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SHORT REVIEW

Catechins and Theaflavins: An Overview on Therapeutic Application

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Abstract

Flavonoids are a sort of natural substance which are basically plant secondary metabolites having a polyphenolic structure present in a wide range of food products. Flavonoids have become a vital constituent in nutraceutical, pharmacological, therapeutic, and cosmetic fields. This is owing to their capability to regulate essential cellular enzyme activity along with anti-cancer, anti-oxidative, anti-mutagenic, and anti-inflammatory effects. Through the revelation of a minimal cardiovascular death rate and the deterrence of CHD, research on flavonoids has gotten a boost. The functional mechanisms of flavonoids are still not completely known. Molecular docking and bioinformatics information are also been used to forecast potential flavonoid functions. Flavonoids are divided into several categories. Catechins and Theaflavins (TF's) are two types of flavonoids that have been discussed in this review. ROS scavenging property of tea catechins and polyphenols have been demonstrated in vitro, and they may also serve as indirect antioxidants via their influence on transcription features and enzyme actions. There are a number of antioxidant polyphenols called collectively as "theaflavins" that are produced during the enzymatic oxidation (sometimes referred to mistakenly as "fermentation") of black tea leaves by flavan-3-ol condensation Theaflavin-3-gallate, theaflavin-3'-gallate, and theaflavin-3-3'-digallate are the major theaflavins.

Keywords: Catechins, Flavonoids, Plants, Secondary Metabolites, Theaflavins

1. Introduction

Flavonoids are a sort of natural substance which are basically plant secondary metabolites having a polyphenolic structure present in a wide range of food products such as fruits, plant-based products, and beverages. In terms of biochemical and antioxidant qualities, they are associated with a slew of ailments, including cancer, alzheimer's, and atherosclerosis[1-3]. In a variety of nutraceutical, pharmacological, medicinal, and cosmetic products due to their numerous health-promoting properties, flavonoids are an essential component. This is owing to their capability to regulate essential cellular enzyme activity along with anti-cancer, anti-oxidative, anti-mutagenic, and anti-inflammatory effects. Xanthine oxidase (XO), cyclooxygenase (COX), lipoxygenase, and phosphoinositide 3-kinase (PI3K) are all enzymes that flavonoids may block[4-6].

It is possible to find flavonoid compounds in different parts of the plant as they are derived from plants. Flavonoids are essential for the health and growth of vegetables, as well as their defence against plaques[7]. These phenolic compounds having least molecular weight have been distributed all over the plant kingdom. They are also one of the most unique compounds found in advanced plants. Several

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flavonoids are readily identifiable as flower colours in the majority of angiosperm groups. In addition to flowers, they can be found in other areas of plants[8]. Fruits, vegetables, tea, chocolate, and wine are just a few examples of the many plant-based foods and beverages that include dietary flavonoids as an antioxidant. Flavonoids are further subdivided into chalcones, flavones, flavonols, and isoflavones, each with their own unique chemical structure and biological activity. Each of these subcategories has its own primary sources of information. Onions and tea, for example, are rich sources of flavonols and flavones.

Flavonoids are used by plants, animals, and microbes for a wide range of biological purposes. Certain areas in plants have long been known to produce flavonoids, which is linked to flower and fruit colours and odour which entice pollinators as a consequence, fruit dispersion that aids in the development of seedlings as well as seed and spore germination[9]. Plants are protected from numerous biotic and abiotic challenges by flavonoids and act as characteristic UV filters, which are indicator molecules, allopathic components, phytoalexins, detoxifying chemicals, and antimicrobial defensive compounds[10].

Flavonoids may serve a performing job in plant heat adaptation and cold tolerance, as well as frost hardiness and drought resistance. According to Jorgensen,[11,12] the first developments in floral genetics were made mostly through mutation approaches that affected flavonoid-originated flower colours, and he found that functional gene silencing in plants has something to do with flavonoid biogenesis.

Human and animal health has been linked to increased consumption of flavonoids, which are currently being studied for their role in disease treatment and prevention. Flavonoids, the pigments that give fruits, herbs, vegetables, and medicinal plants their brilliant hues, number approximately 6000. Dixon and Pasinetti researched plant flavonoids and isoflavonoids in depth and explored their use in agriculture and human neuroscience[13]. Flavonoids have been studied for their anti-disease properties in humans and plants by Kumar and Panday[14]. While reviewing Alzheimer's Disease (AD) and current therapy techniques, Panche *et al.* went into great length about the utilisation of flavonoids for the management of AD and the processes involved[15]. The purpose of this study is to highlight current investigations and advanced trends on flavonoids, as well as their functions as nutritional and health advantages, wide classification, and prospect research directions.

2. Chemistry and Classification of Flavonoids

Flavonoids are a group of natural chemicals generated from plants with various phenolic structures. Studies on oranges directed to the identification of a novel chemical, vitamin P, in early 1930, which was assumed to be a vitamin of a novel class. Later, it was discovered that this chemical was flavonoids (rutin), and there are now over four thousand kinds of flavonoids known. The structure of flavonoids is composed of two rings of benzene (A and B as depicted in Figure 1), having a

