate (EGCG), (-)-epicatechin gallate (ECG), (-)-epigallocatechin (EGC) and (-)-epicatechin (EC). In black tea, the main compounds of tea polyphenols include theaflavins and thearubigins[16,19] (Table 1). At the same time, tea contains an enzyme called polyphenol oxi-

Table 1
The phytochemical contents in six typical teas from six different categories (mg/DW).

Phytochemicals	Green Tea (Dianqing Tea)	Black Tea (Dianhong Congou Black Tea)	Oolong Tea (Tieguanyin Tea)	White Tea (Gongmei White Tea)	Yellow Tea (Junshan Yinzhen Tea)	Dark Tea (Fuzhuan Brick Tea)
Catechin	1.315 ± 0.084	ND	0.775 ± 0.052	ND	1.366 ± 0.043	4.930 ± 0.240
EC	5.970 ± 0.210	0.796 ± 0.047	13.723 ± 0.216	ND	6.196 ± 0.178	10.357 ± 0.268
EGC	13.094 ± 0.256	8.479 ± 0.500	139.854 ± 1.075	8.419 ± 0.143	13.661 ± 0.196	23.430 ± 0.375
ECG	35.395 ± 0.568	2.583 ± 0.077	6.471 ± 0.235	3.144 ± 0.123	30.491 ± 0.101	10.881n ± 0.105
EGCG	59.354 ± 1.131	0.539 ± 0.013	23.663 ± 0.308	6.010 ± 0.083	50.777 ± 0.224	10.885 ± 0.259
Theaflavin	ND	0.526 ± 0.019	ND	ND	ND	0.480 ± 0.008
Caffeine	39.764 ± 0.382	35.283 ± 0.340	14.842 ± 0.167	27.466 ± 0.059	41.457 ± 0.322	27.075 ± 0.166

Notes: DW, dry weight; ND, not detected. Dianqing tea, Dianhong Congou black tea, Tieguanyin tea, Gongmei white tea, Junshan yInzhen tea and Fuzhuan brick tea are the six representative teas from six categories.

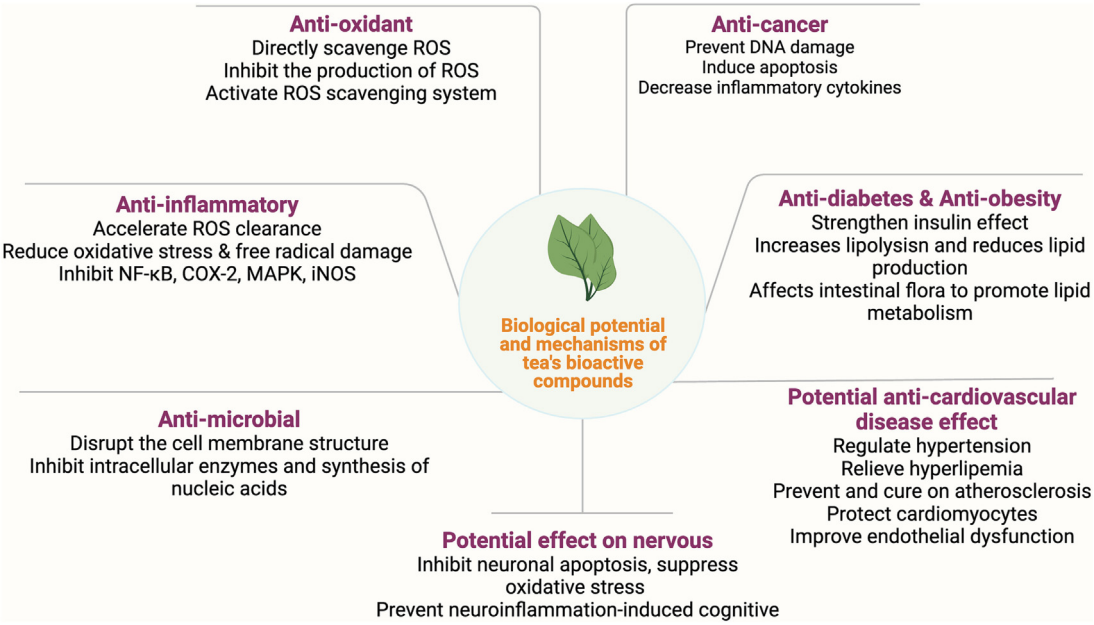

Fig. 2. The main mechanisms of the potential pharmacological action of tea (anticancer, antioxidant, anti-inflammatory, antimicrobial, anti-cardiovascular, anti-diabetes, anti-obesity and the effect on the central nervous system) are summarized.

dase, which has poor thermally stable and enzyme activity retention[20]. By using high temperatures to destroy the polyphenol oxidase activity in fresh tea leaves in a short period and inhibiting the enzymatic oxidation of polyphenols, the contents can form the color, aroma, taste, and other quality characteristics of tea without enzymatic action [21]. This also explains why black tea and other teas do not have green tea's superior antioxidant qualities.

Many studies and clinical cases have evidence to support that tea polyphenols show good antioxidant, anti-inflammatory, anti-cardiovascular disease, anti-obesity, anti-diabetic and other properties [22–24]. For instance, strong evidence links free radicals to diseases, such as atherosclerosis, emphysema, and cancer [24–27], and tea polyphenols are indicated to have the ability to prevent and treat various ailments by neutralizing harmful free radicals and controlling the function of enzymes in the body. In addition, computer simulation showed that tea polyphenols may have treatment effect on COVID-19 through the targets of 3CLpro, RdRp, HE, Plpro, 2′-O-Mtase, Nsp13, RBD, ACE2 receptor and GRP78 [28]. Therefore, tea polyphenols are described as a vital active substance that benefits human health.

Amino acids

Tea has 26 different types of amino acids, including 20 kinds of protein amino acids and 6 kinds of nonprotein amino acids (Supplementary Fig. 2) [29]. Some protein amino acids are important factors in the volatilization of tea aroma. For example, phenylalanine has a rose-like aroma, and alanine and glutamic acid have a floral aroma. Among the nonprotein amino acids, L-theanine is a special amino acid in tea and is rare in general plants. A sweet flavor can be generated by L-theanine, but the flavor is decreased during tea fermentation. In general situation, the L-theanine content varies with tea varieties and parts, is similar to the brain-active substances glutamine and glutamic acid in chemical structure and accounts for 1 %-2 % of the weight of dry tea [30]. Tea amino acids have significant biological activity and can regulate a variety of physiological functions[31]. Especially in neuroprotection, amino acids in tea can alleviate neural fatigue, improve memory [32], protect cerebral vessels, and have potential neuroprotective effects on neurotoxin damage related to Parkinson's disease (PD) and Alzheimer's disease (AD)[24,33,34].

Polysaccharides

Another bioactive component in tea is polysaccharide, which often combines with protein to form an acidic polysaccharide or acidic glycoprotein. Polysaccharides have good biological activities, such as biodegradability, nontoxicity and biocompatibility[35], and can be used to prepare nanocarriers. The active polysaccharides in tea are generally water-soluble polysaccharides with a content of

1.5 %-13 %, mainly composed of glucose (Glc), galactose (Gal), arabinose (Ara), rhamnose (Rha), xylose (Xyl), galacturonic acid (GalA), mannose (Man), ribose (Rib) and glucuronic acid (GluA) [36,37]. Unlike the amounts of tea polyphenols in tea, the amount of polysaccharides in tea can rise as raw tea matures, and this is a distinct phenomenon. The structural characteristics of tea polysaccharides, including their chemical composition, molecular weight, glycosidic linkages, and orientation, all impact their biological activity. Black tea polysaccharides contain many low molecular weight components, and their biological activity is higher than that of green tea polysaccharides and oolong tea polysaccharides [38,39]. For example, the tea polysaccharide composition with low polyphenol content has higher antioxidant activity than the tea polysaccharide composition with high polyphenol content. Combining with selenium can significantly improve the antioxidant activity of polysaccharides. According to studies, tea polysaccharides may contribute to the antioxidant[40], immune regulation[41,42], anticancer, antidiabetic[43] and antiobesity effects[44–46]. Therefore, the effective extraction of tea polysaccharides is conducive to fully utilizing tea resources and is of great significance to preventing diseases and promoting human health.

