REVIEW ARTICLE

Camellia sinensis: Insights on its molecular mechanisms of action towards nutraceutical, anticancer potential and other therapeutic applications

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Abstract   The *Camellia sinensis* plant provides a wide diversity of black, green, oolong, yellow, brick dark, and white tea. Tea is one of the majorly used beverages across the globe, succeeds only in the water for fitness and pleasure. Generally, green tea has been preferred more as compared to other teas due to its main constituent e.g. polyphenols which contribute to various health benefits. The aim of this updated and comprehensive review is to bring together the latest data on the phytochemistry and pharmacological properties of *Camellia sinensis* and to highlight the therapeutic prospects of the bioactive compounds in this plant so that the full medicinal potential of *Camellia sinensis* can be realised. A review of published studies on this topic was performed by searching PubMed/MedLine, Scopus, Google scholar, and Web of Science databases from 1999 to 2022. The results of the analysed studies showed that the main polyphenols of tea are the four prime flavonoids catechins: epigallocatechin gallate (EGCG), epicatechin gallate (ECG), epigallocatechin (EGC), and epicatechin (EC) along with the beneficial biological properties of tea for a broad heterogeneity of disorders, including anticancer, neuroprotective, antibacterial, antiviral, antifungal, antiobesity, antidiabetes and antiglaucoma activities. Poor absorption and low bioavailability of bioactive compounds from *Camellia sinensis* are limiting aspects of their therapeutic use. More human clinical studies and approaching the latest nanoformulation techniques in nanoparticles to transport the target phytochemical compounds to increase therapeutic efficacy are needed in the future.

1. Introduction

Different types of teas are consumed regularly and are obtained from *Camellia sinensis* (L.) Kuntze, the main variety is *C. sinensis* var. *assamica* (J.W.Mast.) Kitam. Based on fermentation degree, teas are categorized into dark tea (post-fermented tea), black tea (fermented tea), oolong, yellow and white tea (partially fermented), and green tea (completely fermented). Among all, dark tea is unique as it requires microbial fermentation and its production is restricted to the areas of Japan and China (Zheng et al., 2015). Black and green teas are commonly consumed and therefore are more broadly investigated. Yellow tea is the least explored tea but now it's gaining attention in western countries due to its good quality, refreshing taste, better flavour, and therapeutic benefits (Xu et al., 2018).

However, many of the health care benefits are related to the consumption of green tea since the starting of its history, research-based evaluations on this tea and its components have been ongoing for lesser than three decennaries (Cabrera et al., 2006). Various epidemiological investigations, as well as research in animal models, have established the protection that green tea and other teas can provide, against different types of cancers such as lung, prostate, skin, liver, and breast (Hayat et al., 2015). Besides its anticancer properties, epigallocatechin gallate (EGCG) has been documented to be hypocholesterolemic, anti-angiogenic, anti-thyroidal, anti-thrombotic, and anti-mutagenic. In the case of age-related pathologies, green tea and other teas have been determined to offer remarkable defence against Parkinson's and Alzheimer's disease (Chaturvedi et al., 2006, Khadrawy et al., 2017). Tea has also exhibited anti-diabetic effects in pre-clinical trials and encouraged the expenditure of energy. Other valuable credit includes anti-bacterial, anti-obesity, anti-fungal, antiphotoaging, anti-HIV, anti-viral, anti-inflammatory, and life-prolonging activities. Due to its greater antioxidant content, green tea is used as a nutritional supplement or nutraceutical aid, and as an element in anti-ageing, cosmetics, masks, and shampoos emulsions (Gopal et al., 2016). Although, the outcome of clinical and epidemiological investigations of the connection between the consumption of green tea and organism fitness is quite diverse. For example, divergent outcomes among human studies may rise relatively, from disregarding lifestyle, and socioeconomic factors, and by insufficient technique to describe the preparation and consumption of tea (Cabrera et al., 2006). Therefore, this paper aims to review the pharmacological properties, underlying the molecular mechanisms of action and the latest studies on the different types of teas and to examine their promising therapeutic potential.

2. Review methodology

This review is concentrated on the literature in the English language. The literature survey was carried out in databases such us PubMed/MedLine (1999–2022), NCBI (1999–2022), Google scholar (1999–2022) and BMC Complementary and Alternative Medicine (BMC, 1999–2021). The keywords utilized for the search were chosen from the following terms: polyphenols, white tea, black tea, green tea, catechin, health benefits, yellow tea, dark tea, oolong tea, anticancer, and diabetes. More than 200 articles on different forms of tea have been recognized by utilizing the search databases mentioned above. The scientific names of the plants were validated according to World Flora Online (WFO 2021) and the chemical formulas with ChemSpider and PubChem (PubChem 2022). The precise information about these articles is described below.

3. Phytochemical constituents

The processing, origin, taste, colour, and composition of different teas are discussed in Table 1 and Fig. 1 (Graham 1992, Belitz and Grosch 1997, Vinson 2000, Sano et al., 2001, Khokhar and Magnusdottir 2002, Chacko et al., 2010, Skotnicka et al., 2011, Dias et al., 2013, Zheng et al., 2015, Ng et al., 2018, Xu et al., 2018) and the structure of common chemical components that are responsible for the therapeutic value of teas is represented in Fig. 2 and Fig. 3.

Table 1 Properties of different forms of tea.

Properties	Green tea	Black tea	Oolong tea	White tea	Yellow tea	Brick dark tea
Processing	Involves fixation, rolling & drying processes (Cabrera et al., 2006)	Involves a withering, rolling, fermentation & drying process (Sharma and Rao 2009)	Involves a withering, rocking, rolling & drying process (Chen et al., 2010)	Involves a withering & drying process (Hajiaghaalipour et al., 2015)	Involves fixation, rolling, yellowing & the process of drying (Zhang et al., 2019)	Involves fixation, post-fermentation, shaping & the process of drying (Zhang et al., 2019)
Origin	China (Sinija and Mishra 2008)	Asia and Europe (Skotnicka et al., 2011)	Fujian Province of China (Zheng et al., 2015)	Fujian Province of China (Ning et al., 2016)	China (Xu et al., 2018)	China & Japan (Zheng et al., 2015)
Taste	Bitter (Soni et al., 2015)	Distinct taste (Soni et al., 2015)	Bitter, sweet, brisk & mellow (Liu et al., 2018)	Mild taste (Hilal and Engelhardt 2007)	Caramel flavor (Guo et al., 2019)	Mellow taste (Zheng et al., 2015)
Colour	Green or yellow (Soni et al., 2015)	Red to black (Soni et al., 2015)	Appear red from the edges & green in the center (Chen et al., 2010)	Pale yellow colour (Hilal and Engelhardt 2007)	Yellow color (Xu et al., 2018)	Brick red to brown color (Zheng et al., 2015)
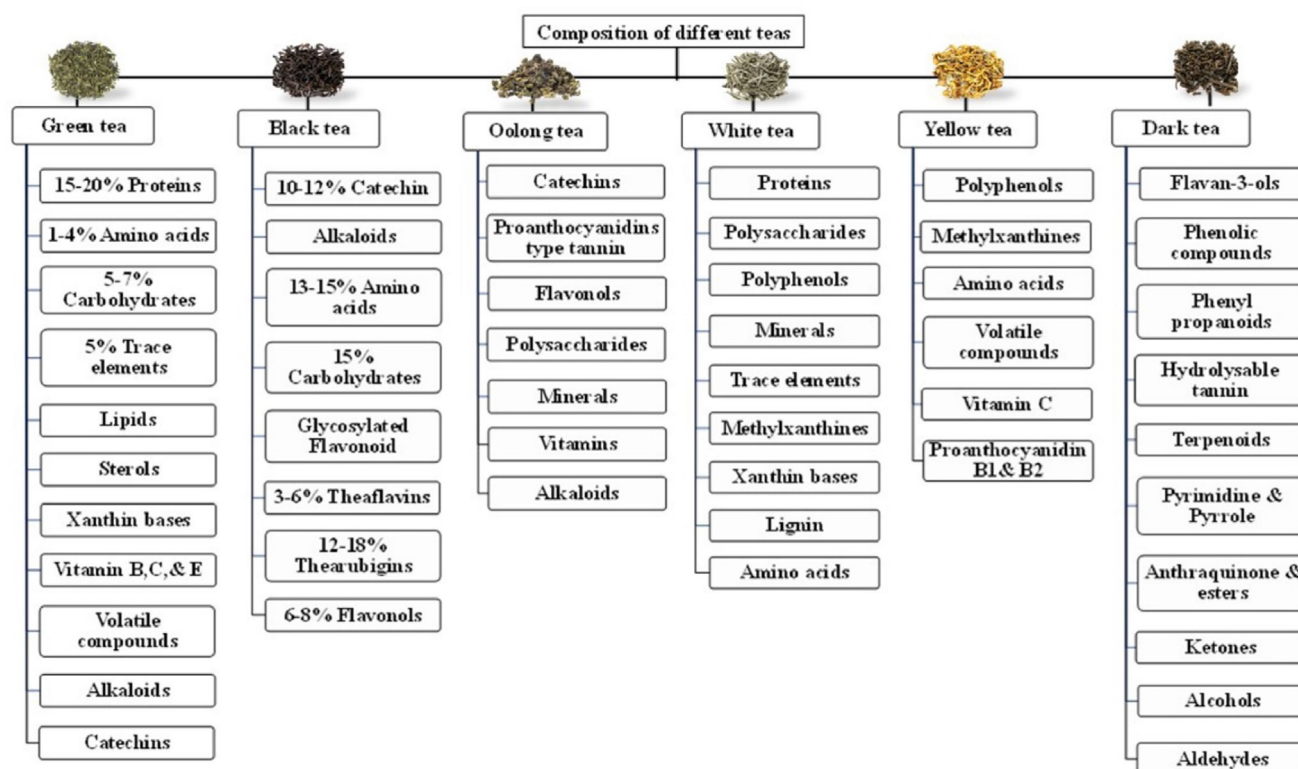
Fig. 1 Composition of different forms of tea.

4. Pharmacological properties

4.1. Anticancer effect

Cancer is a life-threatening disease with increasing incidences that have generated a sense of concern for the healthy lifestyle of the human being (Ianoşi et al., 2019, Sharifi-Rad et al., 2020, Janmeda and Chaudhary 2021).

Normal cells divide neatly and die when they are worn out or damaged, and new cells take their place. Cancer occurs when cells start to grow and divide uncontrollably (Buga et al., 2019, Georgiadis et al., 2020). Cancer cells continue to grow and produce new cells that destroy normal cells (Coêlho et al., 2022, Iqbal et al., 2022, Motyka et al., 2023).