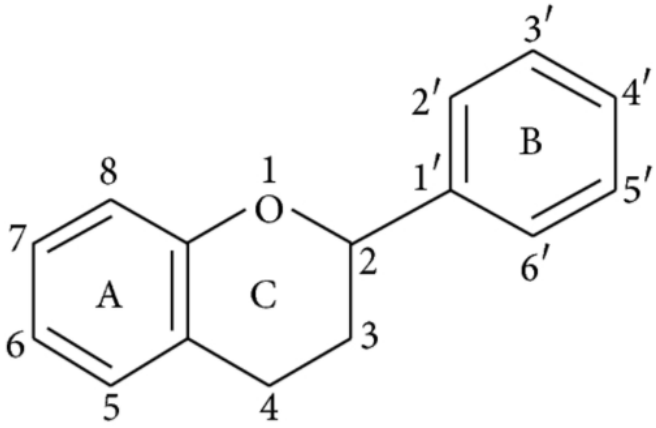
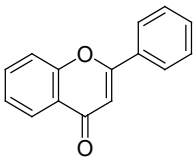
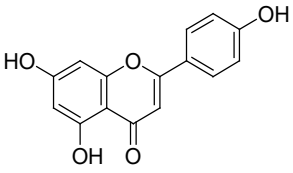
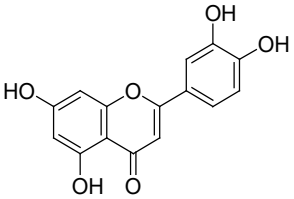
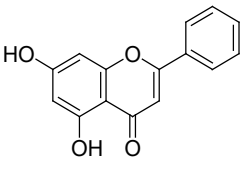
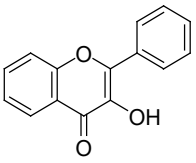
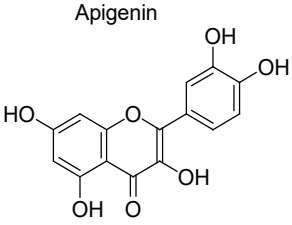
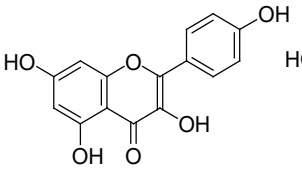
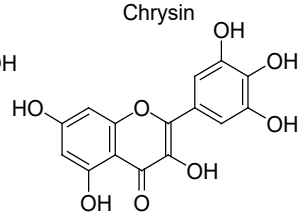
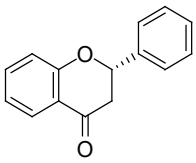
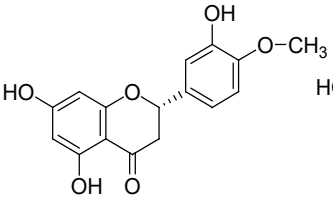
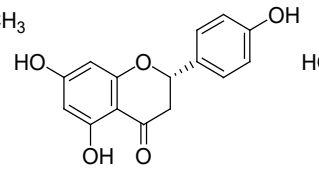
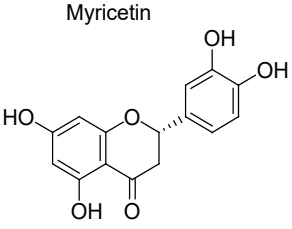
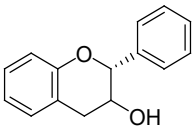
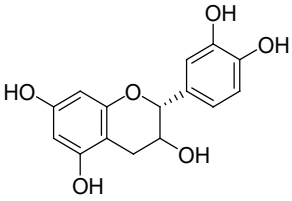
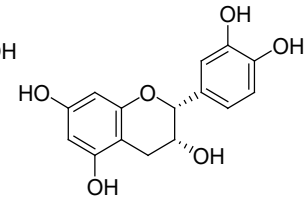
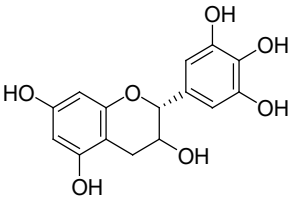
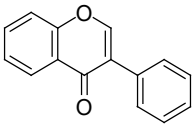
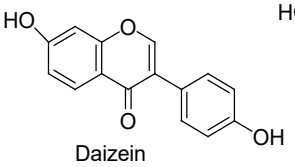
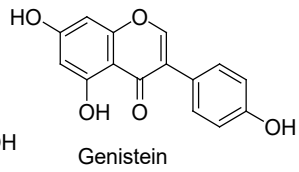
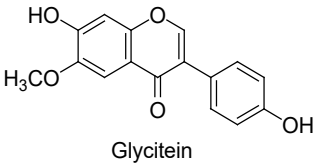
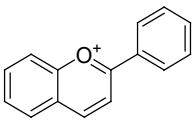
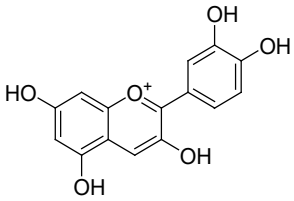
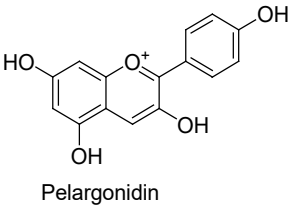


Figure 1. Basic structure of flavonoids.

Table 1. The structure of important flavonoids

Groups	Structure backbone	Examples
Flavones		 Apigenin;  Luteolin;  Chrysin
Flavonols		 Quercetin;  Kaempferol;  Myricetin
Flavanones		 Hesperetin;  Naringenin;  Eriodictyol
Flavanols		 Catechin;  Epicatechin;  Gallocatechin
Isoflavones		 Daizein;  Genistein;  Glycitein
Anthocyanins		 Cyanidin;  Pelargonidin

fifteen-carbon structure joined through a heterocyclic pyran ring (C).

Flavonoids are divided into flavones (chrysin, apigenin, luteolin), flavonols (myricetin, isorhamnetin, kaempferol and quercetin), flavanones (eriodictyol, hesperetin and naringenin), and flavanols (epicatechins, catechins, gallocatechin, and theaflavins). The structure of flavonoids is shown in Table 1. The oxidation and replacement patterns in the C ring of various flavonoids differ. Single compounds within a class, on contrast, differ in the way the A and B rings are substituted[16].