Alkaloids

Tea alkaloids refer to a class of organic compounds with heterocyclic nitrogen structures rich in traditional tea plants. These compounds are mainly purine bases but also contain a small amount of pyrimidine base compounds, including uracil, thymine, cytosine and 5-methylcytosine. One of the key chemical components of tea alkaloids is the purine base, which is mainly found in caffeine (Table 1), theobromine (0.05 %), and theophylline (0.002 %), which are methyl derivatives of xanthine[47,48]. The principal alkaloid in tea is caffeine; it is easily soluble in water and is an important substance in forming a tea taste. Scientific research results have supported that tea alkaloids may have useful effects on the physiological processes, including the circulatory, respiratory, digestive, endocrine, and metabolic systems as well as the central nervous system[46,49–51]. However, excessive intake of caffeine and other tea alkaloids not only easily causes palpitations, tremors, gastrointestinal physiological dysfunction, and high blood pressure adverse reactions but also may cause anxiety, insomnia and other clinical reactions of the central nervous system.

Others

In addition to the above active substances, tea active substances also include terpenoids and some nutritional components (such as mineral elements and vitamins). Terpenoids, mainly monoterpenoids and sesquiterpenes, are the most important metabolites in tea. Terpene volatile compounds determine the aroma of tea, and monoterpenoids dominate (over 60 %) the aroma volatilization of tea, including linalool, geraniol, and nerol[52]. At present, hundreds of terpenoids in tea have been separated and identified through gas chromatography-mass spectrometry (GC–MS). The results showed that different enantiomeric distributions of terpenoids can trigger different aroma characteristics, and the arrangement and combination of terpenoids with different enantiomeric excess values significantly affect the aroma quality and concentration of tea[53]. In addition, terpenoids have various biological activities, including antibacterial, anti-inflammatory, antitumor, antioxidant, analgesic, and antiparasitic potential [54–57].

Tea contains many essential elements for the human body. The macro minerals of tea include sodium, phosphorus, magnesium, calcium, potassium and sulfur. The trace elements of tea are composed of manganese, copper, iodine, selenium, iron, fluorine and zinc[58–62]. The zinc content in tea is relatively high, especially in green tea, with 73 μg of zinc on average per gram of green tea. Black tea contains 32 μg of zinc on average per gram. The iron concentration in tea is typically 123 μg per gram of dry tea, but it is 196 μg per gram of black tea[63,64]. These components are crucial to the physiological processes of humans. Drinking tea is one of the important channels to obtain these mineral elements. The dissolution rate of various minerals in warm water varies, generally approximately 20 %[65]. Compared with general drinks, tea drinking is significant for Se, Mn, Zn, I and Fe[63,66]. Among them, selenium shows important bioactivity in tea, and is reported as a cofactor of many selenium-dependent enzymes to protect cells from oxidative damage.

Moreover, the variety of vitamins in tea[67] can be divided into two categories: water-soluble and fat-soluble. Vitamins that can dissolve in water include ascorbic acid (vitamin C), thiamine (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3) and pantothenic acid (vitamin B5). Vitamins A, D, E, and K are the main components of fat-soluble vitamins[68,69]. Vitamin C is easy to be oxidized in the process of tea making. Vitamin C is partially oxidized under high temperatures during green tea curing and drying. Generally, green tea contains 100 to 500 mg of vitamin C per 100 g. Black tea and green tea are nearly identical in their B vitamin levels. The vitamins that comprise vitamin B complex are B1, B2, B3, B5 and B11. In the process of making tea, more than 90 % of these B vitamins can be dissolved in the tea water. In general, most of the vitamins in tea are indispensable to the human body and can be used against many diseases[70].

Biological and pharmacologic mechanisms

Tea contains many bioactive substances, such as tea polyphenols, amino acids, polysaccharides, alkaloids, terpenoids, macro minerals, trace elements, and vitamins, which have been shown to have various medical benefits due to their biological activities. These benefits include anticancer, antioxidant, anti-inflammatory, antimicrobial, anti-cardiovascular, anti-diabetes, and anti-obesity effects and effects on the central nervous system (Fig. 2). These pharmacological characteristics and mechanisms have been explored and studied widely, suggesting that tea can positively affect the human body.

Anticancer activity

In terms of incidence rate and mortality, cancer is recognized as one of the deadliest diseases in the world. It is estimated that 9.55 million people die of cancer every year[71]. However, finding safe anticancer drugs is still a significant problem for cancer treatment. Natural substances are an excellent alternative to conventional anticancer medications, which have side effects and high costs. With essentially no adverse effects, they can control a variety of important cell signaling molecules. Tea is a natural herbal product with a long history worldwide. Because of its various pharmacological properties and natural, nontoxic effects, it is being studied in various fields of medicine. Especially, the bioactive substances of tea have shown potential anticancer effects[72]. Whether tea is used as a dietary supplement or in combination with other drugs, the anticancer effects of tea have been observed[73]. Tea polyphenols, amino acids, polysaccharides, and other bioactive components achieve anticancer experimental effects in several ways, including antioxidant activity, anti-inflammatory activity, cell cycle control, and other methods to suppress cancer progress[74] (Table 2) *in vitro* and *in vivo*[4,75].

Some *in vitro* experiments have revealed the potential anticancer effects of bioactive compounds in tea. One study showed

Table 2
Potential bioactive effects of tea.

Effects	Details/ Mechanisms	Bioactive substances	*In vitro*/ *In vivo*
Anticancer	Regulation of P53/Bcl-2 signaling pathway[80]	EGCG	*In vitro*
	Induce apoptosis in ovarian cells[230]	Green tea extract	*In vitro*
	Prevent a molecular chaperone that promotes the malignant phenotype from functioning [231]	EGCG	*In vivo*
	Impede the invasion of tumor-associated macrophages and M2 polarization to slow the development of tumors [126]	EGCG	*In vivo*
	Repair the IL2Rcc/Jak-3/Stat-5A signal to guard against PGE2-induced apoptosis in CD4 + T cells [232,233]; Upregulate the expression of PARP, Bax, BIM, and PUMA; activate ATM, CHK1/2, p53, CASP8/3, ASK1, JNK, and c-Jun[234]	Theaflavins	*In vitro* and *vivo*
Antioxidant	Boost the activity of antioxidant enzymes and control the Nrf2 pathway[133]	Flavonoids, Theabrownins, Phenolics, Polysaccharides	*In vitro*
	Adjust the expression of antioxidant enzymes at the mRNA and protein levels[235]	Polyphenols	*In vitro*
	Prevent hepatotoxicity by excessive acetaminophen in mice[236]	Green tea extract	*In vivo*
	Enhance the activity of antioxidant enzymes CAT and SOD; Attenuate Salmonella typhimurium-induced ileal damage by reduce oxidative stress[104]	Polyphenols	*In vivo*
	Destroy radical chain to exert antioxidant capacity[237]	Polysaccharide	*In vitro* and *vivo*
Anti-inflammatory	Reduce inflammation by preventing the release of inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and iNOS[135]	L-Theanine	*In vitro*
	Interfere with NF-κB, MAPKs, and the Notch signaling pathway, preventing the release of inflammatory cytokines and their gene expression[238]	Polyphenols	*In vitro*
	Block NF-κB pathways to make I-κB kinase complex in epithelial cells inactivation[239]	Polyphenols	*In vitro*
	Reduce the generation of pro-inflammatory cytokines brought on by LPS by altering the TLR4-NF-B pathway[240]	EGCG	*In vivo*
	Limit the expression of JNK and p38 MAPK, as well as the activity of LPS-induced TNF-α, IL-1β, and IL-6[241]	Theaflavin	*In vitro* and *vivo*
Antimicrobial	Inhibit the growth and reproduction of many kinds of bacteria and fungi[135,242]	Polyphenols	*In vitro*
	Inhibit intracellular enzymes and the synthesis of nucleic acids, disrupt cell wall and cell membrane[243]	EGCG	*In vitro*
	Prevent vacuolating cytotoxin A (VacA) produced by *Helicobacter pylori*[244]	Catechin	*In vitro*
	Restrict the production of the JNK and p38 MAPK as well as the LPS-induced TNF-α, IL-1β, and IL-6 activities[245]	EGCG	*In vitro*
	Target listeriolysin O to prevent the development of *L. monocytogenes* in macrophages[246]	EGCG	*In vivo*
Potential anti-cardiovascular disease effect	Inhibit oxidation, vascular inflammation, and thrombogenesis[247]	Catechin	*In vitro*
	Increase nitric oxide production and arterial vasodilation[248]	L-Theanine	*In vitro*
	Improve endothelial dysfunction and hypertension by influencing nitric oxide generation and vasodilation[247]	Catechin	*In vivo*
	Decrease ROS production in the blood, and enhance the aorta's endothelium-dependent relaxation[16]	Polyphenols	*In vivo*
	Reduce cardiomyocyte apoptosis by preventing telomere shortening and telomere repeat-binding Factor 2 (TRF2) loss in cardiac cells[249]	EGCG	*In vivo*
Anti-diabetes & Anti-obesity	Increase longevity and reduce fat content reliant on the insulin/IGF-1 signaling pathway and DAF-16/FOXO; Lower AGE levels by controlling the SKN-1/Nrf and MAPK pathway[15]	Dark tea extract	*In vivo*
	Suppress the pentose phosphate pathway, starch, sucrose and methane metabolism, fatty acids synthesis, primary bile acid biosynthesis, and secondary bile acid biosynthesis[250]	Phenolics	*In vivo*
	Regulate the expression of lipid metabolism-related genes and proteins[251]	Dark tea extract	*In vivo*
	Interfere with the circadian cycle, and prevent fat and insulin resistance[252]	Theabrownin	*In vivo*
	Exhibit hypolipidemic activity[253]	Theabrownin	*In vivo*
Potential effect on the central nervous system	Stimulate caspase-dependent and PI3K/Akt signaling Pathways in SH-SY5Y cells[196]	Catechin	*In vitro*
	Downregulate mGluR5 and Homer[254]	Dark tea extract	*In vitro*
	Inhibit iNOS activity to reduce hypoxic-ischemic brain injury[255]	EGCG	*In vivo*
	Control extracellular signal-regulated kinase 1/2 (ERK1/2) and PKC signaling pathways to shield cells from stress-related damage[256]	EGCG	*In vivo*
	Inhibit PC12 cell death to restore mitochondrial dysfunction and dynamics[197]	EGCG	*In vitro and vivo*