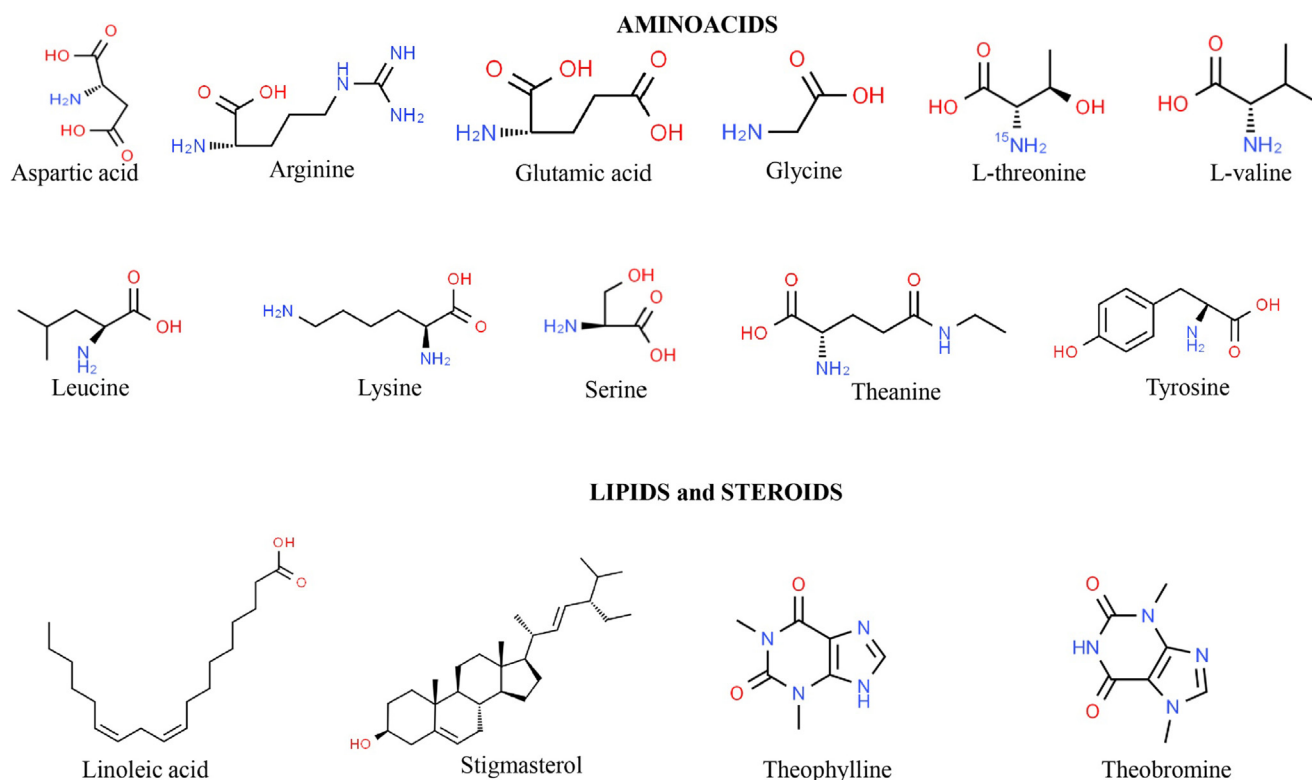Potential green tea catechins mechanisms of action against cancer:

AMINOACIDS

Aspartic acid   Arginine   Glutamic acid   Glycine   L-threonine   L-valine

Leucine   Lysine   Serine   Theanine   Tyrosine

LIPIDS and STEROIDS

Linoleic acid   Stigmasterol   Theophylline   Theobromine

Fig. 2 Chemical stuctures of the most representative aminoacids, lipids and steroids from *Camellia sinensis* (L.) Kuntze.

(i) Anti-oxidant and pro-oxidant activities

Reactive oxygen species (ROS) are unstable molecules with roles in intracellular processes(Salehi et al., 2019, Tsoukalas et al., 2019, Iordache et al., 2020, Sharifi-Rad et al., 2021a, Sharifi-Rad et al., 2021b). Excess accumulation of ROS is associated with increased oxidative stress and the development of many chronic diseases such as diabetes, cardiovascular disease, neurodegenerative diseases and cancer(Calina et al., 2020, Calina et al., 2020, Islam et al., 2020, Islam et al., 2021, Salehi et al., 2021). Catechins provide anti-oxidant properties by counteracting the unstable free reactive molecules. Among green tea catechins (GTCs), epicatechin gallate (ECG) has the highest potential as a radical scavenger, followed by EGCG, epigallocatechin (EGC), and epicatechin (EC). The antioxidant activity is because of the occurrence of phenolic groups with sensitivity to oxidation which results in the production of quinine. The activity is further intensified due to the presence of a trihydroxy structure in the D-ring of the molecule (Bernatoniene and Kopustinskiene 2018).

Green tea polyphenols can produce ROS which are required for the initiation of the apoptosis process and the restriction of the growth of the tumour cell. Both pro- and anti-oxidant properties of GTCs are found to be the major ones for the control of cancer (Shirakami and Shimizu 2018).

(ii) Apoptosis induction and cell cycle arrest induction

Apoptosis is an orderly process during which the cell's genome is broken down, the cell is fragmented into smaller pieces and the remains are consumed by nearby cells (phagocytes) that clean up the cell fragments (Sharifi-Rad et al., 2020, Scheau et al., 2021, Taheri et al., 2022). Apoptosis leads to programmed cell death to remove unwanted or abnormal cells from the body and maintain a stable internal environment (Sharifi-Rad et al., 2021c, Dhyani et al., 2022, Semwal et al., 2022). Treatment with EGCG-induced programmed cell death due to the formation of ROS and activation of caspase-9 and −3, majorly to cell-cycle arrest at the G1 phase via regulating the expression of p21, cdk4, and cyclin D1 (Shirakami and Shimizu 2018).

(iii) Nuclear factor-κB (NK-κB) and activator protein-1 (AP-1) inhibition

NK-κβ is recognized to play a pivotal part in restricting the process of programmed cell death in cancerous cells, leading to tumorigenesis (Jain et al., 2021, Javed et al., 2022, Quetglas-Llabrés et al., 2022, Varela et al., 2022). Treatment with EGCG restrained the activation of NF-κB in the lung, breast, and human neck and head squamous carcinoma. When NF-κB is turned on, it is moved into the nucleus and directs the multiple expression of genes related to tumorigenesis and its progression, further including inflammation, chemo-resistance, radio-resistance, metastasis, invasion, proliferation, and cellular transformation. Another factor is AP-1 which maintains the levels of gene expression associated with cellular proliferation and apoptosis(Pezzani et al., 2023). It is evaluated that AP-1 encourages multiplications via down-regulating the tumour suppressor genes p21 and p53 and up-regulating the expression of the cyclin D2 gene. EGCG was outlined to suppress the activation of AP-1 and transformation of cells and to
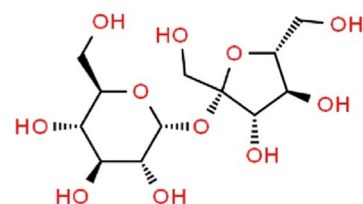
CARBOHYDRATES
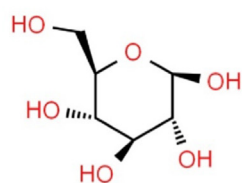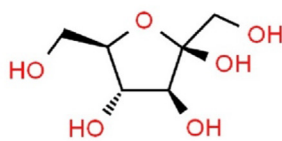
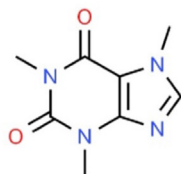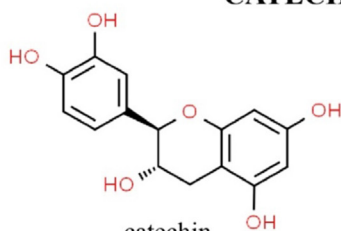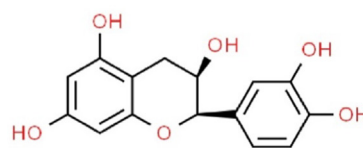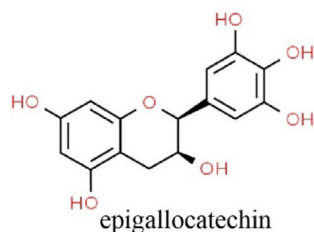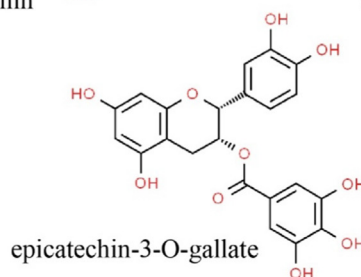**CATECHINS**

Fig. 3 Chemical structures of carbohydrates and catechins from *Camellia sinensis* (L.) Kuntze.

restrict Ras-activated AP-1 in the epidermal cell line of a mouse (Shirakami and Shimizu 2018).

(iv) Receptor tyrosine kinase (RTK) pathway inhibition

RTKs plays an important role in the proliferation and apoptosis of cell and are proposed to be targeted by GTCs for the cure of cancer. RTKs and their downstream signals, such as phosphatidylinositol 3-kinase (PI3K)/ Akt signaling and the Ras/extracellular signal-regulated kinase (ERK) pathways, maintain the expression levels of different target genes related to apoptosis and proliferation. Irregularities in a few RTKs, such as vascular endothelial growth factor receptor 2 (VEGF-R2), insulin-like growth factor-1 receptor (IGF-1R), and epidermal growth factor receptor (EGFR) are deeply linked with the properties of malignancy (Cheng et al., 2020). Treatment with EGCG repressed the production of VEGF via restricting the activation of NF-κB, activator transcription STAT-3 and signal transducer in human breast and HNSCC (Shirakami and Shimizu 2018).

(v) Anti-angiogenesis

Angiogenesis involves the growth of new capillaries from pre-existing ones, which is necessitate in various processes such as metastasis, tumour growth, and wound healing(Pezzani et al., 2023, Prasher et al., 2023). Green tea extract may restrict

the progression of breast tumours by sealing angiogenesis (Jung and Ellis 2001). Polyphenon E (PPE), an isolated extract of green tea hinders vascular endothelial (VEGF) and matrix metalloproteinase 9 (MMP9) expression and human dermal microvascular endothelial (HMVEC) cell migration in the case of MDA-MB231 breast cancer. Additionally, PPE discouraged VEGF-directed angiogenesis *in vivo*. Further, it restricted the signal transducers and STAT signaling by restraining interferon (IFN)-γ-directed gene transcription with the help of IFN-γ-activating sequence (GAS) elements and downstream activation of STAT3 by restricting STAT3 and STAT1 dimerization in MDA-MB231 cells. A momentary expression of fundamental active STAT3 considerably limits the inhibitory outcome of PPE on the migration of cells and the expression of MMP9 and VEGF. These results designate that the extract of green tea partly inhibits angiogenesis via the disorganization of STAT3-directed gene transcription, involving VEGF (Leong et al., 2009). EGCG can restrict the angiogenesis of experimental endometriosis in the model of mice, but it encounters poor bioavailability. EGCG prodrug (EGCG octaacetate) is employed to improve the bioavailability and stability of EGCG *in vivo*. Pro-EGCG markedly limited the growth and angiogenesis in mice and leads to the development of higher potency, superior bio-availability, and greater anti-angiogenesis and anti-oxidation capacities as compared to EGCG (Wang et al., 2013).