3. Sources of Flavonoids

Flavonoids are components present in the majority of plant parts, particularly photosynthesizing cells of plant, and they are a broadly dispersed set of plant phenolic constituents. These are an important constituent of both human and veterinary foods[17,18]. Flavonoids are plant-derived phytochemicals that cannot be synthesised by humans or animals. Veterinary foods made with plants are the only resource of flavonoids discovered in animals because they are incompetent in producing flavonoids in situ. Plant-derived flavonoids have been isolated in thousands of variations from a variety of plants. Table 2 lists the subgroups of flavonoids that are typically found in dietary sources [19-21]

4. Flavanols

Catechins, epigallocatechin gallate, epicatechin, procyanidin, gallocatechin, and theaflavins are examples of flavanols. Black tea, apples, fruit juice, tea, beer, wine and hops are all rich in this type of flavonoids. Flavonols are the flavonoids found abundantly in food, with kaempferol, myricetin, quercetin being the other three highly frequent flavonoids. Citrus fruits and celery have the most flavanones and flavones, respectively. Catechins are abundant in green and black teas, as well as red wine, and berries and strawberries are rich in anthocyanins. Isoflavones are not present in other foods except soy foods. Flavonoids, a primary colouring elements found in all plant-based meals, are found in flowering plants. Flavonoids, which give food its colour and flavour, play an important function. Furthermore, they are found to have protective action against enzymes and vitamins[22].

4.1 Catechins

Catechin is a 3,3',4',5,7-pentahydroxyflavan exist in two steric forms of (+)-catechin originated from catechu of the *Acacia catechu* L extract. Figure 2 shows the structural formula of eight catechins as well as their enantiomers[23-25]. Furthermore, catechin is the chemical family identity for the substances formed from catechin in a comprehensive sense. Catechins can be found in berries, persimmons, tea, apples, cacao, grapes among other foods and herbs.

Tea, which is made from the leaves and flower heads of the *Camellia sinensis* plant, is the most abundant catechin resources. Catechins, comprising of (-)-epicatechin, (-)-epicatechin-3-gallate (ECg), (-)-epigallocatechin, and (-)-epigallocatechin-3-gallate, are the primary components in green tea (EGCg) and contains (-)-epigallocatechin-3-gallate (EGCG) as the primary catechin (Figure 2), which has various health benefits including neuro-protective, anti-malignant, anti-fattening, anti-cardiovascular, hypoglycemic, anti-infectious and liver protective activities.

Tea has been proven to have anticancer qualities in a variety of human epidemiological and clinical trials, and these findings have been backed up by cell and animal based experimental procedures, while there have also been studies with contradicting results. Furthermore, detailed chemical mechanisms for EGCG and other catechins' activities have been proposed. One of the more intriguing processes is the participation of reactive oxygen species (ROS). EGCG is recognized to have anti-oxidant and pro-oxidant properties in regard to ROS. According to many lines of evidence, EGCG may both scavenge and increase ROS production[26].

Tea catechins are being used in therapeutic, pharmaceutical, and beautifying goods as a result of these beneficial effects, and they are being explored in a variety of ways.

4.1.1 Anti-oxidant Activity

Catechins have been well documented for having anti-oxidant properties. They are also studied in order to improve their stability and absorption rate into the humans. Recent research has centred on maximising anti-oxidant effectiveness. Catechins and Gallic acid have sustained anti-oxidant properties due to galactan

Table 2. Subgroups of flavonoids that are typically found in dietary sources

Group	Flavonoids	Sources
Anthocyanins	Cyanidin	Fruits and flowers
Flavonols	Isorhamnetin, kaempferol, myricetin, Quercetin, rutin, rhamnetin,	Apples, broccoli, berries, buckwheat, cherries, kale, onions, tomatoes, tea, red wine
Flavones	Apigenin, chrysin, diosmetin,luteolin, tangeretin	Cereals, flowers, fruits, herbs parsley, thyme, vegetables
Flavanols	Catechins, epicatechin, epigallocatechin gallate, gallocatechin, procyanidin, theaflavins	Apples, black tea, beer, fruit juice, hops, wine
Flavanones	Eriodictyol, Hesperitin, naringenin, neohesperidin	Citrus fruits, cumin, grapefruits, oranges, peppermint