that EGCG induced heme oxygenase-1 and suppressors of cytokine signaling-3 to protect against TNF-α-mediated lung inflammation by attenuating oxidative stress, MAPK activation, and STAT-3 and intercellular adhesion molecule-1 expression in A549 cells[76], indicating that the regulation of inflammatory factors by EGCG can prevent and treat cancer to a certain extent. From the perspective of the cell cycle, catechins can inhibit ROS, which is essential to trigger apoptosis and stop the spread of cancer cells. From another aspect, research has shown that EGCG therapy can prevent cancer cell proliferation and apoptosis. EGCG of catechin can induce cancer cell apoptosis and eliminate cancer cell proliferation in the presence of low doses of H_2O_2[77,78]. By preventing Wnt/β-catenin signaling in an HBP1-dependent way, treatment with EGCG decreased tumor cell proliferation and invasiveness (Fig. 3). Inhibiting cell growth, activating caspase-3 and caspase-9 to cause apoptosis, and inducing proapoptotic Bax, Bak, and Bcl-Xs while inhibiting antiapoptotic Bcl-2 and Bcl-X_L were all conducted by EGCG[79,80]. EGCG can reduce the activity of nuclear transcription factor NF-κB by inhibiting the NIK/IKK signaling pathway, which will significantly induce cancer cell apoptosis and inhibit the subsequent development of carcinogenesis[81] (Fig. 3).

For tea polysaccharides, the biological anticancer activity shows minimal side effects in the process. Previous studies have shown that tea polysaccharides can inhibit colitis-related colorectal cancer through the IL-6/STAT3 pathway. Moreover, green tea polysaccharides can inhibit PC-3 cells by inactivating AKT and ERK1/2 signals[82]. Furthermore, research has shown that the potential antitumor mechanism of tea polysaccharide conjugates is mainly

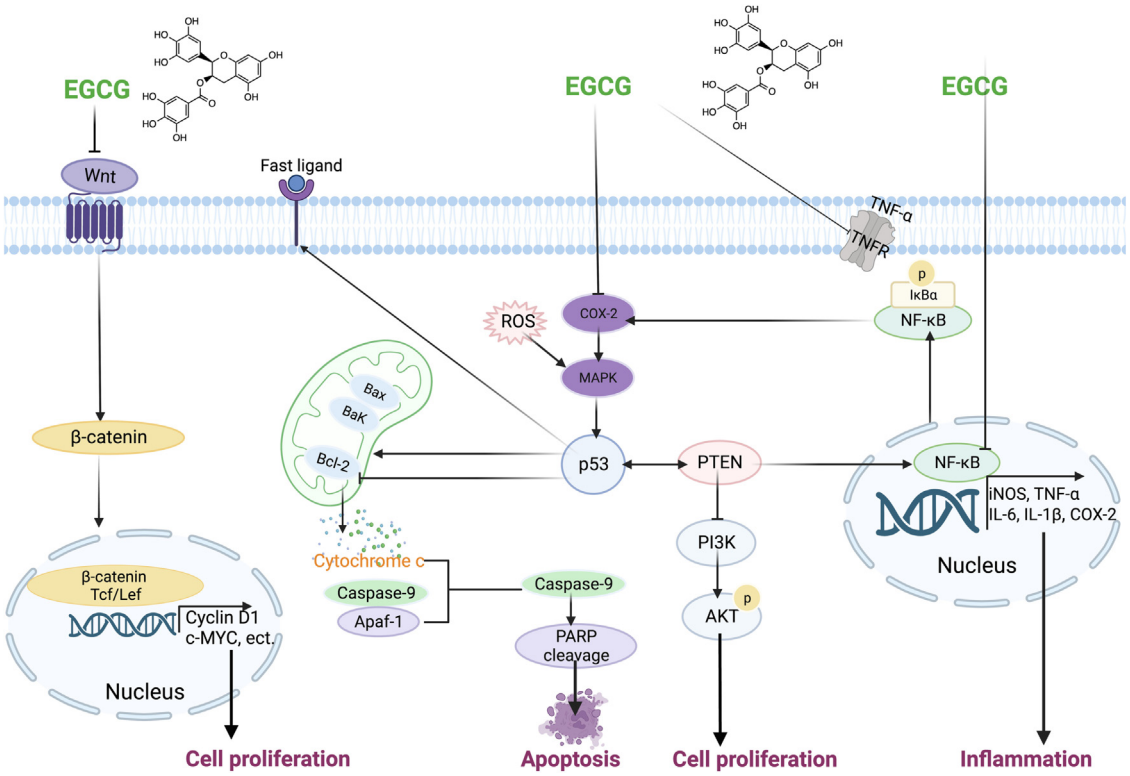

Fig. 3. EGCG is the key bioactive substance for anticancer activity. It can inhibit cell proliferation, induce cell apoptosis and decrease inflammation in cancer cells. By preventing Wnt/β-catenin signaling, EGCG slows the growth of tumors. EGCG can cause apoptosis to prevent tumor growth by activating caspase-3 and caspase-9 and inducing proapoptotic Bax, Bak, and Bcl-Xs while inhibiting antiapoptotic Bcl-2 and Bcl-X_L. EGCG can regulate NF-κB and reduce inflammation to exert anticancer effects.

to directly inhibit tumor cell growth, promote tumor cell apoptosis, or promote early apoptosis of cancer cells by improving the immune system. The immune regulatory effect is one of the important activities of natural plant polysaccharides. Previous studies have shown that tea polysaccharides can exert immune regulatory effects by increasing natural killer cell activity and regulating inflammation-related cytokines[83]. During the growth process of tumor cells, they gradually invade surrounding normal tissues and transfer to other tissues in the body with blood. In this process, glutamate plays a crucial role, and theanine, as a structural analog of glutamate, can competitively inhibit the synthesis of glutathione (GSH) by glutathione, thereby reducing the complexation of GSH with antitumor drugs. This prevents anticancer drugs from being pumped out of tumor cells in complexes with GSH. Therefore, theanine can inhibit the growth and invasion of tumor cells by interfering with the metabolism of glutamate in tumor cells while also significantly increasing the concentration of other anticancer drugs in tumor cells[84]. *In vivo*, green tea polyphenols were added to drinking water in vivo utilizing animal models and the research of TRAMP mice to prevent the growth of prostate cancer and its metastatic lesions[85]. The experimental results suggest that this treatment can reduce the level of IGF-1 and restore the level of IGF-binding protein-3 (IGFBP-3) by reducing the levels of phosphorylated ERK, PI3K and Akt[85,86]. Other studies by the research group also showed similar experimental results. In a mouse colorectal cancer model, drinking EGCG significantly inhibited colorectal precancerous lesions[87]. Another study implied that a combination of theanine and other antitumor chemotherapy drugs could greatly reduce the toxic side effects of chemotherapy drugs. For example, when theanine is combined with idarubicin to treat leukemia, theanine can significantly improve the toxic side effects caused by idarubicin, such as bone marrow growth inhibition and reduced white blood cell count[88].