Table 2, Table 3 and Fig. 4 summarize the molecular mechanisms of anticancer activities of green tea.

4.2. Neuroprotective effect

Different components of tea are reported to be used in the treatment of neurodegenerative diseases (Fig. 5). The neuroprotective effect of the tea component along with their mechanism is discussed below.

4.2.1. Alzheimer's disease (AD)
AD is reported to be the most frequent acute disorder globally. Its occurrence is steadily hiking due to an ageing population vital statistics (Sharifi-Rad et al., 2022). AD is determined by a deduction in thinking and memory, as well as due to some behavioural issues (Calina et al., 2020, Tsoukalas et al., 2021). Some authors explained that the tiny binding monomers of beta-amyloid result in the formation of beta-amyloid oligomers. With time, these oligomers can hold together and direct the generation of toxic beta-amyloid plaques. Researchers found that EGCG block the emergence of beta-amyloid plaques which is a hallmark of AD, by disrupting the outcome of beta-amyloid oligomers (Sharifi-Rad et al., 2022).

4.2.2. Parkinson's disease (PD)
PD is distinguished by the deterioration of dopaminergic neurons in the pars compact of the substantia nigra of the basal ganglia (Alexander 2004, Islam et al., 2021). The exact source of this disease is not known but it can be stimulated by the mutations in genes and revelation to environmental risk factors such as 1-methyl-4-phenyl 1, 2,3,6-tetrahydropyridine (MPTP), which is an agent able to produce the symptoms of PD in individuals and pesticides like dichlorodiphenyltrichloroethane (DDT) or rotenone persuade PD-like symptoms, and irreparable decaying of dopaminergic neurons (Siokas et al., 2021). The inflammation-raised concentration of iron in substantial pars compacta (SNC), deduction in glutathione (antioxidant enzyme), and oxidative stress (OS) are some chief factors in the pathogenesis of PD. Further prompting factors include aggregation of alpha-synuclein (α-Syn), deduction in the activity of mitochondrial complex I, the liberation of cytochrome C, and lowering of reduced glutathione (GSH)(Siokas et al., 2021). The patients with PD have also displayed instability in the electron transport chain that directs the accretion of ROS, the unstable molecules responsible for lipid peroxidation and cellular damage (Jurado-Coronel et al., 2016).
Potential mechanisms of green tea to minimize PD:

(i) Inhibitor of monoamine oxidase B (MAO-B): MAO is a mitochondrial enzyme linked to the oxidative deamination of dopamine; therefore, inhibitors of MAO most probably could be a valuable agent to cure diseases related to the malfunction of dopamine such as PD. It has been reported that catechin possesses MOA-B inhibitory activity that is found to be capable one to treat PD (Bortolato et al., 2008, Jurado-Coronel et al., 2016).
(ii) Activation of potential signaling pathways: green tea polyphenols can exhibit constructive action with the help of several mechanisms such as:

-depletion in the delivery of cytokines such as tumour necrosis factor TNF-α or interleukin IL-1β, the renewing of signaling pathways that minimize the mass production of ROS and inducible nitric oxide synthase (iNOS) such as nicotinamide adenine dinucleotide (NADH) oxidase activation, and the restriction in the translocation of NF-κB to the nucleus, a major event triggered the inflammation process in the brain (Yahfoufi et al., 2018).

-protection of dopaminergic neuronal, provided by EGCG may depend upon the mitogen-activated protein kinases (MAPKs), PI3K/Akt, and activation of protein kinase C (Zhao et al., 2018). EGCG protects neurons by inhibiting the pro-apoptotic gene expression, such as TNF-α related apoptotic ligand TRAIL, Fas ligand, cell cycle inhibitors such as Gadd45, Bax, and Bad or by restricting the aggregation of α-Syn and iron in MPTP induced model of mice, probably due to its iron-chelating and antioxidant properties.

- the iron-chelating activities are attributed to the chelating groups such as the presence of the gallate group and 3,4-dihydroxyl group in the B ring of EGCG, which counteract the ferric iron to result in redox-inactive iron, and may safeguard the neuronal cells from the damages caused by OS.

- EGCG restricts the iNOS expression, avoid peroxidation of lipid, inhibit catechol-O-methyltransferase (COMT), thus reducing the metabolism of dopamine residue, and is demonstrated to be a determent of microglial activation and an anti-apoptotic agent (Jurado-Coronel et al., 2016).

4.3. Antiobesity and anti-dyslipidemic effects

Obesity is a metabolic and nutritional problem, which has a clinical presentation of fat cell hypertrophy and hyperplasia (Salehi et al., 2020). Fat cell hyperplasia results due to the differentiation and proliferation of preadipocytes which could direct the uncontrolled deposition of lipids in adipose tissue, and mainly impact the composition of the body and the mortality of adiposity and associated disorders. Whereas fat cell hypertrophy often occurs when the intake of energy exceeds the expenditure of energy (Huang et al., 2014, Muir et al., 2016).
After consumption, GTCs intrude with the mechanism of energy metabolism and absorption in organisms:

(i) hindrance in the multiplication of preadipocytes,
(ii) affects the programmed cell death of the pre and mature adipocytes,
(iii) restrict the preadipocyte differentiation and the mature adipocyte adipogenesis,
(iv) restrain the function of the digestive enzymes of the gastrointestinal tract, the luminal emulsification, the solubilization of micelles and the hydrolysis of lipids
(v) obstruct the processing and intracellular uptake of lipids, secretion and assembly of chylomicrons in enterocytes,
(vi) raises the faecal energy excretion,
(vii) stimulate the oxidation of fatty acids
(viii) increase the uptake of glucose by skeletal muscles
(ix) activates the expression of the gene responsible for the oxidation of fatty acid and lipolysis-associated genes in adipose tissue
(x) repress the intake of glucose and the expression of genes related to fat synthesis (Huang et al., 2014).

Table 2 The molecular mechanisms of anticancer activities of green tea.

Form of tea	Cancer type	Model	Dose/IC$_{50}$	Anticancer activity	Ref.
Polyphenon E (PPE)/ Caffeine/ Green tea	Adenocarcinoma	mice _in vivo_	Dose = 0.5 %-0.44 % orally	↓lung adenomas progression to adenocarcinoma	(Lu et al., 2006)
Green tea polyphenols	Malignant melanoma	melanoma cells _in vitro_	IC$_{50}$ = 30 and 60 µg/mL	↓progression of malignant melanoma ↓circMITF/miR-30e-3p/HDAC2	(Wu et al., 2021)
EGCG	Breast cancer	4 T1 cells _in vitro_	IC$_{50}$ = 50 µg/mL	↓ growth of tumor ↓tumor-related M2 polarization ↓macrophage infiltration	(Jang et al., 2013)
	Cholangiocarcinoma	CCA cells (HuCC-T1) _in vitro_	IC$_{50}$ = 5 µg/mL	↓growth of cancer cells ↓migration, ↓ invasion	(Kwak et al., 2017)
	Bladder cancer	SW780 cells _in vitro_	IC$_{50}$ = 70.2 µM at 24 h IC$_{50}$ = 113.6 µM at 48 h	↓migration, ↓proliferation ↓MMP-9, ↓NF-kB	(Luo et al., 2017)
	Lung cancer	H1299 cells _in vitro_	IC$_{50}$ = 10 and 50 µM	↓tumourigenicity ↓stemness directed by AXL receptor tyrosine kinase	(Namiki et al., 2020)
	Colorectal cancer	Rats _in vivo_	Dose = 50,100,200 mg/kg orally	↓ colorectal cancer induced by dimethylhydrazine	(Wang et al., 2020)
Green tea	Cervical adenocarcinoma	HeLa cells _in vitro_	IC$_{50}$ = 100 µg/ mL	↓ cancer cells growth	(Krstic et al., 2015)
Green tea catechins	Breast cancer	MCF-7 cells _in vitro_	IC$_{50}$ = 500, 100, 50, 10, 1 µM/ mL	↓ PTP1B ↓viability of cancer cells	(Kuban-Jankowska et al., 2020)
	Lung cancer	A549 lcells _in vitro_	IC$_{50}$ = 600 µmol	↓pAKT ↓cyclin E1 ↑ cyclin kinase inhibitior p21	(Sun et al., 2020)
	Lung cancer	mice _in vivo_	Dose = 0.3 % orally	↓ PD-L1 ↓growth of tumor	(Rawangkan et al., 2018)
Green tea	Lung cancer	murine model _in vivo_	Dose = 1 % orally	chemopreventive effect against benzo(a)pyrene-induced lung cancer at low concentration	(Farooq and Sehgal 2021)
Catechin hydrate	Cervical cancer	SiHa cells _in vitro_	IC$_{50}$ = 196.07 µM/mL	↓proliferation ↑apoptosis	(Al-Hazzani and Alshatwi 2011)
Aqueous extract of oolong tea	Hepatic cancer	AH109A cells _in vitro_	concentration = 0.04 %	↓invasion ↓proliferation	(Zhang et al., 1999)
	Breast cancer	MDA-MB-468, MDA-MB-436, MDA-MB-231, SKBR3, T47D, MCF-7 cells/ _in vitro_	concentration = 1 %	↑ damage to DNA ↓tumorigenesis ↓growth of cancer cells	(Shi et al., 2018)

(continued on next page)

Table 2 (*continued*)

Form of tea	Cancer type	Model	Dose/IC$_{50}$	Anticancer activity	Ref.
Yellow tea extract	Breast cancer	MDA-MB-231 cells *in vitro*	IC$_{50}$ = 100–800 µM/ml	↑anticancer activity ↓ growth of cancer cells	(Lin et al., 2013)
	Hepatic cancer	HepG2 cells *in vitro*	IC$_{50}$ = 0, 0.125, 0.25, 0.5, 1 mg/mL	↓AKT, ↓PI3K phosphorylation ↑ Bax/Bcl-2	(An et al., 2019)
	Liver cancer	Rats *in vivo*	Dose = 10 g/kg feed orally	↑ protection against NDEA-directed liver cancer	(Kujawska et al., 2016)
White tea extract	Colon cancer	HT-29 cells *in vitro*	IC$_{50}$ = 0–500 µg/mL	↓proliferation, ↑caspases protect the normal cell against oxidative damages	(Hajiaghaalipour et al., 2015)
	Lung cancer	A549, H521 cells *in vitro*	IC$_{50}$ = 3.5, 5, 7, 10 µg/mL	↑apoptosis ↑PPAR-γ, ↑15-LOX	(Mao et al., 2010)
Black tea extract	Colon and breast cancer	HT-29, MCF-7 cells *in vitro*	IC$_{50}$ = 5 µg/mL	↑apoptosis, ↑oxidative damage ↑DNA strand break	(Koňariková et al., 2015)
Black tea thearubigins and theaflavins	Colon and lung cancer	HT 460, HCT116 cells *in vitro*	IC$_{50}$ = 50,100,150,200,250 µg/mL	↓proliferation ↑cell cycle arrest, ↑apoptosis	(Imran et al., 2019)