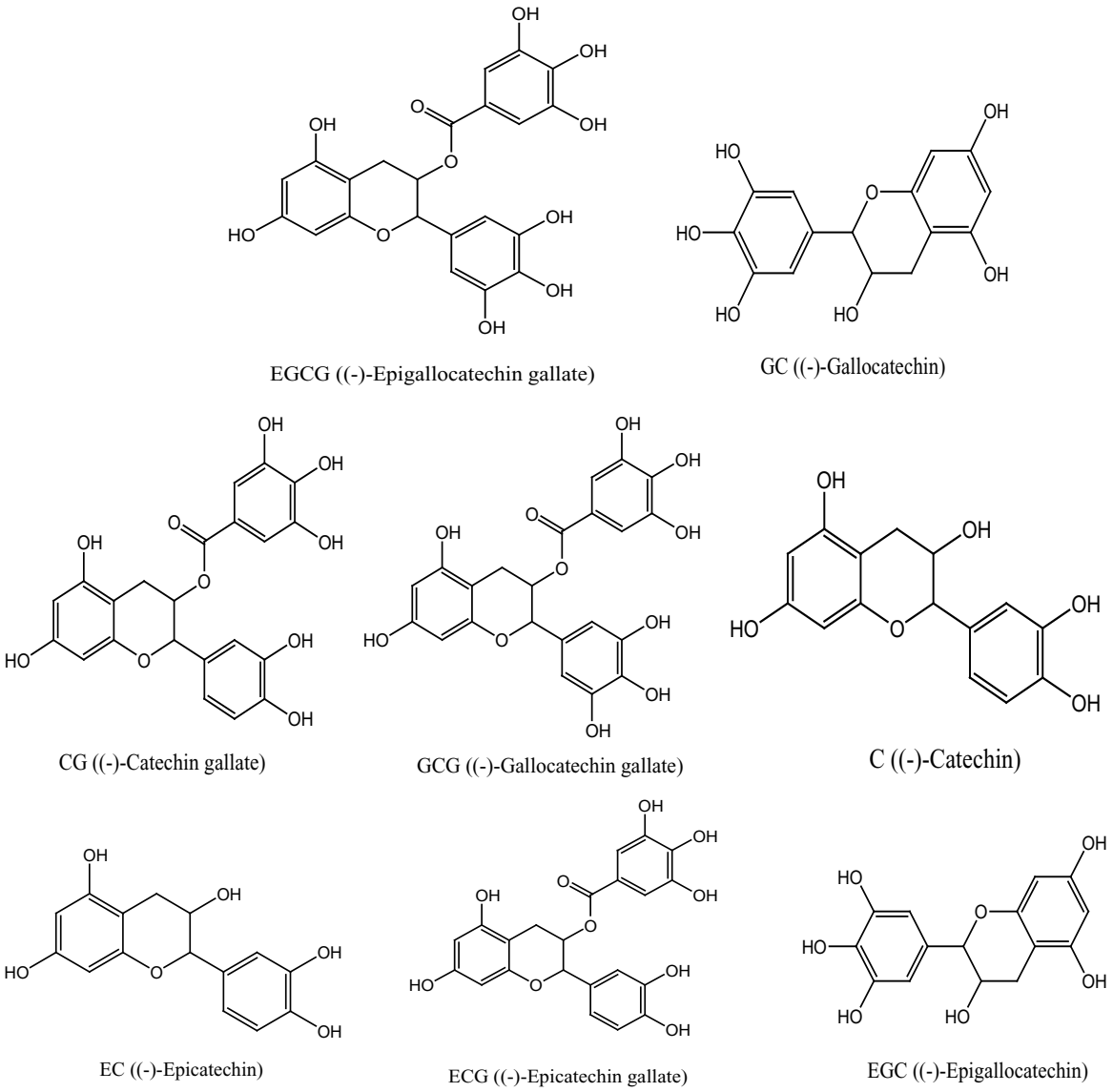


Figure 2. Structural formula of eight catechins.

manufacture, and catechin anti-oxidants attach to protein chains covalently[27]. Autochthonous germplasm from the Campania region has stronger anti-oxidant activity than non-autochthonous germplasm, according to LC-MS analysis[28]. Enzyme-mediated caffeic acid glucosylation and EGCG increases antioxidant capability of UV-prompted skin ageing cellular model[29]. The flamboyant tree, Delonixregia possesses strong antioxidant and antimicrobial properties[30]. The anti-oxidant ability of EGCG protects human dermal fibroblasts from H_2O_2-induced damage[31]. Antioxidant activity is boosted in lipophilized EGCG derivatives[32]. The anti-ageing properties of ECG and EGCG found in marula tree extract are beneficial[33]. *Cocos nucifera* bark demonstrated anti-oxidant and antidepressant effects through oxidative alterations in the prefrontal brain[34]. Amongst Tibetan tea merchandises, "Kangzhuan" is the highest in demand. The "Kangzhuan" lyophilized aqueous extract has reducing and cytoprotective effects[35]. Gallic acid and four other catechins, among other phenolic compounds, are regarded to be the primary cause of these effects. For these phenolic components to display anti-oxidative or cytoprotective activities, electron transfer, H^+ transfer, and Fe^{2+} chelating pathways may be necessary.

Catechin and protein collaboration is thought to be important in the mechanisms through which catechins employ their biological actions, besides ROS-related mechanisms. Saeki *et al*. looked at how EGCG-protein collaborations could explain health-promoting benefits of green tea/EGCG. Dot assays, X-ray crystallographic analysis (XCA), surface plasmon resonance, affinity gel chromatography and computational docking analyses (CDA) have all been used to demonstrate EGCG-protein collaborations and in what manner EGCG can take a position in or nearby functional positions and bring about a conformational alteration, as well as a quaternary conformational alteration. Therefore, EGCG is suggested as a lead chemical for therapeutic development by these writers[36].

4.1.2 Anti-microbial Activity

The natural antimicrobial properties of catechins are being used in research to create biological and functional cosmetics. *Porphyromonas gingivalis* (*P. gingivalis*) adherence to epithelial host cells is inhibited by the interaction of flavan-3-ols and proanthocyanidin from *Limonium brasiliense (L. brasiliense)* with gingipains in human epithelial KB cells[37]. To check the antimicrobial activity of fullerene and its derivatives, C_{60} $(OH)_{44}$ was employed as a control which was proved to be very effective and powerful similar to the catechins[38]. Further, Green tea extracts significantly reduced the amounts of *Streptococcus mutans (S. mutans)* in children's saliva and plaque of teeth[39].

4.1.3 Anti-neurodegenerative Activity

Recently, it has been found that many patients over the age of seventy are suffering from neurodegenerative illnesses like dementia (Alzheimer's disease). The pathogenic mechanism behind alzheimer's disease includes oxidative stress. The reason for this disease might be due to imbalance between ROS and molecules having antioxidant activity. Neuro-inflammation may be triggered by this imbalance. Ide *et al*. compiled new information and perspectives on catechins' anti-oxidative, protein kinase and neurotransmission related effects on alzheimer's disease based on molecular mechanisms[40].

Likewise, Pervin *et al*. presented recent research on catechins' positive effects on neurodegenerative disorders. Several human investigations have confirmed these findings, but others have not[41]. The discrepancy, according to these authors, may be due to differences in factors such as measurement technique, beverage temperature, smoking, alcohol intake, and changes in genetic and environmental influences like lifestyle, ethnicity, gender and age. This problem could be used in human epidemiological research of various diseases, such as cancer.