In addition, the findings of numerous epidemiological and intervention studies research also showed that tea might have relevant potential clinical and noteworthy effects on cancer [89–92]. Seventy men with prostate cancer and 120 healthy individuals of matched age participated in clinical research in Algeria. According to the research, drinking 5 cups of a beverage made from 2 g of green tea leaves each day for six months lowered the risk of prostate cancer and significantly decreased oxidative stress[90]. Caffeine may have a preventive effect against nonmelanoma skin cancer (NMSC), according to the results of epidemiological studies in people of European heritage with NMSC. Meanwhile, black tea drinking may have a lowering impact on the risk of NMSC in Chinese populations. However, it must be noted that the conclusions drawn from these studies are not uniform in nature[93]. Inconsistent findings from experimental and nonexperimental epidemiological research were discovered in an update of Filippin's earlier assessment, offering scant support for a protective impact of green tea consumption on overall cancer risk or specific cancer locations [94]. Kim and Yi reviewed the correlation between cancer risk and tea consumption. According to their research, drinking a large amount of tea was linked to lower rates of leukemia, ovarian cancer, mouth cancer, biliary tract cancer and thyroid cancer. Subsequent investigation indicated a relationship between increased green tea consumption and decreased risk of endometrial, breast, and liver cancer[95,96]. Another finding from a combined study of 8 population-based cohort studies conducted in Japan was that Japanese women who drink modest amounts of tea experience lower rates of total cancer and respiratory death[97]. However, a prospective cohort analysis of five million adult Chinese individuals showed no association between tea consumption and the incidence of all cancers (lung, colorectal, liver, female breast and uterine) among daily tea drinkers who did not smoke or consume excessive alcohol[98,99].

In conclusion, the anticancer effect of tea has been studied in various fundamental studies, but its mechanism of action is still not logically and fully explained, especially in the clinical aspect. It is still critical to further explore the role of tea in cancer prevention and treatment, determine the gap between experimental and clinical results, and improve its bioavailability.

Antioxidant activity

According to epidemiological studies, tea consumption may decrease the risk of chronic diseases, such as diabetes, cardiovascular disease, and cancer, due to its antioxidant activity[100]. Tea has excellent antioxidant activity because it is rich in polyphenols. Among these compounds, catechin compounds have strong antioxidant activity due to the large number of hydroxyl groups in their chemical structure[101,102]. They can provide protons to bind with excess ROS in the body and are oxidized to form phenol oxygen radicals, which are stable due to the catechol structure, thus inhibiting the chain reaction of ROS[103]. Additionally, these compounds can reduce free radicals by activating and increasing the ability of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT)[104] (Table 2). ECG is the most effective free radical scavenger among tea polyphenols, followed by EGCG, EGC and EC[105–107]. In addition, theaflavins (TFs) and thearubigins (TRs) rich in black tea have also been indicated to regulate biomolecules of oxidative damage, the pathway of endogenous antioxidants and mutagens due to their antioxidant ability [108]. Apart from polyphenols, the natural alkaloids found in tea, such as caffeine and theophylline, along with the amino acid L-theanine, have been scientifically shown to exhibit antioxidant properties. These constituents aid in defending against harmful free radicals, offering protection to cells and tissues[109,110]. Interestingly, the antioxidant activity of tea compounds was also temperature dependent, with tea brewed for 5 min at 100 °C having a stronger antioxidant capacity than tea brewed for a shorter time at a lower temperature [31,111].

In vitro and *vivo* experiments mainly focus on the antioxidant effect of tea polyphenols, especially EGCG for its potent antioxidant ability. Tan et al. found that tea catechins regulated the expression of antioxidant enzymes and reduced oxidative stress, thus protecting primary goat hepatocytes *in vitro*[112] (Table 2). Chao et al. found that EGCG reduced the high level of ROS in diabetic oocytes and improved their quality[113]. In addition, Xie et al. found that EGCG cleared ROS through Nrf2 signaling, thus inhibiting apoptosis and ferroptosis in human intestinal epithelial cells and improving intestinal injury induced by radiation[114]. EGCG can protect human skin fibroblasts from UV-induced photoaging through its antioxidant activity and ability to regulate related gene expression[115]. In another study, tea polyphenols were demonstrated to enhance the antioxidant capacity and induce heat shock proteins (HSPs) to protect cardiomyocytes when subjected to heat stress in vivo and *in vitro*[116]. In addition, EGCG ameliorated the CCl_4-driven liver damage by reducing oxidant activity, causing a decrease in MDA and an increase in GSH. The experimental results also indicated that EGCG significantly reduced the expression of TNF-α, NF-κB, IL-1β, and TGF-β genes and downregulated the expression of p-ERK and p-Smad1/2 protein[117]. As mentioned earlier, caffeine and L-theanine also possess antioxidant properties, and research has found that the antioxidant activity of green tea extract is dose-dependent, with the antioxidant activity of three components ranked as follows: tea polyphenols > L-theanine > caffeine[118].

EGCG has been developed as a raw material for many effective nanoparticles as a natural antioxidant with safety and availability in recent years. Yi et al. prepared polyphenol nanoparticles of adjustable size and high activity, which inherit the remarkable properties of EGCG and possess strong antioxidant ability[119]. To enhance the cytocompatibility of EGCG, EGCG and human hair keratin were combined and assembled into nanoparticles (NANOs). This novel nanoparticle effectively prevented cellular oxidative damage and reduced cellular inflammation expression, indicating that NANOs have good antioxidant and anti-inflammatory effects on cells and can be employed in a multitude of diseases associated with oxidative stress[120]. Due to their excellent antioxidant and antibacterial properties, tea polyphenols show great potential in wound healing. Lan et al. successfully fabricated a novel fiber membrane with a core layer of tea polyphenols and a shell layer of ε-poly (ε-PL), which are excellent wound dressings with dual delivery of antioxidant and antimicrobial delivery[121].

Among the multifaceted pharmacological properties attributed to tea, its antioxidant activity stands out as a prominent feature, offering significant therapeutic potential for various diseases. Beyond traditional tea consumption, innovative biomedical research has harnessed the powerful properties of EGCG by transforming it into a novel nanomaterial, thereby improving its bioavailability with promising implications in treating critical illnesses, including cancer.

Anti-inflammatory activity

Inflammation is the first biological response of the immunological system to infection, injury, or stimulation and leads to serious organ dysfunction through the development of oxidative stress and inflammatory damage. The components of functional tea that act against inflammatory processes mainly inhibit the synthesis of various chemokines and proinflammatory mediators. They show great anti-inflammatory activity by regulating mitogen-activated protein kinase (MAPK), inducible nitric oxide synthase (iNOS), lipoxygenase (LOX) and cyclooxygenase-2 (COX-2), inhibiting NF-κB, and reducing the synthesis of ROS[122].

Different kinds of tea have different substance bases and different anti-inflammatory effects. In a review by Huang et al., tea can generally treat inflammatory bowel disease by reducing oxidative stress and free radical damage, modulating inflammatory factors, and regulating signaling pathways and intestinal flora, but the main therapeutic pathways are different for green, black, and dark teas[123]. Wu et al. found that white, green, yellow, oolong, black and dark teas were able to reduce liver damage and dysfunction induced by carbon tetrachloride. Among them, green tea and dark tea were the most effective, but their therapeutic mechanisms differed. Dark tea attenuated liver injury mainly by inhibiting the NF-κB pathway, thus relieving the consequent inflammatory response, while green tea attenuated liver oxidative stress by activating the Nrf2/HO-1 pathway[124]. Hu et al. found that aged Pu-erh tea promoted macrophage M2 polarization by inhibiting inflammatory signaling pathways mediated by intestinal oxidative stress and upregulated tight junction protein (MUC-2, ZO-1, occludin) expression, thereby improving the intestinal immune barrier and reducing intestinal inflammation[125,126] (Table 2).