Abbreviations and symbols: ↓ (decrease), ↑ (increase), histone deacetylase (HDAC), lipoxygenase (LOX), matrix metalloproteinase (MMP-9), nuclear factor kappa light chain enhancer of activated B cells (NF-κB), protein tyrosine phosphatase 1B (PTP1B), peroxisome proliferator-activated receptor gamma (PPAR-γ), protein tyrosine phosphatase 1B (PTP1B), melanocyte inducing transcription factor (MITF*)*, protein tyrosine phosphatases (PTP1B), Phosphorylated AKT(pAKT)*,* Programmed death-ligand 1*(*PD-L1), Deoxyribonucleic Acid (DNA), *N*-nitrosodiethylamine (NDEA), epigallocatechin gallate (EGCG).
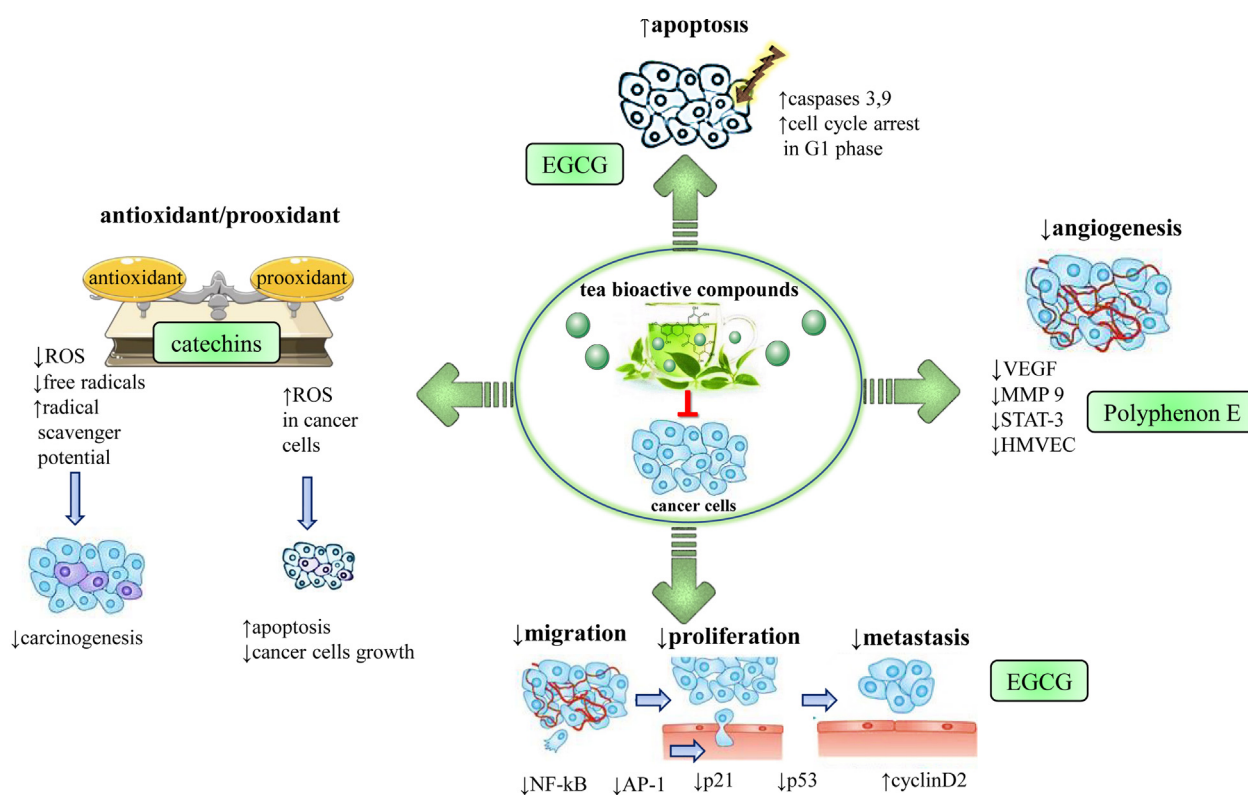
Fig. 4 Illustrative scheme with the most representative anticancer molecular mechanisms of bioactive compounds from tea. Abbreviations and symbols: ↑increase, ↓decrease, ⊥ inhibition, vascular endothelial growth factor (VEGF), lipoxygenase (LOX), matrix metalloproteinase 9 (MMP9), activator transcription (STAT-3), human dermal microvascular endothelial (HMVEC), epigallocatechin gallate (EGCG).

Supplementation of GTC remarkably reported increased liver and body weights and the raised level of liver triglyceride and serum. Meantime, GTCs raised the level of peroxisome proliferator-activated receptor-γ (PPAR-γ) in subcutaneous white adipose tissue (SWAT) and reduced the level of PPAR-γ in visceral white adipose tissue (VWAT). Additionally, the treatment with GTC up-regulated the PPAR-δ level in brown adipose tissue, VWAT, and SWAT and encouraged the gene expression for the oxidation of fatty acid in brown adipose tissue. These results determine that GTC provides the anti-obesity effect by altering the signaling pathway of PPAR (Yan et al., 2013). Babu and Liu (2008) explained that cardiovascular disease (CVD) is a foremost cause of disability, fatality, and morbidity across the globe. GTC or green tea can suppress coronary heart disease and atherosclerosis through their low-density lipoprotein-cholesterol-decreasing activity. Zheng et al., (2011) revealed that catechin with gallate moiety was determined to interfere with the system of biliary micelle in the intestine by making insoluble precipitates of cholesterol and rising the cholesterol fecal excretion. This noticeable lowering in the absorption of cholesterol and depletion in the concentration of cholesterol in the liver leads to a promotion of low-density lipoprotein (LDL)-receptor activity and expression. This receptor is available on the uppermost side in most of the cells, particularly in hepatic cells, it can eliminate cholesterol-containing low-density lipoproteins from the circulation.

Recently, *in vitro* study has reported that GTC is a selective and strong inhibitor of a rate-limiting enzyme i.e. squalene epoxidase in cholesterol biosynthesis. Green tea remarkably restricts the concentration of LDL and serum total cholesterol, and these changes are not affected by the study quality, status of individual health, dose of treatment, duration of the study, and intervention type (Singh et al., 2009).

4.4. Antidiabetes effect

Diabetes mellitus is a chronic non-communicable disease that occurs when the pancreas can no longer produce insulin (or no insulin at all), or when the body can no longer use insulin properly. Additionally, it also resulted due to various impairments like fat, carbohydrate and protein metabolism by either inadequate quantity of insulin production or decreased sensitivity of target tissue to insulin (Painuli et al., 2022, Quispe et al., 2022). Type 1 Diabetes Mellitus (T1DM) include impaired β-cells of the pancreas and decreasing or no production of insulin whereas Type 2 Diabetes mellitus (T2DM) is determined by the resistance of target tissue to insulin and the relative scarcity of insulin produced by the islet of β-cells (Meng et al., 2019). Meng et al., (2019) reported that in T1DM, EGCG could preserve pancreatic β-cells function by restricting ROS and inflammatory factors *in vitro* or by down-regulating the generation of iNOS. Additionally, green tea was also able to lower the sugar level of blood with the help

Table 3 Pharmacological preclinical studies of different teas and their constituents.

Tea components	Pharmacological properties	Model	Dose/ routes	Results/Potential mechanisms	References
EGCG/green tea extract	Neuroprotective	mice/ in vivo	2–10 mg/kg	↑neuroprotection against N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurodegeneration	(Levites et al., 2001)
	Antiobesity	mice/ in vivo	0.5–1 mg/kg orally 50 mg/kg, i.p.	↓body weight ↓white adipose tissue weight ↓mitochondrial DNA ↓TNF, ↓IL-6, ↓ IL-8	(Okuda et al., 2014)
	Cardioprotective	rats/ in vivo	10 mg/kg, i.p.	↓ventricular arrhythmia	(Shi et al., 2017)
	Anti-Pulmonary fibrosis	rats/ in vivo	25 mg/kg, i.p.	↓ irradiation-directed pulmonary fibrosis	(You et al., 2014)
Caffeine/ Polyphenon E (PPE)	Neuroprotective	rats/ in vivo	30 mg/kg, i.p	↑neuroprotection against rotenone-induced Parkinson's disease	(Khadrawy et al., 2017)
Catechin	Anti-angiogenic	mice/in vivo	50 mg/kg, i.p.	↓initiation of endometriosis ↑anti-angiogenic effect	(Xu et al., 2009)
Black tea extract/ water extract of black tea/ polyphenols	Neuroprotective	rats/in vivo	1.50 % orally	↑neuroprotection against 6-hydroxydopamine lesioned-directed Parkinson's disease	(Chaturvedi et al., 2006)
	Antiobesity	rats/in vivo	a high-fat rich diet with black tea polyphenols	↑the fatty acid level in faeces, regulates the fat metabolism	(Islam 2011)
	Antidiabetic	mice/in vivo	0.01 %, orally	↓ level of blood glucose	(Tang et al., 2013)
	Anti-inflammatory	rats/in vivo	0.5–1.0 mg/kg bw orally	↑ anti-inflammatory activity against adjuvant-directed arthritis	(Ramadan et al., 2017)
	Pulmonary fibrosis	mice/in vivo	25–50 mg/kg bw orally	↓the effect of fibrotic markers	(Chakraborty et al., 2019)
	Antifungal	Candida species/in vitro	MIC = 6.25 mg/ml	↑antifungal activity	(Sitheeque et al., 2009)
	Cardioprotective	Humans	150 mg, twice daily, orally	↑ protection to blood vessels ↑increased flow of angiogenic cells	(Tang et al., 2019)
	Antibacterial	Humans with Helicobacter pylori infection	≥ 1 day/week, orally	↓risk of bacterial infection	(Boyanova et al., 2015)
Oolong tea	Neuroprotective	neuro-2a, HT22 cells/ in vitro	IC$_{50}$ = 5,10, 25 μg/ml	Prove to be a potential one for the cure of neurodegenerative diseases	(Zhang et al., 2020)
	Antiobesity	mice/ in vivo	high-fat rich diet with 5 % oolong leaf powder; orally	↓fatty liver ↓obesity	(Han et al., 1999)
	Antidiabetic	diabetic patients	1500 ml daily, orally	antihyperglycemic effect	(Hosoda et al., 2003)
White tea	Neuroprotective	striatal cells/in vitro	IC$_{50}$ = 25, 100,200 μg/mL	protect striatal cells line against oxidative stress-directed cell death	(Almajano et al., 2011)
	Antiobesity	mice/in vivo	0.5 %, orally	↓oxidative stress,	(Teixeira et al., 2012)
	Antidiabetic	rats/in vivo	0.5 %, i.p.	↓triacylglycerol ↓diabetes-related abnormalities of streptozotocin-induced diabetes	(Islam 2011)
	Cardioprotective	rats/in vivo	1 g/100 ml	↓cardiac glycolytic activity ↑antioxidant activity	(Alves et al., 2015)
	Antimicrobial	Pseudomonas aeruginosa; Staphylococcus aureus; Escherichia coli	Disc agar diffusion assay	inhibit P. aeruginosa, E.coli, S. aureus	(Enzveiler et al., 2011)
Yellow tea	Hypoglycemic	mice/in vivo	50 mg/kg bw	↑epimerized catechin level ↓alpha-glucosidase	(Zhou et al., 2018)
	Lipids reducing	mice/in vivo	0.5 %; orally	↑ efficacy in lowering lipid profile	(Xu et al., 2018)
Dark tea	Lipids reducing	rats/in vivo	100, 300, 500 mg/kg bw	↑antioxidant enzymes ↓absorption of lipids ↓hyperlipidemia	(Mao et al., 2018)

Abbreviations and symbols: ↑increase, ↓decrease, mg/kg: milligram per kilogram, i.p.: intraperitoneally, μg/ml: microgram per milliliter, A/J mice: the inbred strain of mice, AH109A cells: cellosaurus cell line; BW: Body weight, i.g.: intragastarically.

of β-cells to secrete more amount of insulin in the case of diabetic mice.