4.1.4 UV Protection Activity

Extensive research on catechins' potential to protect skin from UV rays has shown that catechins can improve photo stability and UV protection. Catechins have also being studied to see if they may be used in a variety of disciplines, including the protection of aging process of skin, by improving their effectiveness and stability. Catechins boost the stability of EGCG nanoethosomal suspensions, enhancing their capacity to protect skin from UVB damage[42]. Catechins that have been emulsified have increased skin permeability,

UV protection, and anti-aging properties[43]. Numerous studies, including 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and western blot assays[44], demonstrate that ECG is an effective therapy for UVB-induced damage to HaCaT keratinocytes. Because of their high light stability and red shift over the whole UVA and UVB ray index, grape seed extracts offer broad-spectrum protection when exposed to simulated solar radiation with sunscreen sorbents[45]. In the preservation and release of methacrylic acid-grafted poly (N-vinyl pyrrolidone)[46], flavonoids demonstrate excellent light and heat stability. Components derived from *Neolitsea aciculate* inhibit mushroom tyrosinase, indicating that this plant may be a source of chemicals that produce antimelanin effect[47].

4.1.5 Anti-cancer Activity

Green Tea Extract (GTE) or EGCg has been studied in numerous animal experiments employing biomarkers of cancer risk or development. GTE or EGCg guards against chemical carcinogens in several organs like the breast, respiratory organs, prostate, intestine and liver according to many of these studies. According to many researchers, it has been found that catechins present in green tea seem to have some protective effect against disease of degenerative nature in animal models. In immune dysfunction due to transplanted tumours or carcinogen therapy, green tea catechins could function as anti-tumorigenic agents and immunological modulators. Green tea exhibits anti-proliferative and hypolipidemic properties in hepatoma-treated rats, has been shown to reduce hepatoxicity in some studies, and may be used as a post-initiation breast cancer preventative agent. Polyphenol-abundant *Lawsonia inermis* (Henna) extracts reduce oxidative radicals and spreading of cancer cells[48].

4.1.6 Anti-viral Activity

Numerous studies for preventing and treating viral infections have been done (chicken pox, ebola, measles, AIDS, SARS, MERS, etc.). Green tea catechins were found to have anti-influenza virus action in an experimental work[40]. Flavonoids present in *Cassia javanica* did not have effect on cell viability and spread but affected herpes simplex virus cell infiltration and adhesion[49]. It has been found from several studies that consuming green tea daily reduces frequency of infection due to influenza virus and symptoms of common cold. It has also been shown that rinsing the oral cavity with tea catechins may guard against infection due to influenza virus. Another study focused on epidemiological/clinical studies to assess the effectiveness of tea catechins on influenza virus and cold, indicating the need for more research to corroborate clinical effectiveness[50].

4.1.7 Anti-obesity Activity

EGCG, methylation EGCG, Theaflavins and polyphenol metabolites present in green tea, oolong tea, black tea and dark tea respectively have all been proven to have anti-obesity benefits in numerous studies. Rothenberg *et al*. suggested the "Short Chain Fatty Acid (SCFA) theory" to describe how the weight loss is associated with different types of tea. To explain how different tea kinds can all efficiently cause weight loss, SCFAs produced in the stomach as a result of interactions between undigested carbs, catechins, and gut microbiota may improve fat metabolism by activating AMP-stimulated protein kinase, resulting in anti-obesity effects[51].

4.2 Theaflavins (TFs)

Major health-boosting compounds in black tea are catechins and theaflavins (TFs), according to numerous epidemiological and clinical researches. Theaflavins (TFs) are a major category of polyphenols found in black and oolong teas in abundance. TFs are a kind of bi-flavonoid with a benzotropolone structure that accounts for around 2% of dry tea leaves. TFs are the chief oxidative substances of catechin fermentation process, which accumulates during this process[52,53]. The oxidation of certain catechins (epicatechin and epigallocatechin-3-gallate) in the presence of polyphenol oxidase and peroxidase enzymes results in the formation of TFs[54]. The catechins are transformed to TFs such as theaflavin, theaflavin-3-gallate, theaflavin-3′-gallate, theaflavin-3,3′-digallate known as TF1, TF2A, TF2B and TF3 respectively and some arubigin polymers during fermentation[55] (Figure 3). The TFs have structure-specific biological activities[56].

4.2.1 Health Effects and Pharmacological Properties of TFs

Anticancer, skin defence, liver protective, neuro protective, anti-inflammatory, gut microbiota modulation, antioxidant, cardioprotective, antimicrobial, and nephroprotective properties have all been investigated in both in vitro and in vivo settings. In the next sections, health impacts of theaflavins will be discussed in more detail.

4.2.2 Anticancer Activities

TFs have been widely researched in vitro and in vivo cancer models for their anticancer properties. Ovarian cancer is the malignant gynaecologic issue with the greatest mortality rate, and TF3 plays an important part in reducing this[57].

Way *et al*. discovered that theaflavins TF1, TF2a/b, and TF3 suppressed aromatase action in MCF7 breast cancer cells. DHEA-induced proliferation was reduced by theaflavins to the same amount as the aromatase inhibitor 4-OH-A. Notably, treatment with theaflavins lowered tamoxifen resistance, a chemotherapeutic drug routinely used to treat oestrogen positive breast cancer[58]. Overall, the data support the function of theaflavins as aromatase inhibitors, suggesting that theaflavins may be effective in the treatment of oestrogen receptor-positive breast cancer.

The expression of the androgen receptor was substantially inhibited by theaflavins in prostate cancer LNCaP cells. Furthermore, there were considerable inhibitory effects on the promotor region of the androgen receptor[59].

The treatment of human lung cancer cells with a formulation comprising the four theaflavins (21.4% TF1, 29.9% TF2a, 15.2% TF2b, 27.5% TF3) resulted in a dose-reliant decrease of cell growth and a reduction in cell survival. High concentrations of theaflavins (100 M) significantly induced apoptosis (77%) in H661 cells[60].

Treatment with theaflavins blocked the progress and viability of HT-29 human colon cancer cells[61].