Tea polyphenols have been shown to have good anti-inflammatory activity and are the main anti-inflammatory component of tea[127,128]. Among the tea polyphenols, EGCG has been a hot spot for research because it has the strongest biological activity [129]. EGCG reduced Hla-induced ROS overproduction and MAPK signaling pathway activation, thereby significantly attenuating NLRP3 inflammasome-associated protein expression in THP-1 cells. EGCG also inhibited Hla-induced inflammasome NLRP3, ASC and caspase-1 protein expression, reducing IL-1β and IL-18 production in damaged mouse liver tissues[130]. When LPS causes systemic inflammation, EGCG shows protective effects against the inflammatory damage mainly through the modulation of Treg and B cells, thus restoring immune homeostasis[131]. Theaflavin

is an important oxidation product of catechins and aggregates during fermentation[22]. Theaflavin can effectively prevent inflammation by inhibiting the expression of COX-2, iNOS and NF-κB and decreasing the induction of TNF-α[132]. According to a recent study, Teng et al. found that theaflavin-3,3′-digallate (TFDG) inhibited the expression of pro-inflammatory factors and matrix-degrading enzymes and protected the extracellular matrix components of chondrocytes. Through Nrf2 signaling pathway activation, TFDG accelerated ROS clearance induced by IL-1β[133] (Table 2). At the same time, TFDG retarded the inflammatory process by inhibiting PI3K/Akt/NF-κB and MAPK signaling pathways[134]. In addition to the well-known tea polyphenols, other active components in tea also have anti-inflammatory activity. L-Theanine has been shown to reduce inflammation by preventing the release of inflammatory cytokines, such as TNF-α, IL-1, IL-6, and iNOS[135] (Table 2). *In vivo* and *in vitro* caffeine can also inhibit inflammation by modulating the MAPK/NF-κB signaling pathway[136–138].

The modulation of inflammation-related effects by functional tea components presents multiple pathways and targets, which work together to exhibit significant anti-inflammatory effects. Therefore, to treat the disease caused by the inflammatory response, functional tea components can be considered for their multiple targets and pleiotropic properties.

Antimicrobial activity

Bacteria and fungi are widespread in nature, and some pose a threat to the physiological health of humans, animals, and plants. The extracts of various kinds of tea have shown antimicrobial activity. Liu et al. reported that extracts from black, oolong, green, and Fuquan (fully fermented) teas had antibacterial activity, while Gram-positive bacteria were more sensitive than gram-negative bacteria. It is noteworthy that green tea extract has the most significant pathogenic inhibitory effect on bacteria[139]. Sasagawa et al. also found that matcha green tea had an excellent inhibitory effect on pneumococci[140]. Among the numerous tea compounds, tea polyphenols have a broad-spectrum antibacterial effect, inhibiting or terminating the growth and reproduction of many bacteria and fungi[141]. Because of special polyphenol hydroxyl groups, tea polyphenols have good antibacterial and antioxidant activity. The polyphenol hydroxyl groups can bind to bacterial cell membrane proteins, change the membrane permeability, and disrupt the cell membrane structure. At the same time, tea polyphenols can also regulate bacterial physiological metabolism and produce growth inhibition, so tea polyphenols exhibit a broad spectrum of antibacterial activity. Tea and its compounds can exert antibacterial effects by inhibiting intracellular enzymes and the synthesis of nucleic acids, disrupting cell walls and membranes [141,142]. In the concentration range of 62.5 to 2000 μg/mL, caffeine exerts inhibitory effects on bacteria, rendering it a potential antimicrobial agent suitable for application in food products [143]. Furthermore, numerous studies have unveiled the notable antimicrobial properties of tea polysaccharides[109,144].

New materials have been developed based on the excellent antibacterial ability of tea polyphenols. To solve the problem of joint replacement failure caused by periprosthetic joint infection, Ren et al. used tea polyphenols to create a unique ultrahigh molecular weight polyethylene implant, which could produce excess intracellular ROS and disrupt bacterial membrane structure and thus possess excellent antibacterial ability[145]. In addition, antioxidant and antibacterial hydrogels with tea polyphenols, polydopamine and polyvinyl alcohol as the main components were prepared and showed tremendous potential in wound healing [146]. Apart from polyphenols, preparing nanocarriers using tea polysaccharides has enhanced antimicrobial activity, showcasing prolonged and sustained antibacterial efficacy[147].

As antibacterial agents with novel resistance mechanisms, tea extracts and tea compounds will serve as alternative antimicrobial chemotherapies aimed at inhibiting the growth of microbes and the spread of antibiotic resistance and may be used in the pharmaceutical, cosmetic and food industries.

Anti-cardiovascular disease

Epidemiological studies and meta-analyses have shown a negative association between tea consumption and cardiovascular disease[148–150]. A comprehensive analysis of recent prospective studies suggests a strong link between green tea consumption and specific cardiovascular mortality rates[151]. The cardiovascular protective effects of tea include hypotension, hypolipidemia, anti-atherosclerosis, protection of cardiomyocytes, anti-myocarditis and improvement of endothelial dysfunction (Fig. 4).

Hypertension is a common chronic disease and a dangerous risk factor for cardiovascular disease, posing a serious risk to human health. Many experiments have shown the modulatory effect of tea on hypertension due to its antioxidant and anti-inflammatory properties. Garcia et al. induced hypertensive rats with the nitric oxide synthase inhibitor and found that short-team green tea treatment could lower blood pressure, improve cardiovascular function and relieve systemic oxidative stress[152]. In addition, green tea could improve the renin-angiotensin-aldosterone system, increase the expression of the sodium–potassium pump, and enhance nitric oxide synthesis in endothelial cells to lower lipids and blood glucose, thus improving hypertension induced by salt [153,154]. Notably, the gut microbiota plays a crucial role in the blood pressure-lowering effects exerted by tea. Ye et al. evaluated the ability of green tea and oolong tea to prevent hypertension in Wistar rats fed a high-salt diet. They found that green tea and oolong tea improved endothelial dysfunction, modulated the levels of oxidative stress, inflammation, and gene expression and prevented the elevation of blood pressure. In addition, green tea and oolong tea supplements could improve intestinal flora disturbance, which may be a potential mechanism for the protective effects of tea[155].

Hyperlipidemia is a key factor triggering cardiovascular disease and tea can protect the cardiovascular system by attenuating hypercholesterolemia, which has been demonstrated *in vivo*. Huang et al. found that dark tea and green tea extracts could improve hyperlipidemia by lowering total cholesterol, triglycerides, and low-density lipoprotein cholesterol levels, increasing fecal bile acids and cholesterol, and enhancing peroxidase and glutathione peroxidase activities[156]. Wen et al. studied the effects of tea polyphenols and EGCG on improving hyperlipidemia. Both reduced body weight, while tea polyphenols effectively reduced serum cholesterol and triglycerides in hyperlipidemic rats[157]. In addition, theabrownin in Pu-erh tea exerts its anti-hypercholesterolemia and anti-hyperlipidemia effects by decreasing intestinal BSH microbes and/or reducing FXR-FGF15 signaling, which is accompanied by increasing gene expression of enzymes in the alternative BA synthetic pathway, producing hepatic chenodeoxycholic acid, activating hepatic FXR, and hepatic lipolysis [158].