In T2DM, EGCG could trigger the 5′-adenylic acid-activated protein kinase (AMPK) pathway to surpass the insulin stress signaling pathway closure, resulting in the insulin receptor substrate-1 (IRS-1) phosphorylation. It could surpass the sensitivity of insulin by upregulating the level of insulin signaling proteins in insulin-resistant rats. EGCG was able to improve insulin resistance by counteracting ROS, which was capable to stop insulin signal transduction and inhibit the binding of IRS-1 to the receptor of insulin by reducing the TNF-α-directed c-jun NH2-terminal kinase (JNK) phosphorylation.

EGCG can play an insulin-like role and down-regulate the expression of protein and gene of hepatocyte nuclear factor (HNF4), a major transcription factor controlling the enzymes of gluconeogenesis, such as glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, respectively. Moreover, catechin could assist the differentiation of adipocytes and raises insulin sensitivity by majorly triggering the PPAR-γ (Boucher et al., 2014).

4.5. Effect on thyroid disorders

The thyroid gland is present in the neck and directs the production of thyroid hormones. An enlarged thyroid gland (goitre) leads to the production of just enough, too little, & too much thyroid hormone (Calina et al., 2019). This improper production affects the rate of metabolism of the body

(Haugen et al., 2013). The extract of green tea resulted from hypothyroidism at a higher dosage in the model of rats by changing the functional and morphological aspects of the thyroid. Furthermore, commercial catechins have showcased a promising effect in inducing hypothyroidism which proved that the efficacy of GTE may be due to the goitrogenic or antithyroid properties of catechins that exist in tea (Chandra and De 2010). Chandra and De (2010) revealed that oral consumption of green tea at the concentration of 2.5 % and 5.0 % for about 30 days altered the histology and morphology. There are significant restricted activities of 5′-monodeiodinase type 1 (5′-DI1) and thyroid peroxidase (TPO) with upraised K+, Na + ATPase and resultant dropping in serum triiodothyronine (T3), thyroxine (T4), and rise in serum thyrotropin (TSH) level which initiates a state of total biochemical hypothyroidism. All these results suggested that GTC has beneficial effects as adjuvant treatment in hypothyroidism.

4.6. Anti-inflammatory effect

Neutrophils play a crucial part in inflammation and host defence but later may activate and assist the pathogenesis of a wide range of chronic and acute diseases (Calina et al., 2020, Islam et al., 2020, Kostoff et al., 2020). Green tea has been proven to employ anti-inflammatory activity via an unspecified molecular process. GTC, EGCG, actively restrained neutrophil elastase. Furthermore, EGCG in micromolar concentration represses the activity of ROS and restricted the process of apoptosis of activated neutrophils,
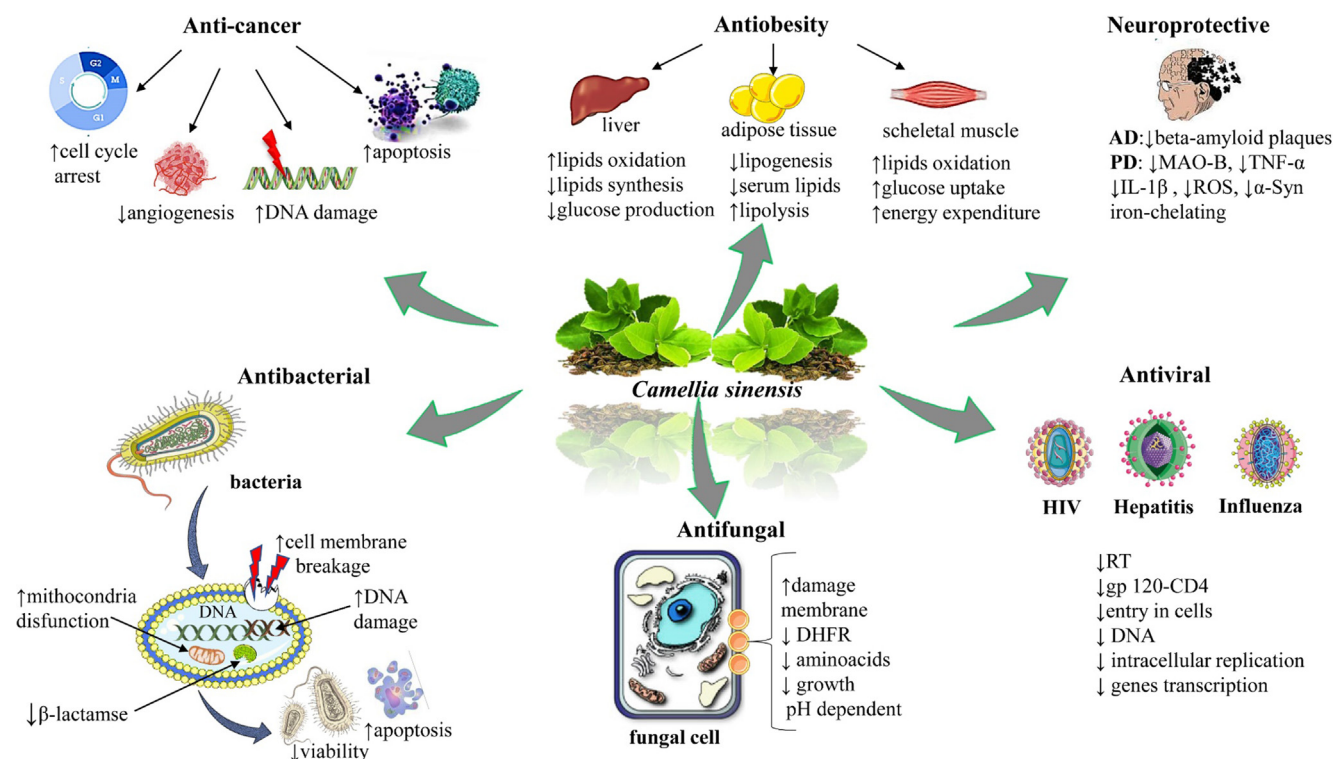
Fig. 5 The most important and representative pharmacological effects of bioactive compounds from *Camellia sinensis* (L.) Kuntze. Abbreviations and symbols: ↑increased, ↓decreased, DNA (Deoxyribonucleic acid), MAO-B (monoamine oxidase B), TNF-α (tumour necrosis factor alfa), IL-1β (interleukin 1beta), ROS (reactive oxidative species), α-Syn (alfa synuclein), DHFR, (dihydrofolate reductase), RT (reverse transcriptase), HIV (human immunodeficiency virus), AD (Alzheimer disease), PD (Parkinson disease).

and hinders chemokine-directed neutrophil chemotaxis *in vitro*. Both green tea extract and EGCG obstruct neutrophil-directed angiogenesis in an angiogenesis model, and oral application of green tea extract improves the resolution in a pulmonary inflammation model, thus remarkably suppressing the consequent fibrosis. These outcomes furnished molecular and cellular insights into the affirmed therapeutic properties of green tea and specified that EGCG is a powerful anti-inflammatory molecule with a curative ability (Donà et al., 2003).

Rheumatoid arthritis (RA) is a persistent inflammatory disease determined by the triggering of synovial tissue that lines the joint capsule, which implicates in the invasion of the bone and cartilage distinguished the advanced joint dysfunction (Ahmed 2010, Mititelu et al., 2020). Haqqi et al., (1999) suggested that green tea polyphenols (GTPs) prosperous in antioxidants can minimize the reoccurrence of pathogenic Th1-type cells and related pathogenic CII-specific IgG2a antibodies in the diseased joints. These affected joints also had lesser concentrations of inflammatory mediators (cyclooxygenase 2 (COX-2) and TNF-α) and cytokines (Rogoveanu et al., 2018). This data revealed that the GTPs decrease the severity and incidence of collagen-directed arthritis in the case of DBAy1 mice.

Pulmonary fibrosis is represented by the composite process of inflammation that results in the uncontrolled proliferation of fibroblast and escalating sedimentation of connective tissue in the parenchymatous cells of the lungs (El-Safti et al., 2014). There are different types of pulmonary fibrosis, but the major one is the "idiopathic" form. You et al., (2014) reported that the therapy with EGCG, not dexamethasone (DEX) diminished the rate of mortality and index scores of the lung, surpassed histological alterations in the lung, decreased precipitation of collagen, decreased content of malondialdehyde (MDA), increased activity of superoxide dismutase (SOD), the restricted proliferation of protected alveolgenisteinar epithelial type II (AE2) cells, (myo) fibroblast, and controlled serum levels of TNF-α, IL-10, IL-6, and transforming growth factor (TGF)-β1. EGCG treatment triggered Nrf-2 and other antioxidant enzymes (NQO-1 and HO-1) at the downstream level. Taken together, these outcomes determined that EGCG therapy remarkably improves irradiation-induced pulmonary fibrosis.

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the small intestine and colon which influenced a large populace of individuals across the globe. GTPs are certainly efficacious for application in ameliorating IBD and other related unusual complications, with their acknowledged anti-bacterial, antioxidant, and anti-inflammatory activities.GTPs are appeared to have minimum inflammatory reactions in signaling pathways, by downregulating NF-κB, IKK, and cytokines such as Bcl-2, Cox-2, inflammatory markers, and TNF-α, to protect against liver and many other inflammatory diseases (Liu et al., 2017). Many studies reported that GTPs have prebiotic effects which created a healthy and strong microbiota that may be responsible for the anti-inflammatory effects through the production of short-chain fatty acids via direct impact on claudin and occluding proteins (Sharifi-Rad et al., 2020). Ultimately, GTPs may stabilize the flora of the intestine which helps in the retrieval of IBD (Oz 2017).