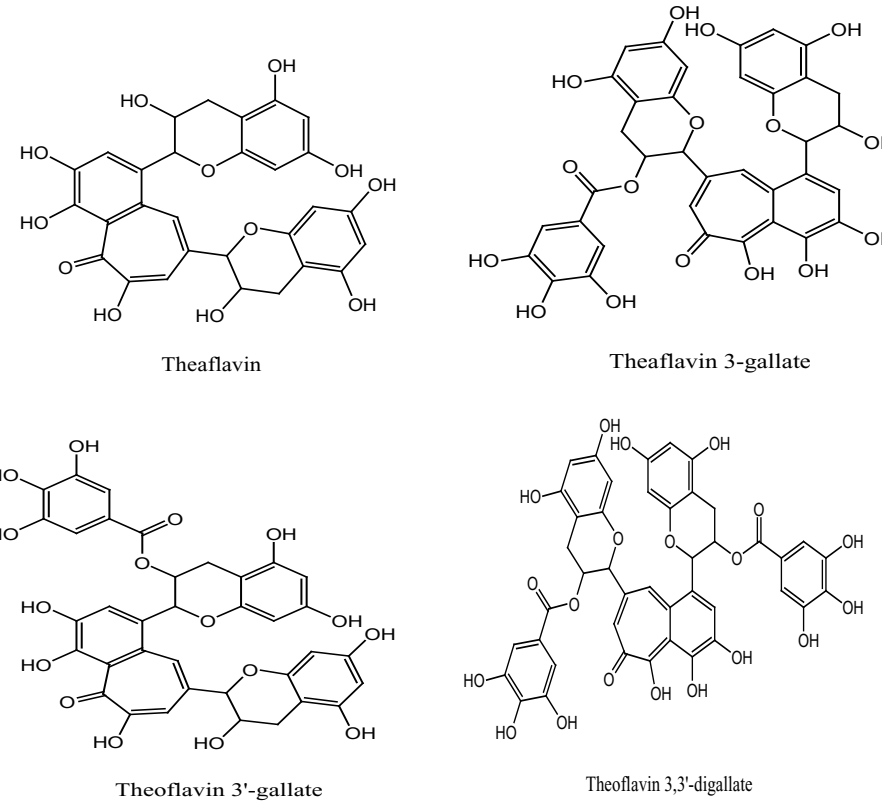


Figure 3. Structure of some important theaflavins.

Lu *et al*. found that TF1 and TF3 had little influence on Caco-2 cell development[62], however 10 and 50 μM TF2 produced a drop in rate of growth over an 8-day period[63].

Unadulterated TF1 and Darjeeling and Assam black tea extracts inhibited the progression and proliferation of HL-60 and K-562 leukemic cells in a dose-reliant manner. Furthermore, a dose-reliant decrease in cell sustainability was observed[64]. Tu *et al*. found that treatment with theaflavins (TF1, TF2b, and TF3) inhibited the development of human liver cancer cell BEL-7402, with IC50 values of 180 μM for TF1, 110 μM for TF2b, and 160 μM for TF3[65]. Only a few researchers have looked into the impact of theaflavins on stomach malignancies. As shown by the presence of apoptotic bodies and fragmented DNA, KATOIII cells treated with black tea theaflavin extract, TF1 or TF3 died more rapidly than untreated controls[66].

4.2.3 Hepatoprotective Properties

Non-alcoholic fatty liver disease (NAFLD) happens when the liver gathers large levels of lipids (5-10%) in the absence of alcoholic consumption, which can develop to cirrhosis, non-alcoholic steatohepatitis, hepatocellular carcinoma (HCC), and in serious cases, liver transplantation is the last alternative[67]. Green tea, dark tea (Pu-erh),[68] Fuzhuan tea,[69] Black tea and Oolong tea, have been discovered to contain a variety of physiologically active components, including TFs, which function as key dietary anti-NAFLD agents[70,71]. These anti-NAFLD compounds largely block the fatty acid production pathway in hepatic cells; rather, it encourages fatty acid oxidation. Avoiding the consumption of high fat diet which is responsible for liver inflammation and steatohepatitis led to the reduction in adipocyte stress and increase in both glucose tolerance and insulin sensitivity.

In HepG2 cells, TF3 also effectively prevents OA-persuaded lipid build up. Yang and colleagues[72] found that drinking 3-4 tea cups per day (200-250 g/ month) significantly reduced metabolic disorders like NAFLD. Black tea polyphenols may help to lower fat accumulations, general body weight, lipid generation, and over weightness, all of which are crucial factors of NAFLD. Theaflavins are the main resource of anti-NAFLD compounds in food, which help to prevent hepatic steatosis and inflammation caused by a fat rich diet shown in Figure 4.

Moreover, through the AMPK/ACC and IL-6/ STAT3 signalling pathway, as well as ECHS1, TNF-, COX-2, PGAM1andACAC-expression in studies carried out in vivo and in vitro, TFs hamper fatty acid biogenesis, up-regulate oxidation, and minimize liver and adipose tissue strain by enhancing glucose tolerance and insulin sensitivity[74,75].

4.2.4 Neuroprotective Properties

The brain is the human body's chief oxygen-consuming organ, and ROS-facilitated cellular oxidative spurt and redox-stimulated metal ions can harm it[76]. These free radicals are scavenged by TFs, which are key bioactive phytochemicals and innate antioxidants found in black tea. Due to its ability to scavenge free radicals and chelate metals, TFs have significant antioxidant properties and may thus provide neuroprotection[77,78]. Moreover, by reducing Aβ and α-synuclein noxious effects, TFs have equalled the antioxidant effectiveness of EGCG[79]. TFs also safeguard PC12 cells from oxidative strain caused by H_2O_2[80]. Due to their antioxidant and anti-apoptotic actions, TFs exhibit neuroprotective actions against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) poisoning, which causes Parkinson's disease[81]. These findings clearly demonstrated that TFs can successfully prevent neurodegenerative illnesses; nevertheless, more research, including in vivo and clinical trials, is required.