Atherosclerosis (AS) is the most general disease of the cardiovascular system and a common risk to human health. Tea polyphenols have been found to have a preventive and curative effect on atherosclerosis[159]. The protective effect of tea on atherosclerosis has also been demonstrated in vivo and *in vitro*. Lu et al. compared Sichuan dark tea with Pu-erh and Japanese green tea to study their effects on atherosclerosis. The results showed that Sichuan dark tea reduced lipid deposition in the aorta, stimulated AMPK pathways, increased lipoprotein lipase and decreased plasma triglycerides to reduce atherosclerosis[160]. Li et al. demonstrated that

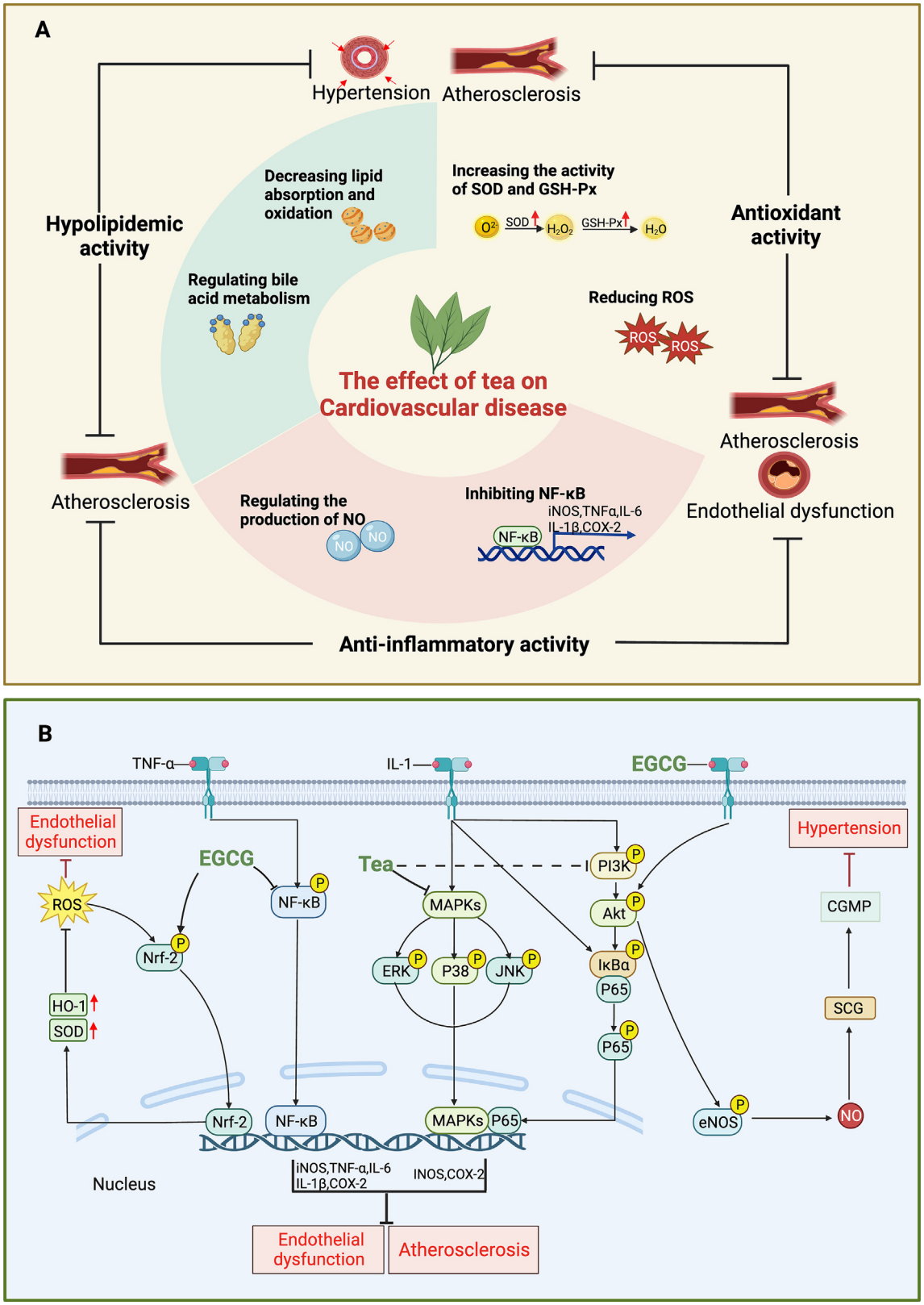

Fig. 4. The effects of tea on the cardiovascular system and its mechanisms. (A) Tea protects cardiovascular health in multiple ways. Tea consumption can improve hypertension by reducing ROS, regulating the production of NO and decreasing lipid absorption and oxidation. At the same time, decreased absorption and oxidation can prevent hyperlipidemia and atherosclerosis. Endothelial dysfunction can be inhibited by tea due to its ability to reduce ROS, inhibit inflammation and regulate the production of ROS. Tea can also alleviate atherosclerosis by reducing ROS and inhibiting inflammation. In addition, tea can regulate intestinal flora to improve hyperlipidemia; (B) The signaling pathways involved in the cardiovascular protective function of tea. EGCG regulates the Nrf-2 pathway to increase the expression of HO-1 and SOD, reduces ROS and thus prevents endothelial dysfunction. Tea and its compounds can also inhibit the activation of the MAPK, NF-κB and PI3K pathways to inhibit the expression of iNOS, TNF-α, IL-6, IL-1β and COX-2 to inhibit endothelial dysfunction and atherosclerosis. EGCG can activate Akt/eNOS/NO pathway to regulate the production of NO and thus prevent hypertension.

ECG could inhibit vascular smooth muscle cell proliferation and migration, reduce the inflammatory response, and stabilize atherosclerosis[161].

In addition, the protective effect of tea on cardiomyocytes has been confirmed. Shibu et al. reported oolong tea's cardioprotective effects and mechanisms under hypoxic conditions. Oolong tea could inhibit JNK-mediated hypertrophic effects, improve innate antioxidant mechanisms, and inhibit caspase-3 cleavage and apoptosis from attenuating 24-hour hypoxia-induced cardiomyocyte loss. Besides, it could also enhance IGFIR/p-Akt-related survival mechanisms to help cells adapt to hypoxic challenges, thus protecting cardiomyocytes[162]. Yin et al. also found that adding 0.2 g/L tea polyphenols effectively reduced heat stress injury to the cardiomyocytes of hens at 38 °C[116]. Moreover, the myocardial protective effect of L-theanine has also been studied. Li et al. reported that L-theanine treatment increased cell viability and superoxide dismutase activities, while decreasing the levels of ROS and NO. Additionally, L-theanine reduced H2O2-induced apoptosis in H9c2 cells[163]. In addition, it has been shown that both theaflavin-3,3'-digallate and EGCG can inhibit angiotensin II-induced cardiomyocyte hypertrophy[164–166].

Endothelial dysfunction, characterized by reduced vasodilation and inflammation, is considered central to the pathogenesis of cardiovascular disease, and has emerged as a key therapeutic area. Some studies have shown that EGCG has an ameliorative effect on endothelial dysfunction and cardiomyocyte inflammation [167]. EGCG reduced inflammatory gene transcription and protein expression in endothelial dysfunction by inhibiting the TNF-α-induced NF-κB signaling pathway. Furthermore, EGCG could block the activation of type II endothelial cells, which is the major regulator of the inflammatory response[168]. He et al. found that EGCG attenuated coxsackievirus B3 (CVB3)-induced myocarditis, significantly inhibited CVB3 replication, and downregulated protein expression levels of coxsackievirus and adenovirus receptors, which are the main receptors for CVB3-infected cardiac myocytes [169]. Liang et al. found that EGCG attenuated oxidative stress by inhibiting ERK1/2, p38MAPK and NF-κB activation in AC16 cardiomyocytes, thereby preventing inflammation and apoptosis [170].

Although the underlying mechanism of the cardiovascular protective activity of tea polyphenols is not yet well understood, tea polyphenols and their main bioactive components have been widely recognized in the prevention and treatment of cardiovascular diseases, with apparent antioxidant, anti-inflammatory, hypotensive, hypolipidemic, intestinal flora regulation, cardioprotective, and other biological activities.

Anti-diabetes and anti-obesity activity

The chronic metabolic condition known as diabetes is largely defined by unusually high blood glucose levels[171]. Type 2 diabetes is caused by the poor response of the body's cells to insulin and can usually be controlled through lifestyle modifications, such as diet and exercise. The natural therapeutic products in tea, flavonoids including EGCG and quercetin, have been shown to have a therapeutic effect on diabetes[172]. A study on the risk of diabetes among Chinese people who drink tea showed that black tea consumption was associated with a 45 % reduction in the risk of diabetes[173]. A prospective cohort study also showed a negative correlation between green tea intake and diabetes, but it was only effective for Japanese women[174].