Polyphenols work as anti-inflammatory compounds that restrict the symptoms of UTIs, Catechins persuade the production of cytokines such as IL-10 and IL-12, GTP reduces the expression of the TNF-α gene which is principal in *Escherichia coli* pathogenesis.

4.7. Antibacterial, antifungal and antiviral activities

4.7.1. Antibacterial

Urinary tract infections (UTIs) are the usual type of infection in males and females. *E. coli* is the main reason for this infection (Flores-Mireles et al., 2015). The expansion of antibiotic resistance in *E. coli* is a major complication (Taheri et al., 2021). Tea polyphenols at a concentration ≥ 5000 µg, showed bactericidal activity and at a concentration of 500 µg can restrict *E. coli* growth (Noormandi and Dabaghzadeh 2015). According to Reygaert and Jusufi (2013), the bactericidal effect is based on the fact that tea polyphenols downregulate the generation of proteins intricated in the biosynthesis of amino acid, proteins tangled in energy, carbon, and phospholipid metabolism and EF-2 (elongation factor for protein translation).

Catechins, by stopping the link of conjugated R plasmid inside the *E.coli*, have antitoxin and bactericidal effects. EGC can inhibit the gyrase enzyme activity by attaching to the site of ATP of the DNA gyrase β subunit of bacteria. The bactericidal function of catechin is because of the generation of hydrogen peroxide (Rahman et al., 2018). Hence, tea exhibits antimicrobial activity due to the presence of catechin and polyphenols as they damage the bacterial cell membrane. Catechins interfere with the β-lactamases expression in *Staphylococcus* sp. and restrict the extracellular release of verotoxin from enterohemorrhagic *E. coli* (EHEC) 0157 (Noormandi and Dabaghzadeh 2015).

Acne results in the inflammation, activity of *Propionibacterium acnes* bacterium, production of sebum by the sebaceous gland, and keratinization of the follicular keratinocytes. *Staphylococcus aureus, Propionibacterium granulosum, Staphylococcus epidermidis,* and *P. acnes* are the different bacteria present on acne-prone skin (Lee et al., 2019, Sifaki et al., 2020). Investigations suggested that tea polyphenols control the problem of acne via several mechanisms, by acting as anti-inflammatory, anti-lipogenic, and anti-microbial molecules (Saric et al., 2016). EGCG decreased sebum production by altering the AMPK-SREBP-1 signaling pathway in SEB-1 sebocytes. It also decreases inflammation by restricting the AP-1 and NF-κB pathways. It also directs the cytotoxicity of SEB-1 sebocytes via apoptosis and reduces the viability of almost all pathogenic microorganisms responsible for causing acne (Yoon et al., 2013).

EGCG not only do catechins restrict the extension of both Gram-positive and Gram-negative bacteria, but they raise the number of beneficial bacteria, such as bifidobacteria and lactobacilli (Taylor et al., 2005).

Streptococcus mutans are gram-positive bacteria and grow in rods and chains. These bacteria mainly account for oral health problems, such as plaque and tooth decay. They deteriorate carbohydrates, such as sucrose and lactose, with the help of lactic acid, which erodes the enamels of the tooth. *S. mutans* spread on teeth by metabolizing sucrose into a sticky sugar that let the attachment and aggregation of plaque. The plaque gathers in the mouth at indentations, dips, and fissures. Moreover, *S. mutans* are capable to cause deep-rooted infections in

the mouth of humans due to their toleration of acidity (Lemos et al., 2019). *Streptococcus sobrinus* is another species of oral bacteria with finer sticking abilities than *S. mutans*. However, *S. sobrinus* are not as usually available in fissures as *S. mutans*. Furthermore, *S. sobrinus* has been determined to be cariogenic. Because *S. sobrinus* and *S. mutans* have resembling shapes and results in dental caries, so, it becomes inconvenient to differentiate between these two (Conrads et al., 2014).

Staphylococcus epidermidis, bacteria that majorly grow on the membrane of mucous and skin of a human, are also gram-positive type. These white facultative anaerobic bacteria are the main concern in some hospitals because of their potential to cause an infection. Contained in a polysaccharide intercellular adhesion capsule, these bacteria can stick to the extracellular matrix and blood and assemble with other bacteria, resulting in biofilms that are related to infections. Moreover, they show a broad range of tolerance to several antibiotics comprising vancomycin, ciprofloxacin, and other glycopeptide drugs (Otto 2009).

Porphyromonas gingivalis is a very powerful and fatal bacterium that also presents in the mouth of a human. *P. gingivalis* captures cells and detriment their immune responses with the deterioration of the cellular matrix. Furthermore, *P. gingivalis* debilitate leukocytes, reorganize the infected cells' cytoskeleton, and degenerate the IgG antibodies. *P. gingivalis* utilize well-modified fimbriae to hold and assemble oral cells and saliva-coated apatites in the human mouth. Additionally, this bacterium can produce different enzymes with the capability to degrade host proteins both *in vitro* and *in vivo*. Green tea is important for dental health as it prevents the adherence of *S. sobrinus* and *P. gingivitis*(Palm et al., 2013, How et al., 2016).

The process of plaque emergence starts when bacteria cling to the tooth surface and produce a glycocalyx film. This film contains a glucan devised from glucosyltransferases (GTF) and arbitrates its attachment to the tooth. Numerous studies have concentrated on GTFs for the prevention of oral diseases. Many experiments reported the inhibitory property of GTC against the growth of *S. sobrinus* and *S. mutans* with a minimum concentration of restriction between 50 and 1000 μg/ml, and 250–500 μg/mL in the case of *P. gingivalis*(Bowen et al., 2018). Lakshmi and Parameswari (2017) reported the anti-cariogenic activity of EGCG against *S. mutans* by suppressing the specified virulence factors related to its cariogenicity. Moghbel et al., (2011) revealed a herbal mouthwash preparation including Iranian green tea extract with 1 % tannin could minimize the load of aerobic bacteria from the human mouth up to 26–32 % and also, due to this moderation it may inhibit plaque formation and consequently, halitosis.

The activity of EGCG was evaluated against the *S. aureus* and the *in vitro* investigation determined that the interaction of EGCG (negatively charged) to the lipids of the membrane (positively charged) destruct the structure of the membrane resulting in intramembranous seepage. EGCG carried out the inhibition of biofilm generation by *S. aureus* and further results in bacterial cell death by restricting the DNA gyrase of bacteria. Thus, EGCG manifests antifolate activity against DHFR and assists in the inhibition of DNA synthesis (Taylor et al., 2005).

Helicobacter pylori are well recognized as the causative agent of gastric cancer, peptic ulcer, and chronic gastric diseases. EGCG is safe and natural with physiochemical stability in the presence of acid in the stomach, which makes it a cura-

tive agent for the cure of gastric disorders at a concentration (inhibition) of 100 μg/ml in the case of *H. pylori*(Taylor et al., 2005, Kusters et al., 2006). EGCG blocks out the glycosylation of TLR-4 (toll-like receptor), resulting in *H. pylori* infection, which destroys *H. pylori*-directed host cell signaling and provides protection from gastric cytotoxicity (Taylor et al., 2005).

Mycobacterium tuberculosis (MTB) is the causative agent of tuberculosis, which activates and induces the pro-inflammatory cytokines (TNF-α) and ROS for its proliferation inside the host cells (Fatima et al., 2012, Fatima et al., 2013). EGCG acts as an inhibitor of reactive nitrogen intermediates and ROS pathways. It also results in stronger inhibition of MTB 85B and TNF-α gene expression in comparison to the first line of antibiotics (Fatima et al., 2012, Fatima et al., 2013).

4.7.2. Antifungal

More than 600 varied species of fungi are discovered to cause usually life-threatening diseases in mankind. The results of EGCG are mainly studied against dermatophytes such as *Trichophyton rubrum* and *Trichophyton mentagrophytes*; and yeast strains such as *Candida glabrate* and *Candida albicans*(Das et al., 2014). In the case of catechins, pyrogallol catechin showcases greater antifungal activity against *C. albicans* as compared to catechol catechin. The combined use of EGCG with fluconazole and amphotericin B in well-defined concentrations restricted the growth of amphotericin B and fluconazole-resistant *C. albicans*(Lakshmi and Parameswari 2017). According to Farhad Mollashahi et al., (2015), the antifungal activity of green tea was based on time and its inhibitory action which did not reduce over time. Das et al., (2014) documented that the formation of biofilm by *C. albicans* was damaged by the EGCG. It also produces spores in the membrane by attaching to ergosterol and interrupting the osmotic integrity. This results in the seepage of intracellular ions, therefore damaging the cell. Some researchers have reported the antifolic activity of EGCG against dihydrofolate reductase (DHFR), restriction to this important enzyme required for the biosynthesis of different amino acids, pyrimidines, and purines, results in inhibition of the growth of the fungal cells. They also determined that EGCG has a pH-dependent effect such that the inhibitory concentration of microorganisms was diminished by 10 times at more pH in comparison to low pH.

4.7.3. Antiviral

Recent studies revealed that EGCG can boost the immunity of an organism, therefore serving to treat HIV (Fig. 5). For HIV infection to occur, the HIV requires to get enter into CD4 (+) lymphocytes via a step based on the attachment to the CD4 molecule and further proliferation of the virus intracellularly (Boda et al., 2018, Popović-Djordjević et al., 2022). EGCG manifested a vigorous affinity for CD4 and, by interacting with them, could successfully restrict the attachment of the HIV envelope (gp120) (Sinija and Mishra 2008). HIV-1 infection eventually results in diminished immunity because of the binding of envelope glycoprotein 120 (gp120) of HIV-1 virion to the receptor of CD4 in complex with the receptor of chemokine on the surface of the T cell. The infection resulting from the viral entry and the successive deterioration of T cells leads to acquired immunodeficiency syndrome (AIDS). Isolates of HIV-1 are recognizable by the prime co-receptor utilized for

cell entry, chemokine receptors CCR5 (R5) or CXCR4 (X4). Based on the genomic variation, HIV-1 has been expressed into three groups: O, M and N. Majorly the infection of HIV-1 has resulted from the M group viruses, and these are further classified into 9 subtypes (K, J, F-H, and A-D) with C and B as the usual one (Wilen et al., 2012).

Nance et al., (2009) explained that a diversity of natural products, like polyphenols, flavonoids, alkaloids, and ribosome-inactivating proteins possess great anti-HIV activity. EGCG has been stated to limit the replication of HIV-1 by focusing on the numerous steps in the HIV-1 life cycle, such as obstructing the protease and reverse transcriptase (RT) activity, sealing interaction of gp120-CD4 by attaching to CD4, and deactivating virions, but all of this was possible at a greater non-physiologic concentration (i.e. greater than 10 μM) of EGCG. EGCG restricted the infectivity of HIV-1 on macrophages and human CD4 + T cells in a dose-dependent manner. At 6 μM concentration, ECGC inhibited the production of HIV-1 p24 antigen across a wide spectrum of both laboratory-adapted subtypes and HIV-1 clinical isolates.