4.2.5 Anti-inflammatory Properties

TFs are important in the treatment of inflammation. The expression of cytokines like IL-6 increased following acute tissue damage and apoptosis. Theaflavin derivatives were used as anti-inflammatory drugs, and the level of IL-6 expression was dramatically reduced during viral infections[82]. Via lowering leukocyte inflow and ICAM-1 expression and suppressing the over expression of iNOS and COX-2 in the ischemic brain by minimizing STAT-1 phosphorylation, TFs greatly reduce neuronal damage from cerebral ischemia repurfusion[83]. TF3's gallic acid component is also critical for its potent anti-inflammatory properties[84].

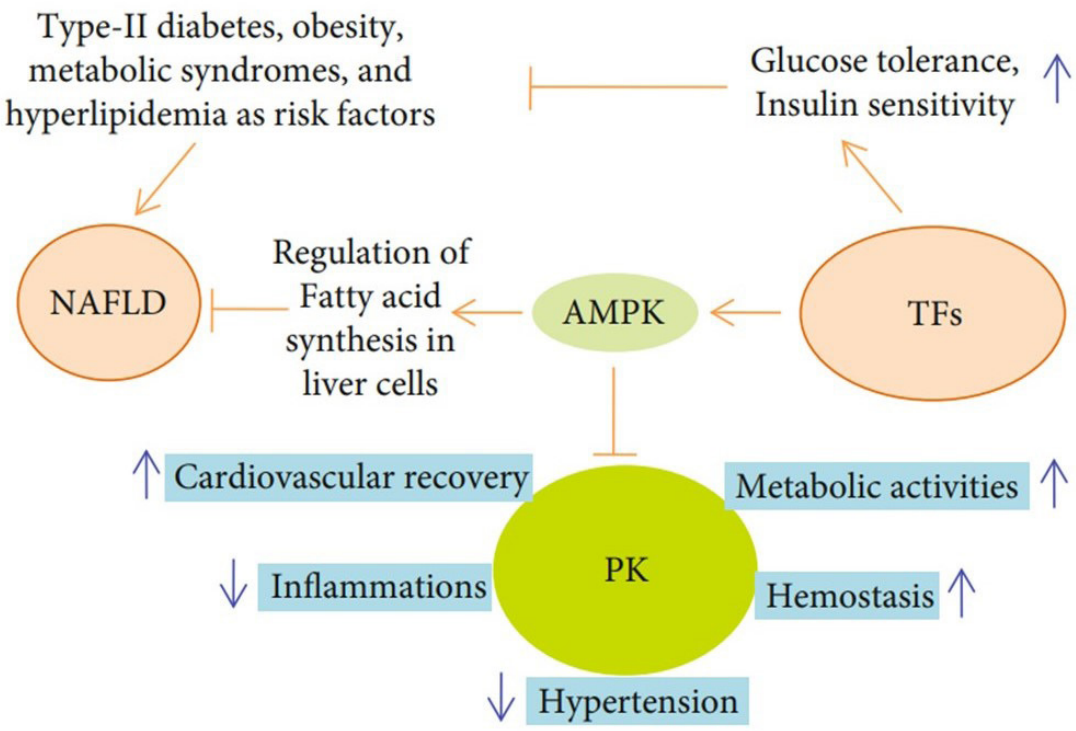


Figure 4. Non-alcoholic fatty liver disease (NAFLD) and its related risk factors are suppressed by the TFs, which also regulate the creation of unneeded fatty acids in liver cells73.

4.2.6 Management of Gut Microbial Populations

Catechins and TFs from the phenolic class have a variety of health benefits. The bioavailability of TFs, the catechin dimer derivatives, is minimal in the small intestine. Theaflavins and associated phase II metabolic metabolites are not detected in voided urine after 0-30 hours after ingestion[84]. As a result, a significant fraction of the depleted catechins and TFs would enter the large intestine, where they will be bio converted by resident microbes[85]. TF3 is degraded by the gut microbiota into TF1, TF2A, and TF2B[86,87]. TFs are later transformed to small phenolic substances such as 5-(3′,4′-dihydroxyphenyl)-y-valerolactone and 3-(3′,4′-dihydroxyphenyl) propionic acid after degalloyation. Catechins were transformed to metabolites by metabolism of microbes in the same way[88]. Microbial metabolism can produce metabolites that are comparable to those produced by catechins and TFs. This suggests that consuming unadulterated catechins or TFs, as well as green or black tea, may alter the structure and metabolic activity of the gut microbiota, resulting in a more favourable health profile[89-91]. Green and black tea consumption influenced the gut microbiota, with growth-encouraging impacts on Lachnospiraceae and Akkermansia and repressive actions on *Clostridium leptum*[92]. Flavan-3-ol is made up of the same building blocks as TFs and green tea catechins. As a result, it's hypothesised that during the fermentation of these chemicals, they produce comparable metabolites, such as hydroxylated phenyl carboxylic acids, which imitate gut microbiota modulation[93].

4.2.7 Antioxidant Effect

TF3 is a large and copious component of black tea, generated by the chemical reaction of epigallocatechin gallate (EGCG) and epicatechin gallate (ECG) during fermentation[94]. As a result, TF3 has been discovered to have diverse pharmacological properties, together with anti-inflammatory and free radicals or ROS scavenging abilities[73,95]. According to a new study, women who drink a lot of black tea have a lower risk of ageing[96].

Moreover, previous research has shown that TF3 inhibits the expression of matrix metalloproteinase 9 (MMP-9) and treated calvarial osteolysis effectively; therefore, it prevents occurrence of osteoporosis[97]. A latest in vitro investigation revealed that TF3 possesses cell-specific features, such as the ability to create efflux of ROS in cancer cells, while TF3 (250 μM) greatly boosted intracellular glutathione levels to offer antioxidant benefits in normal GN46 fibroblast cells[18]. Polyphenolics are well-known for their antioxidant properties[98].