In addition to epidemiology, experiments have also demonstrated the antidiabetic activity of tea. Li et al. found that EGCG could improve glucose homeostasis in the liver and inhibit the process of gluconeogenesis and fat production. At the same time, EGCG activated PXR/CAR and increased the expression of PXR/CAR-mediated small intestine and liver phase II drug metabolism enzymes[175]. In another study, after supplementing EGCG for 12 weeks, AMPK-α in skeletal muscle was stimulated by restoring GLUT4 and Akt activity expression, making blood glucose and insulin levels drop smoothly[176]. Zhang et al. found that EGCG might ameliorate inflammation, oxidative stress and free fatty acids induced by glucose and palmitic acid to improve insulin resistance by regulating the GLUT2/PGC-1β/SREBP-1c/FAS pathway in HepG2 cells[177]. In addition, EGCG could inhibit adipocyte differentiation and alleviate TNF-α-triggered insulin resistance by inhibiting oxidative stress and regulating mitochondrial function [177]. In addition, quercetin in tea inhibits xanthine oxidoreductase *in vitro* and may be able to reduce blood uric acid in humans. Some experiments have shown that after four weeks of oral quercetin, plasma uric acid concentrations were significantly reduced [178]. In a type 2 diabetic rat model, tea polysaccharides could exert hypoglycemic and hypolipidemic effects in diabetes by modulating gut microbiota and improving host metabolism[179]. The antidiabetic activity of tea has also been shown in clinical studies. It has been reported that green tea can increase adiponectin concentrations in patients with type 2 diabetes and reduce the incidence of diabetes and serum triglyceride concentrations to improve lipid levels[180,181]. Overall, the mechanism of tea anti-diabetic may involve strengthening the insulin effect, improving insulin resistance, activating the insulin signaling pathway, protecting pancreatic β cells, eliminating free radicals, alleviating inflammation, etc[182].

Obesity refers to the imbalance between energy intake and energy consumption, resulting in excessive fat accumulation in the body and possibly promoting cardiovascular disease, diabetes, cancer and other diseases[183]. An epidemiological study has shown that decaffeinated green tea polyphenols have beneficial effects on improving obesity and delaying the early sexual development of girls with obesity without adverse effects[184]. Zhang et al. found that caffeine and oolong tea increased fat oxidation by approximately 20 % within 24 h but did not affect energy consumption. In the postprandial state, the effect is inhibited to a certain extent[185]. Tea polyphenols play an important role in the anti-obesity ability[186]. The polyphenol extract in dark tea can reduce AGE levels by regulating SKN-1/Nrf and MAPK pathways to decrease fat content[15,186]. They prevent preadipocytes from differentiating and proliferating, increase lipolysis and reduce lipid production while affecting intestinal flora to increase the rate of lipid metabolism. However, compared to tea polyphenols, caffeine in tea has an independent mechanism of action in the weight loss process but has synergistic effects[187,188]. In addition, tea polysaccharides also exhibit notable anti-obesity activity through modulating gut microbiota and regulating fatty acid and amino acid metabolism as well as microbiota-dependent adipocyte thermogenesis[189,190]. Moreover, L-theanine has been found to potentially induce browning of white adipose tissue through the AMPK/α-ketoglutarate/Prdm16 axis, thereby improving obesity in mice[191].

In recent years, green foods and functional foods have become popular worldwide. At the same time, due to the rising standard of living, obesity and diabetes have become a worldwide epidemic. Tea with antiobesity and antidiabetic activities is gaining increasing attention and favor from researchers and may provide an opportunity to treat obesity and diabetes.

Effects on the central nervous system

As a functional beverage, tea has been popular worldwide. The potential health effects of tea are attributed to tea polyphenols, caffeine, theanine and other phenolic substances[31,192]. The neuroprotective properties of tea on the central nervous system under

the action of these chemical components have been demonstrated [22,193]. Maiti et al. reported green tea's potent neuroprotective and antioxidant effects against oxidative threat. They found that green tea significantly protected antioxidant components in female rats, prevented inflammatory responses, and reduced lipid peroxidation in the brain, thereby improving tissue integrity. In addition, green tea restored arsenic-induced neurotransmitter damage[194].

Furthermore, EGCG can protect neuronal cells, inhibit neuronal apoptosis, and suppress oxidative stress injury and brain injury marker levels. The protective effect may occur through regulation of the PI3K/Akt/eNOS signaling pathway[195,196] (Table 2). The results of Chen et al. revealed the mechanism behind the neuroprotective effects of EGCG by inhibiting overload $[Ca^{2+}]_i$-induced mitochondrial dysfunction and imbalance of mitochondrial fusion and fission cycles[197] (Table 2).

Cognitive decline is one of the main clinical features of dementia, and many researchers have worked to find strategies to treat cognitive decline in recent years[198]. Epidemiological studies have illustrated the ameliorative effect of tea on cognitive decline. A study suggested that a daily supplement of green tea may prevent cognitive decline in older women[199]. Another prospective study also suggested that tea consumption was related to the low incidence of cognitive impairment in elderly individuals in China. Tea drinking might affect the corpus callosum to prevent memory decline and improve associative learning[200]. The improvement of cognitive decline due to tea has been found *in vitro* and *in vivo*[201]. Jeong reported that Pu-erh tea extract was effective in preventing neuroinflammation-induced cognitive impairment[202]. Pretreatment of neonatal mice with L-theanine prevented and attenuated isoflurane-induced neural stem cell injury and cognitive dysfunction in young mice; this neuroprotective effect may be related to the Akt/GSK-3β signaling pathway [203]. In subjects with subjective cognitive decline subjects, the compensatory brain response and cognitive reserve ability could be improved by tea polyphenols[199].

The protective effects of tea on the nervous system are now well established. However, according to the status of its clinical translation, especially in drug development, more trials are needed to avoid tea-induced toxic reactions and overconsumption.

Applications in the medical field, food and cosmetics industries

The medical applications of tea polyphenols have gained substantial attention, considering the diverse range of active compounds in tea. Despite *in vitro* evidence showing that pretreatment with tea polyphenols enhances their transport[204] and that long-term consumption by humans increases the systemic utilization of free EGCG by over 60 %[205], the limited bioavailability and chemical instability of these polyphenols hinder their practical use and development. To overcome these constraints, nanodelivery has emerged as a promising solution due to its advantageous features, including small particle size, large surface area, strong adhesion, targeted delivery, and controlled release capabilities. Researchers have explored nanotechnology-based delivery systems to enhance the oral bioavailability and chemical stability of tea polyphenols. Chu et al. employed a dual-cancer-targeting nanoparticle platform for co-delivering EGCG and curcumin, resulting in a remarkable synergistic effect in cancer treatment[109]. Ding et al. developed a drug delivery system for encapsulating EGCG, demonstrating favorable targeting and anticancer properties both *in vitro* and *in vivo*[109]. Moreover, Hong et al. incorporated EGCG into a nanomaterial formulation, leading to improved stability within the gastrointestinal tract and notable efficacy against rabbit atherosclerosis[109]. While extensive research has been conducted on nanotechnology-mediated tea polyphenol delivery, practical implementation still faces considerable challenges related to the inherent instability of these polyphenols and the safety concerns associated with nanocarriers. Overcoming these hurdles remains a critical focus for future endeavors to fully harness the potential of tea polyphenols in diverse biomedical applications.

To meet the ever-increasing demand for healthy food, the application of tea in the food industry is expanding[206]. The development of tea-based functional products with cardiovascular protection, prevention of neurological disorders, and antidiabetic and antiobesity properties holds promising prospects. However, further clinical validation and safety assessment are necessary to fully explore their health benefits. In addition, tea components find applications as food additives. Research indicates that tea polyphenols can reduce the digestion rate of starch in bread, increase the strength of gluten, and improve the texture of noodles[207]. Tea components also serve as natural antioxidants, effectively inhibiting lipid oxidation in meat products and extending their shelf life [208]. Moreover, the excellent antioxidant and antibacterial properties of tea polyphenols have been incorporated into biodegradable food packaging films. This inclusion enhances the mechanical strength and barrier properties of the packaging, effectively extending the shelf life of food products[209]. In the realm of tea beverages, Japan has developed a variety of functional tea drinks, including those enriched with EGCG and oolong tea polyphenols[210]. Tea beverages rich in L-theanine have gained immense popularity among young consumers for their authentic stress-relieving and sleep-enhancing effects[210].