Influenza infection is the main source of acute respiratory disease and turns into an epidemic across the world. To reduce the rate of fatality, a wide variety of prevention mediation have been applied which includes coughing etiquette, hand hygiene, gargling, and the use of facemasks (Islam et al., 2020, Neagu et al., 2021, Islam et al., 2022). Influenza viruses (A and B) belong to the Orthomyxoviridae family and are the main reason for respiratory disease. Several antiviral drugs such as rimantadine and amantadine are used to treat this disease. However, numerous strains of viruses have generated resistance to these drugs and therefore, EGCG has been employed as an important source for influenza infection (Das et al., 2014). Matsumoto et al., (2011), registered about 197 eligible healthcare workers and arbitrarily allocated them to an intervention; 98 were allotted to get theanine/catechin capsules and the other 99 to placebo. The occurrence of influenza infection was abundantly lesser in the group of the theanine/catechin (4.1 %) in comparison to the placebo group (13.1 %). The frequency of laboratory-confirmed cases was also low in the catechin/theanine group (1.0 %) than in the placebo group (5.1 %), but this difference was not denotative. Lakshmi and Parameswari (2017) suggested the antiviral property of catechins against the influenza virus is arbitrated not only because of certain interactions but by altering the physical properties of the viral membrane. EGCG carried out the alteration of physical integrity and agglutination of the virus, thus avoiding their absorbance on MDCK cells (Madin-Dardy Canine Kidney). It also stopped the growth of the influenza virus by restricting the acidification of intracellular components like lysosomes, endosomes, etc and restrained the entry by resulting in haemagglutination (Das et al., 2014).

Adenovirus is related to the family of Adenoviridae, a non-enveloped virus comprised of linear, double-stranded DNA and nucleocapsid. About 5–10 % of infections related to the upper respiratory tract in children are resulted due to this virus (Weber et al., 2003). EGCG deactivated the adenovirus by inhibiting the protease's activity. It also restrained the late stages of infection and its inside growth (Weber et al., 2003).

Enterovirus 71 is an RNA virus of single-stranded nature, related to the family of Picornaviridae and causes cutaneous, neurological, and life-threatening mouth, foot, and hand dis-

ease (Ho et al., 2009). EGCG exhibit its antiviral activity by restricting the replication of the virus and further the generation of viral progeny (Ho et al., 2009).

Steinmann et al., (2013) described the Hepatitis C virus as a positive-strand RNA virus that belongs to the Flaviviridae family with hepatic diseases including hepatocellular carcinoma, liver failure, and cirrhosis. Entry into the host cell comprises a relation between the extracellular virion that is coupled with lipoproteins and various receptors on the cell membrane of the host. These include possibly low-density lipoprotein receptor (LDL-R), Niemann-pickC1-like 1 (NPC1L1), occludin (OCLN), claudin 1 (CLDN1), CD81, EGFR, and scavenger receptor type B class 1 (SR-BI). It has been determined that the lipoprotein receptors LDL-R and SR-BI act first then the component of tight junction OCLN and CLDN1 and CD81.

Such relations contribute to the migration of the virus-receptor complex along the cell surface from the blood-side surface of the hepatic epithelium where CD81, DR-BI, and LDL-R are presented to the region of tight junction, where OCLN and CLDN1 are confronted. These events imitated by virion, directed the turn-on of receptor tyrosine kinase signaling like EGFR which results in clathrin-dependent endocytosis of the virion. Endosome acidification assigned a fusion peptide activity inside the glycoproteins E1 or E2, the viral envelope fuses with the membrane of the endosome and released the nucleocapsid into the cytoplasm. EGCG is reported to target the virus particle and restrict its entry by impairing the binding of the virus to the surface of the cell (Steinmann et al., 2013).

Hepatitis B virus is a small enveloped virus that belongs to the Hepadnaviridae family. It can be transmitted perinatally, sexually, and parentally (Das et al., 2014). EGCG was capable of decreasing the extracellular HBV DNA level and HBV-specific antigens expression, and restricting the intracellular intermediates replication, thus resulting in a declined production of covalently closed circular DNA (Das et al., 2014).

Epstein-Barr virus infection (EBV) is a herpes virus that belongs to the family of Herpesviridae. EGCG limited the immediate-early genes transcription and lytic protein expression, thus blocking the lytic cycle of EBV (Das et al., 2014).

Ebola virus infection (EBOV) results in Ebola haemorrhagic fever. A host chaperon protein, HSPS5, was identified as a valuable target for the treatment of EBOV infection and it was determined that EGCG carried out the restrainment of HSPS5, decreased the generation of new viruses via its inhibitory action on HSPS5 (Xu et al., 2017).

4.8. Other pharmacological properties

4.8.1. Anti-glaucoma

Glaucoma is a multifarious optic neuropathy distinguished by the continuing depletion of retinal ganglion cells (RGCs) and their axons. High intraocular pressure (IOP) looks to be associated with the death of RGC, both in the instance of acute closed-angle glaucoma, when there is an unexpected rise of IOP, and in the case of primary open-angle glaucoma (POAG), which evolves steadily over time (Weinreb et al., 2014). Many risk factors linked with the pathogenesis of glaucoma are the use of topical or systemic corticosteroids, diabetes mellitus, myopia, family history of glaucoma, hispanic

origin, black race, and older age (Pimentel et al., 2015). Numerous pathogenic systems seem to be tangled in this disease such as glutamate neurotoxicity, autoimmunity activation, deprivation in neurotrophic growth factor, OS, ischemia, and elevation in IOP (Tezel 2006).

GTCs may protect against glaucoma and other diseases of the eye. Pooman et al., (2018) reported that the tissue of the eye of rats that consume green tea (such as the retina and lens) absorbed catechins present in green tea which upgraded their vision by 20 %.

Two prime mechanisms appeared as protective:

(i) cyclic adenosine monophosphate (cAMP)
(ii) management of mitochondrial dysfunction and OS.

The cAMP is a secondary messenger intricated in discrete cellular pathways. It is important in managing aqueous humour (AH) reabsorption/secretion and in controlling the expression of the neurotrophin gene for RGC durability.

OS is the foremost target of protective agents including melatonin. Especially, the three composites (melatonin, forskolin, and brimonidine) all impart their contribution at a similar time to neuroprotection and IOP control, so that the alliance of these compounds together with the latest therapies of glaucoma could result in auxiliary assistance for patients (Rusciano et al., 2017).

4.8.2. Effects on infertility

Sharpe (2017) determined that the problem of infertility impacts around 15 to 30 % of couples that want to have a baby, therefore, infertility becomes a sensitive issue across the world. ROS are existing in minor concentrations in the genital parts of females and males. Uncontrolled ROS leads to the generation of OS, which causes the deterioration of proteins, lipids, and DNA. Such changes result in reduced sperm motility, raised morphological defects, and compromised vitality in the males whereas, in females, OS interferes with the maturation of the oocyte, and may also restrain the *in-vitro* maturation of the oocyte (Roychoudhury et al., 2017). The major mechanisms of catechins in various pathways (adenosine monophosphate-activated protein kinase, AMPK; low-density lipoprotein, LDL; adenosine triphosphate, ATP; ferric iron, Fe^{2+}; calcium ion, Ca^{2+}; cyclin adenosine monophosphate, cAMP and reactive oxygen species, ROS) suggest that GTPs can improve the fertility problem by upgrading the quality of embryo (Sharpe 2017). Supplementation of GT can minimize the level of OS and enhance the quality of the gametes in both females and males. At a lesser concentration, it exerts promising effects on oocyte and sperm parameters while they greatly obtain a negative effect at analogously raising concentrations.

Green tea supplementation in male candidates can notably upgrade the viability and motility of sperm parameters. In female candidates, appreciable refinement has been determined in the quality of embryo and oocyte along with clinical pregnancy and the fertilization rate as described by various animal model studies. The EGCG has the environment and cell-type-specific responses because of the signaling molecules and expression of a gene that are distinguishingly managed. Hence, a further detailed investigation is needed to evaluate how EGCG works in the case of reproductive gametes *in vivo* (Roychoudhury et al., 2017).

4.8.3. Antithrombotic

Thrombosis is the emergence of a blood clot in the venous and arterial systems(Wojciechowski et al., 2017, Sharifi-Rad et al., 2023). It results in different diseases such as limb ischemia, pulmonary embolism, stroke and myocardial infarction. Jin et al., (2008) evaluated that the GTCs showcase their potential antithrombotic effect by the restriction of platelet accumulation. EGCG provides an antiplatelet activity by regulating the different cellular targets, such as maintenance of Ca^{2+}-ATPase activity, inhibitions of phosphoinositide-specific phospholipase $C\gamma2$ (PLC$\gamma2$), phosphorylation of tyrosine protein, the liberation of amino acid, and elevation of cellular prostaglandin D2 (PGD2) levels, which may underlie its positive result on the atherothrombotic diseases.

4.8.4. Anti-photoaging

The polyphenols in green tea were reported to have great ROS-neutralizing activity, which makes it a prospective agent in anti-photoaging treatment. Recently, tea polyphenols were given to UV-mediated photoaging mice. A remarkable rise in the content of hydroxyproline was noticed *in vitro*, and the activity of catalases is hiked along with reduced content of protein carbonyl. The aqueous extract of green tea was found to upgrade the mice's skin affected by photoaging. It was found to raise the level of elastin and collagen fibres and decreased the collagen-degrading MMP-3 enzyme expansion, hence showcasing the antiwrinkle effect (Prasanth et al., 2019).

5. Therapeutic perspectives

Despite green tea is an eminent fat burner, it is well known to diminish or limit various other factors such as vitamin B12, and haemoglobin. It is indicated that the intake of green tea, beyond regulation, does suppress the level of haemoglobin. This is because of the antioxidants like polyphenols that exist in the tea. These polyphenols hold the iron, inhibiting its absorption in the intestine. Although green tea is one of the best powerful drinks, constant intake of green tea can reduce the level of haemoglobin and hence it is preferable to take an iron-rich diet or couple green tea consumption with iron-rich supplements. Consuming multivitamins and iron supplements will not only overcome the negative effects of green tea but will also help green tea to successfully burn fat and remove the free radicals from circulation (Sachdev and Jothipriya 2017). An interesting and promising therapeutic aspect is represented by the potential effect of prolonging life through chronic consumption of green tea. Drinkers of green tea are at a bottom risk of cancer and other diseases, which gives a clue that it could work as a life prolonger. In an investigation of 40,530 Japanese individuals, those who consume five cups or more than that green tea per day were less probably to die for 11 years: Death with other causes: 23 % lesser in females, and 12 % lesser in males. Death because of heart disease: 31 % lesser in females, 22 % lesser in males. Death due to stroke: 42 % lesser in females, and 35 % lesser in males, respectively. In another investigation of 14,001 elderly Japanese people, it was found that individuals who consume green tea were 76 % less expected to die in 6 years (Suzuki et al., 2009). EGCG prolongs the lifespan through the mechanism that is based on the 5′adenosine monophosphate-activated protein kinase/nicotinamide adenine dinucleotide-dependent

deacetylase sirtuin-1/forkhead pox protein (AMPK/SIRT1/ FOXO) pathway and through mitohormesis. AAK-2/AMPK might be triggered by the EGCG-directed momentary rise in ROS, which regulated EGCG-directed longevity by decreasing the internal level of ROS. AAK-2/AMPK has been manifested to change the metabolism of NAD+, which turns on the SIRT1/SIR-2.1. As a result, SIRT1/SIR-2.1 starts up the FOXO/DAF-16 transcription factor, which carried out the up-regulation of many anti-oxidant genes (Xiong et al., 2018).

5.1. Strategies for enhancing bioavailability and therapeutic efficacy of tea bioactive compounds

EGCG is considered to be a potent antitumor and antioxidant agent, but this has poor absorption and poor stability in the blood and intestinal environment. Research has shown that catechins associated with ascorbic acid can improve their absorption in the digestive system. To increase the bioavailability and therapeutic effect, various methods have been tried, such as chemical structure changes (Dai et al., 2020) and/or incorporation into pharmaceutical nanoparticles to obtain a targeted therapeutic effect (Fig. 6):

i. Methylation- involves modification of either all or part of the eight phenolic hydroxyl groups to methyl ester in the benzene ring. Saijo (1982) isolated a compound named EGCG3''Me whose stability and solubility get modified after methylation. Its stability was 9-fold greater than that of the original EGCG in the case of oral absorption.

ii. Acyclization methods- basically involve the reaction of the phenolic hydroxyl group of catechin molecules with different acylation reagents like acyl chloride to a phenolic ester to decrease the solubility of water and raise the solubility of fat (Wang et al., 2016).

iii. Glycoside modification- involves the addition of monosaccharides of hydrophilic nature to eight phenolic hydroxyl groups of catechin. Moon et al., (2006) utilized sucrose-6-glucosyltransferase to carry the reaction of EGCG with sucrose and produced EGCG-7,4'-O-alpha-D-glucopyranoside, EGCG-4'-O-alpha-D-glucopyranoside, and EGCG-7-O-alpha-D-glucopyranoside with 114, 55, and 49 fold increase in water solubility than of sole catechin, respectively.

iv. Preparation of nanoparticles of tea bioactive compounds.

Nanoparticles are molecules that have dimensions in the nanoscale (Docea et al., 2020; Javad Sharifi-Rad et al., 2022). Due to their versatility, they are considered an excellent carriers for drugs at their specific site and location (Pinzaru et al., 2018, Matei et al., 2021).

Catechins are highly unstable molecules as they are susceptible to different conditions such as metal ions, pH change, stress and oxygen. The nanoparticle-encapsulated delivery method is believed to be the better option to protect the catechin against unfavourable conditions (Salehi et al., 2020).

EGCG loaded in lipids showed improved stability. Most of the nanoformulations are water-based, and the loading of EGCG in liposomes promotes the formation of the hydrogen bond between the polar head group and hydrophilic catechins.
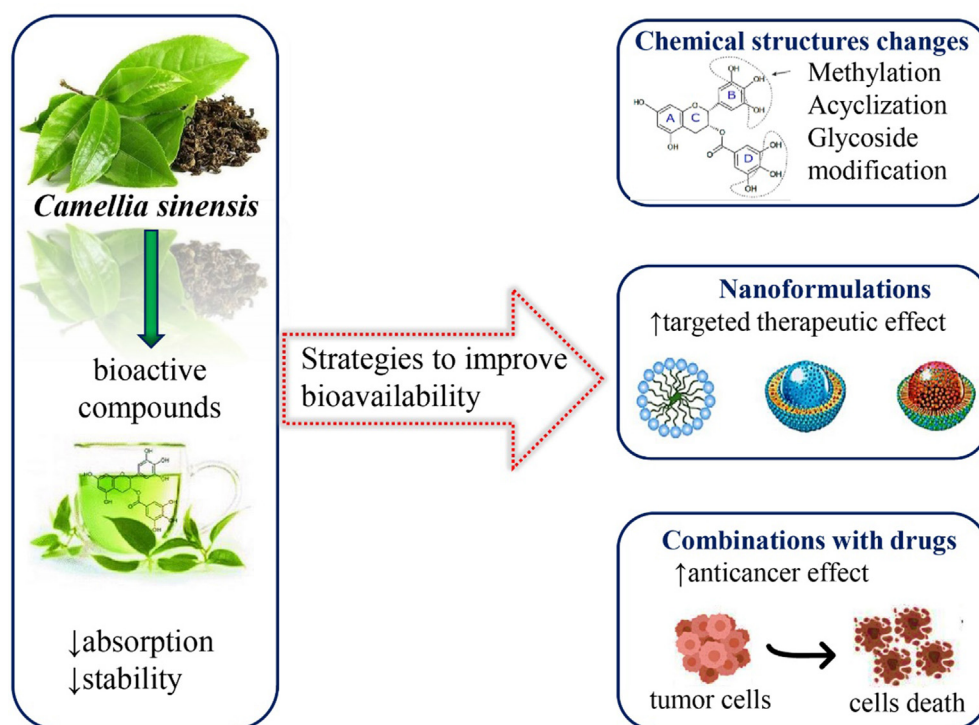

Fig. 6 Summarized scheme with the most important strategies to improve bioavailability of bioactive compounds of Camellia sinensis (L.) Kuntze.

Table 4 Nanoformulations of tea and their potential therapeutic effects.

Nanoparticles of tea components	Biological properties	Therapeutic effects	References
ZnO nanoparticles from green tea leaves	antibacterial	strong inhibition of *Aspergillus niger, Escherichia coli, Staphylococcus aureus*	(Irshad et al., 2018)
Silver nanoparticles from tea leaves	antibacterial	strong inhibition of *Klebsiella pneumonie,Escherichia coli, Corynebacterium diptheriae, Vigna radiata*	(Rajput et al., 2020)
	antimicrobial cytotoxic	↓gram-positive bacterias at less concentration without causing any harm to HaCaT mammalian cells	(Rolim et al., 2019)
DOX-assisted green tea nanoparticle	anticancer	↑ cytotoxicity in HT-29 cells	(Chen et al., 2019)
Polysaccharide nanoparticles of EGCG	anticancer	↓ tumorigenesis in prostate cancer cells	(Rocha et al., 2011)
Gold and silver nanoparticles from green tea	antimicrobial	↑ antibacterial activity	(Onitsuka et al., 2019)
Gold nanoparticles of green tea	anticancer	↑toxicity against MCF-7 and Ehrlich's ascites carcinoma	(Mukherjee et al., 2015)
Green tea nano complex with sunitinib	anticancer	↑anticancer activity of sunitinib	(Yongvongsoontorn et al., 2019)
EGCG/cisplatin-loaded gelatin nanoparticles	anticancer	synergistically overcome the resistance to cisplatin ↑anticancer activity in lung cancer cells	(Chen et al., 2020)
EGCG-loaded gold nanoparticle	anticancer	↑EGCG delivery at the targeted site ↑cytotoxicity in Ehrlich tumour	(Safwat et al., 2020)
EGCG and 5-FU co-loaded nanoparticles	Colon cancer	↑ anti-cancer activity of 5-FU	(Wang et al., 2019)

Abbreviations and symbols: ↑ (increased), ↓ (decreased), ZnO (Zinc oxide); DOX (Doxorubicin), EGCG (Epigallocatechin gallate), 5-FU (5-fluorouracil).

Based on an *in-vitro* study, chitosan-tripolyphosphate nanoparticle was found to be a suitable one to improve the stability of EGCG under alkaline conditions (Cai et al., 2018). Chitosan-encapsulated EGCG exhibited greater stability as compared to free EGCG inside the gastrointestinal tract (Sharifi-Rad et al., 2021d) Additionally, they improve the stability and pharmacokinetics of certain drugs (Chen and Lin 2015) as shown in Table 4.

5.2. Synergistic effect of tea catechins combined with antitumor drugs in cancer treatment

The usage of EGCG along with tamoxifen improved the pharmacokinetics of orally consumed tamoxifen in the liver and intestine by restricting CYP3A and P-Glycoprotein by EGCG. EGCG in combination with sulindac remarkably up-regulated the expression of genes related to growth arrest, with a 3-fold

Table 5 Combination of catechin with anticancer drugs and their synergistic therapeutic effects.

Combinations	Cancer type	Therapeutic effect	References
EGCG + Resveratrol	head and neck cancer	↑ apoptosis ↓cancer cells' growth	(Amin et al., 2021)
Green tea extract + Paclitaxel	ovarian cancer	↑ apoptosis	(Panji et al., 2021)
EGCG + Cisplatin	biliary tract cancer	↑ cell cycle arrest	(Mayr et al., 2015)
Catechin + Doxorubicin	liver cancer	↑anticancer activity of doxorubicin	(Li 2010)
EGCG + Tamoxifen	breast cancer	↑synergistic cytotoxicity	(Chisholm et al., 2004)
EGCG + Celecoxin	pancreatic cancer	↓IL-1 ↓tumorigenesis	(Härdtner et al., 2012)
Catechin + Am80	lung cancer	down-regulation of histone deacetylase 6,5,4 which induced apoptosis cancer cells	(Oya et al., 2017)
EGCG + Tapentadol	breast cancer	↓proliferation ↑cell-cycle arrest	(Bimonte et al., 2019)
EGCG derivative + Paclitaxel/Cisplatin	non-small cell lung cancer	↑anticancer activity ↓ EGFR phosphorylation	(Zi et al., 2020)

Abbreviations and symbols: ↑ (increased), ↓ (decreased), IL-1 (interleukin-1), Am80(synthetic unnatural retinoid; EGFR (epidermal growth factor).

rise in p21WAFI and a 12-fold increase in DNA damage-inducible 153 (GADD153). Meanwhile, a nil effect was reported when these two molecules were tested solely (Cai et al., 2018). Other treatment strategies are listed in Table 5 and Fig. 6.

6. Conclusion

This paper reveals the numerous advantages of different teas for their anti-oxidant, anti-inflammatory, anti-thyroidal, anti-thrombotic, anti-fungal, anti-bacterial and anti-viral properties. They are also being utilized to treat Alzheimer's, Parkinson's, oral cavity, and cardiovascular diseases. There is also a broad range of applications of teas in diabetes mellitus, OS associated with infertility, cancer, angiogenesis, pulmonary fibrosis, skin disorders, and inflammatory bowel diseases. Even though the clinical data is still restricted, this article determines the place of teas in both the alternative and conventional medical applications to prevent or help in the therapeutic conventional approach. There is a need for advancement in the area of bioavailability research of tea catechin and nanoformulations to improve accessibility and possible areas of application[183–186]. Multiple molecular targets and disease targets are expected to be explored and research improved to find a more stable, specific, and potent formulation of catechin.

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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