4.2.8 Cardio-protective Effect

Tea consumption has been linked to a minimal risk of cardiovascular disease (CVD) in numerous epidemiological studies[99]. In addition, tea drinking is inversely related to BMI[100]. Tea polyphenols, particularly TF3, have anti-inflammatory, anti-proliferative, and antithrombotic properties[101]. As a result, those with excessive cholesterol, obesity, heart disease, or hyperlipidemia should consume TFs in their diet. The amount of TF consumed is inversely connected to death from heart diseases. Ischemia/reperfusion (I/R) damage and atherosclerosis are two of the most common cardiovascular disorders caused by oxidative stress. Endogenous antioxidants are up-regulated, resulting in long-term cardioprotection. Reactive oxygen species (ROS) are metabolites which are incompletely reduced like superoxide anions, hydroxyl radicals, and hydrogen peroxide that are generated as a result of oxidative stress. ROS impairs lipids, DNA and proteins. With these evidence, utilising chelators[102], and antioxidants to improve heart function is a good idea[102-104]. They also reduce infarction size in heart I/R damage models and improve myocyte survival. The exceptional anti-atherosclerotic impact of TFs has been attributed mostly to their ability to scavenge ROS[105]. Furthermore, because of the hydroxyl groups in their structure, theaflavins have high electron-donating properties[106]. As a result, TFs are thought to be effective scavengers of free radicals like oxygen in singlet state, peroxynitrite superoxide anions, and NO[107].

4.2.9 Antimicrobial Effect

TF3 has commendable antimicrobicidal properties against *Mycoplasma orale, M. salivarium, and M. pneumoniae*. Friedman found that tea extracts containing TF3 and EGCG were microbicidal and antibacterial against Mycoplasma[108]. The foodborne pathogen *Campylobacter jejuni (C. jejuni)* causes diarrhoea and gastroenteritis in mammals. Clinical isolates of *C. coli* and *C. jejuni* were suppressed by TFs. *Bacillus cereus* is a bacterium present in food that causes humans to have diarrhoea and vomiting[109]. *B. cereus* is effectively inactivated by tea portions containing micro or nanomolar quantities of TF3. Ability of adhesion of TF3 to the bacterial surface restricts the accessibility of outer membrane receptors for attaching new host cells, resulting in the inactivation or suppression of bacterial strains[110]. By targeting the cell wall and membrane, TF3 also reduces cell permeability. TF3 also disturbs and interferes with a variety of cell activities, including electron transport, enzyme activity, food intake, protein synthesis, and nucleic acid synthesis. All of these variables cause bacterial cells to develop slowly or die[111].

4.2.10 Nephroprotective Effect

Acute Kidney Injury (AKI) is a serious medical illness that can result in many complications, like partial nephrectomy, kidney transplantation, severe infection, and renal artery thrombosis[112]. Renal ischemic reperfusion (I/R) is the most common cause of AKI[113]. Renal I/R reduce the amount of blood from the arteries in the kidney and then restore it for re-oxygenation. According to studies, most severe renal I/R is linked to the production of substantial ROS efflux, and henceforth automated cell mortality is the result[114,115]. Intracellular ROS is the by-products of mitochondrial respiration and hence mitochondria act as home for them. Mitochondrial dysfunction produced by renal I/R stimulates the production of ROS[116,117]. Black tea, which is a rich source of polyphenols have been used for a long time for the treatment and prevention of kidney diseases.

Theaflavins, particularly TF3, have a protective effect against major illnesses. The engagement of the oxidative stress-receptive Nrf2 pathway lowers ROS-facilitated oxidative stress. As a result, it has been shown to significantly reduce brain I/R[118] and to improve radiation-facilitated hematopoietic stem cell damage. Li *et al.* created an in vivo kidney model for

I/R damage. This study concluded that TF3 resulted in decrease in the expression of kidney injury molecule-1 (KIM-1) in kidney tissues along with reduction in renal damage due to I/R[119].

Chronic Renal Failure (CRF) is a total breakdown of nephron composition, resulting in tubules, glomeruli, circulatory system vessels and renal interstitium disruption. TFs were found to protect against renal failure. This protective role can be ascribed to their capacity to reduce renal toxins, NO generation, and antioxidant environment up-regulation in the cell. Furthermore, TFs improve the function of liver, which improves blood urea filtration[120].

5. Conclusion

The present review summarises the health benefits of catechins and TFs, as well as the mechanisms that underpin them. Catechins are utilised in materials that enhance health, cosmetic purpose and in prevention and treatment of diseases. Plants and their by-products are the subject of ongoing research due to their significant anti-oxidant activity. TF1, TF2A, TF2B, and TF3 are the key theaflavin derivatives researched for a wide variety of biological actions. At the same time, numerous studies are going on to prove UV protection applications of catechins to improve their photo stability, efficiency, and stability for utilizing them in several fields. This effect is also studied to prove anti skin aging properties of theaflavins. Among these, TF3 has been investigated extensively for its biological impacts, including antioxidant, anti-inflammatory, anticancer, and antibacterial properties. The anticancer effect of TFs has been extensively researched in both in vitro and in vivo models.

The in vitro and in vivo studies summarised in this article indicate that black tea extract and the four theaflavin isomers that are abundant within it have significant anticancer properties. These theaflavins inhibit cell proliferation, migration, and apoptosis in numerous forms of malignancies. In vitro investigations also demonstrate that theaflavins inhibit key signalling pathways linked to cancer. TFs have also been shown to give synergistic action in conjunction with other drugs. There was anticancer activity through the activation of caspases; protection of the skin through inhibiting the MAPK pathway; liver protection through triggering the AMPK pathway; neuroprotection through controlling NO signalling; inflammation reduction through up-regulation of inflammatory-associated prooxidative enzymes; cardiovascular protection through ROS removal and preventing cell-facilitated LDL oxidation; kidney protection through down-regulation of KIM-1. Even though there are several studies (in vitro and in vivo) on the TFs action, only just a few reports on clinical effectiveness have been published, which limits its general application.

6. References

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