In recent years, there has been a significant increase in the use of plants as a source of active ingredients in cosmetics. Herbal cosmetics offer advantages such as high safety, compatibility with the skin, minimal side effects, and wide availability compared to synthetic ingredients[109]. EGCG has been indicated to enhance antioxidant activity through its interaction with hyaluronic acid, making it a beneficial component in sunscreens[211]. The polyphenols in green tea extracts exhibit excellent transdermal penetration and moisturizing properties in cosmetics. Additionally, green tea extracts can inhibit acute skin inflammation caused by UV radiation, reduce skin redness, and improve rough skin texture[212].

Risks

Food safety is a growing concern because of its importance to human health. Tea and bioactive ingredients have prominent health care functions, but their risks cannot be ignored. The potential safety problems of tea consumption mainly include heavy metal pollution, pesticide residues, microbial contamination produced during fermentation and storage, toxic biologically active ingredients in large doses, and inhibition of iron absorption. The studies on the potential risks of tea consumption are listed in Table 3. Heavy metal contamination and excessive levels of pesticide residues should be a serious safety issue, but the results of the health risk assessment showed that these metals might not pose a significant safety risk[213,214]. In addition, excessive levels of pesticide residues in tea are also a concern for tea consumption, but according to the health risk assessment, the level of pesticide residues in tea should not be considered a serious public health problem[215,216]. Mycotoxins are produced when fungi and bacteria contaminate tea during processing and storage. Aflatoxin is one of the most carcinogenic substances and has been identified as a potential threat to the safety of tea beverages[217,218]. Incidents of adverse reactions to tea consumption have rarely been reported. Although aflatoxin has been monitored in tea in the past, the concentrations are within regulations[219,220]. Iron in the body is an important component of hemoglobin and some enzymes. Iron deficiency can lead to a lack of oxygen, weakening the body's functions

Table 3
Potential health risks of tea consumption.

Samples/Kind of tea	Location	Safety risks	Items	Conclusion
Black tea, dark tea, green tea, oolong tea and white tea	China	Heavy metal contamination	Al, Cr, Co, Ni, Cu, Zn, As, Cd and Pb	Co-exposure to the metal may not pose a health risk to humans[213]
Green tea	China	Heavy metal contamination	Cd, Pb, Tl, Hg, As, Sb, Cr and Mn	Target hazard quotients (THQ) and hazard index (HI) are below 1[214]
Tieguanyin tea	China	Pesticide residues		The observed residue levels cannot be considered a serious public health concern[215]
Black tea	India	Pesticide residues		Only 1 out of 468 samples exceeded the EU MRL for hexaconazole residues[216]
Black tea	Iran	Mycotoxins	Aflatoxin	Average concentrations below national and EU standards (10 ng/g)[219]
Pu-erh tea	China	Mycotoxins	Aflatoxin	Aflatoxin was detected in 5.7 % of the samples, but not more than 5 μg/kg [220]
Black tea	England	Inhibition of iron absorption		One hour between iron-containing meals and tea consumption helps to reduce the inhibition of iron absorption[222]
Green tea		Inhibition of iron absorption	Iron deficiency anemia	Excessive consumption of tea may cause Iron deficiency anemia[223]
Green tea		Hepatotoxicity		Tea mixed with herbs or dietary supplements is hepatotoxic[225]
Green tea		Hepatotoxicity		Green tea extract can aggravate hepatotoxicity induced by acetaminophen[257]
Daily drinking tea	China	Carcinogenic risk	Esophageal cancer	Combining hot tea with excessive smoking and drinking increases the risk of esophageal cancer[227]
Green tea		Carcinogenic risk	Gastric cancer	Drinking tea at a high temperature may increase the risk of gastric cancer [226]

and reducing efficiency. Tea polyphenols do not always play a beneficial role, and they also inhibit the absorption of iron[221,222]. As it inhibits iron absorption, tea may lead to iron deficiency anemia[223]. However, tea inhibits the intestinal absorption of nonheme dietary iron; conversely, tea does not significantly affect the absorption of heme iron, so nonvegetarians do not develop iron deficiency anemia from drinking only tea[224].

In addition, the combination of green tea and other compounds also has major safety problems. These components can act and interact with green tea, thus increasing the risk of liver injury [225]. The way people drink tea is also associated with safety risks, with some studies suggesting that hot tea may increase the risk of cancer[226,227]. In addition, habitual caffeine intake of up to 400 mg/day in healthy adults does not pose safety concerns, despite the potential adverse effects on the central nervous and cardiovascular systems associated with excessive consumption [228]. Chinese individuals consume caffeine from tea at levels 3 to 7 times higher than those in Western countries, as revealed by the first national risk assessment on caffeine intake from tea in China[229]. According to this assessment, over 90 % of Chinese adult tea drinkers have a caffeine intake below 400 mg/day[229].

Overall, the side effects and health risks of tea are relatively low. For example, heavy metals, pesticide residues and mycotoxins are within the permissible limits and do not pose a safety risk. However, it is worth noting that the interaction between the daily diet and tea may cause hepatotoxicity and that the temperature of tea should not be too high. Meanwhile, a minority of heavy tea consumers should consider reducing their tea consumption appropriately to mitigate potential risks.

Conclusion

This paper reviews the main bioactive ingredients in tea and their pharmacological effects. Tea contains various components, including tea polyphenols, amino acids, polysaccharides, alkaloids, minerals, terpenoids, macro minerals, trace elements, and vitamins. These ingredients have been shown to have various health benefits, including anticancer, antioxidant, anti-inflammatory, antibacterial, cardiovascular protection, antidiabetic and antiobesity properties. Although numerous studies have demonstrated various health-promoting effects of tea, it is important not to exaggerate these benefits. Most mechanistic research has been conducted using cell models and animal experiments, and human intervention trials are still in their early stages. Therefore, more attention should be given to the results of human studies to further understand the potential health benefits of tea.

Considering the low bioactivity of tea, combining tea with other foods, developing formulations, combining tea with enhancers, and employing fermentation or preprocessing techniques are potential strategies to enhance the bioavailability of bioactive compounds in tea. However, the selection of specific strategies should be tailored based on the type of tea, properties of bioactive compounds, and desired therapeutic outcomes. Further research is warranted to explore the effectiveness of these strategies and their impact on tea bioavailability. There is a need to establish uniform quality standards for tea and to effectively develop its bioactive ingredients to promote its transition from research to clinical application. These are the ongoing challenges that researchers must address.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Fig. 2, Fig. 3 and Fig. 4 are created with BioRender.
Conflict of Interest.
The authors declare they have no conflicts of interest.
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Appendix A. Supplementary data

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Yitao Wang is Chair Professor at the University of Macao, Found Director of the Institute of Chinese Medical Sciences, and Found Director of the State Key Laboratory of Quality Research in Chinese Medicine, as well as Director of Macau Center for R&D in Chinese Medicine. He was also the Chief Scientist for the first National Basic Research Program of China (973 Program) in TCM, and initiated and led the foundation of the first SKL in TCM in China. He has supervised 130 PhD and MSc graduates, published more than 550 SCI papers with a total citation of 27800 times and an h-index of 87, and edited 10 books. Editor-in-Chief of a SCI journal "Chinese Medicine".

Jinmin Zhao is the president of Guangxi Medical University, professor, chief physician. He oversees the organization and organ repair and reconstruction innovation team in Guangxi University Talents Small Highland. He engages in clinical diagnosis and treatment for many years and has a wealth of clinical experience. He has profound attainments in basic research and clinical application of microsurgical techniques, diagnosis and treatment of peripheral nerve injury and brachial plexus injury.

Hua Luo obtained her PhD degree from the University of Macau in 2022. She is currently a post-doctoral fellow of the Macau Center for R&D in Chinese Medicine at the University of Macau, with the title of Macau Young Scholar. Dr. Luo primarily focuses on Chinese medicine for the prevention and treatment of cancer and inflammatory bowel disease, as well as the development of health products in Chinese medicine.

Qiaoxian Luo is currently the postgraduate student at the University of Macau. She used to be the editor of *MedComm* and now work as the research assistant of the State Key Laboratory of Quality Research in Chinese Medicine. Qiaoxian Luo's research is mainly focus on the development of health products in Chinese medicine.

LongbiaoLuo obtained his Bachelor's degree in Pharmaceutical Engineering from Xi'an Jiaotong University (2022), and subsequently worked as a research assistant in State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau.