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REVIEW

Phytotherapy with active tea constituents: a review

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Abstract
Tea is a widely renowned functional beverage originating from processed tender leaves of the *Camellia sinensis* plant after brewing with hot water. This refreshing and revitalizing beverage has been recognized as an essential commodity since ancient times. Tea constituents have many health benefits and hence find usage in functional foods, beverages, and nutraceuticals. Nonetheless, the clinical usage of tea constituents is limited by the high molecular weight, poor stability, and low bioavailability of some active components. We review how fresh tea leaves are processed into different forms of tea such as green, oolong, white, and black teas. The major tea constituents, e.g., catechins, caffeine, and theanine, exhibit numerous health properties such as antioxidant, anti-inflammatory, anticancer, antidiabetic, cardioprotective, and antimicrobial. We discuss methods to enhance the efficacy and applicability of active tea constituents, such as micro- and nanoencapsulation techniques.

Keywords Tea · Catechins · Caffeine · Theanine · Bioactivity · Therapeutics

Introduction

Tea comes from the *Camellia sinensis* plant, which is native to Southeast Asia. Fresh tender leaves of this plant are processed for manufacture of different types of teas. The major occurring phytoconstituents of the tea leaves are catechins, which are a subclass of flavonoids (Stodt and Engelhardt 2013). Apart from catechins, other main constituents present in tea are caffeine and theanine (Rana et al. 2016). A wide array of research studies in the past have revealed the diverse health beneficial properties associated with tea consumption (Sharma and Rao 2009; Shahidi et al. 2009; Engelhardt 2010). Studies have reported the role of major tea constituents in the prevention and delay of various metabolic ailments such as obesity, diabetes, hypertension, atherosclerosis, and cancer (Zhen 2002; Demeule et al. 2002; Stangel et al. 2007; Shahidi et al. 2009; Sharma and Rao 2009; Chacko et al. 2010; Engelhardt 2010; Jankun et al. 2012).

However, despite the numerous pharmacological properties of tea constituents, its clinical applications have sprints likewise other natural products such as limited solubility and poor membrane permeability (Lohith Kumar and Sarkar 2018; Saka and Chela 2020; Paroha et al. 2020). This hindrance in the clinical and therapeutic delivery of tea constituents is due to their poor solubility, bioavailability, and efficacy (Bhushani et al. 2016; Son et al. 2016). Hence, it is very necessary to develop new sustainable techniques for improving the therapeutic delivery of these invaluable natural compounds. This article is an abridged version of the book chapter by Rana and Kumar (2020) in the series Sustainable Agriculture Reviews (https://www.springer.com/series/8380).

Different forms of teas

The manufacturing process of tea varies from country to country, and based on processing techniques, teas are classified as green, black, oolong, and white teas (Sajilata et al. 2008; Chen et al. 2011). All types of teas are prepared from tender leaves comprised of an unopened leaf (apical bud) and subtending two to three leaves of the same plant *Camellia sinensis* (Engelhardt 2010; Rana et al. 2016). Due to variability in processing, different teas impart different colors, tastes, and aromas (Feng et al. 2019). The most prevalent tea (green tea) is manufactured in a way that the majority of natural constituents present in green leaves remain unchanged

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during processing. Thus, freshly plucked tender tea shoots are heat-treated immediately after plucking to inactivate the endogenous enzymes (polyphenol oxidase and peroxidases) through different enzyme inactivation techniques (Gulati et al. 2003; Shitandi et al. 2013) before rolling and final drying steps.

Black tea is further of two types: CTC (cut/crush, tear, and curl) black tea and orthodox black tea. The CTC black tea is manufactured by using a CTC machine which cuts the leaves into small pieces, followed by crushing and rolling into tea granules before drying (Baruah and Mahanta 2003; Engelhardt 2010). CTC tea generally produces a rich reddish-orange-colored infusion when brewed with hot water, whereas the processing of orthodox black or leaf tea involves withering of freshly plucked tea shoots for up to 12–16 h to remove excess moisture up to 50% by weight. Withering is followed by the rolling of tea shoots in tea rollers. The rolling step leads to the instigation of numerous biochemical reactions and hereby initiates the process for the formation of various aroma, flavors, and colored compounds (Carloni et al. 2013; Feng et al. 2019). The rolled tea is further oxidized for color enrichment before drying (Shitandi et al. 2013).

Oolong tea is the traditional form of Chinese tea (Chen et al. 2011; Zhen 2002). This tea processing lies between green and black tea and is manufactured by partial enzyme inactivation (Chen et al. 2011; Carloni et al. 2013; Weerawatanakornet al. 2015). The partially withered tea shoots are processed by rolling before drying with hot air. White tea is a special tea made selectively from apical buds (newborn leaves). For the manufacturing of white tea, the apical buds are collected by handpicking. The whole buds are withered for a few hours and then rolled gently (Carloni et al. 2013; Feng et al. 2019).

Chemistry of major tea constituents

A diverse array of phytochemicals are known to be present in green tea leaves. Among them, catechins along with caffeine and theanine occur predominantly. These foremost tea constituents are also responsible for the taste, color, and aroma of the brewed tea infusion (Pinto 2013; Vuong et al. 2011). Apart from these major constituents, various other compounds are also reported in tea like organic acids, carbohydrates, polysaccharides, minerals, saponins, methylxanthines, proteins, and lipids (Zhen 2002). Catechins are the predominant flavanols derivatives of flavonoids, characterized by meta-5,7-dihydroxy-substituted A-ring with di- or trihydroxylic B-ring (Verloop et al. 2016) and biosynthesized from the basic skeleton of chalcone (Rammohan et al. 2020). They are also called flavan-3-ols due to the occurrence of the hydroxyl group at the third position of the C-ring (Panche et al. 2016). Catechins constitute a group of monomeric flavanol derivatives comprising of epigallocatechin (EGC), epicatechin (EC), epigallocatechin gallate (EGCG), and epicatechin gallate (ECG) (Zhen 2002). The content of catechins in tea leaves is influenced by leaf age, harvest season, and manufacturing processes of tea (Rana et al. 2016; Wakamatsu et al. 2019). The outmost content of these molecules occurs in new tender tea leaves (12–15%) which are normally used for tea manufacture as compared to coarse and mature tea leaves (Rana et al. 2016). Epigallocatechin gallate is the most abundant and highly investigated tea molecule that constitutes up to 50% of all catechins (Singh et al. 2011). Caffeine (1,3,7-trimethylxanthine) is an alkaloid molecule (Engelhardt 2010). It is one of the most widely consumed active food ingredients with various health beneficial properties (Zhen 2002). Caffeine helps in enhancing mood and alertness by acting mainly upon the central nervous system (Heckman et al. 2010). Theanine is another very important compound that occurs exclusively in tea (Engelhardt 2010), and apart from tea it has been reported in a mushroom, *Xerocomus badius*. It is a non-protein amino acid, which imparts umami taste to tea (Zhen 2002). Theanine consumption has been associated with brain relaxation and improving learning ability (Voung et al. 2011).

Pharmacological activities of tea constituents

Tea is widely recognized for a diverse array of health beneficial properties (Fig. 1). Tea consumption has been associated with the prevention and delay of various metabolic diseases. It includes lower risk of cardiovascular diseases like stroke, atherosclerosis, helps in inhibition of inflammation, prevention of cancer, and associated diseases (Ruxton 2008; Sharma and Rao 2009). These pharmacological properties have been associated with the high content of phenolic compounds in tea. It has been evident from various in vitro, in vivo, and animal model studies that tea phenolics have powerful therapeutic potential and have direct effects on various biochemical processes that occur via a range of complex mechanisms (Vuong 2014).

Antioxidant activity

Antioxidants are chemical compounds responsible for scavenging free radicals such as reactive oxygen species and reactive nitrogen species that are generated in the body (Lobo et al. 2010). They have a strong ability to terminate oxidation chain reactions by removing free radical intermediates, and also inhibit other cellular oxidation reactions (Halliwell et al. 1995). They attain this by getting oxidized

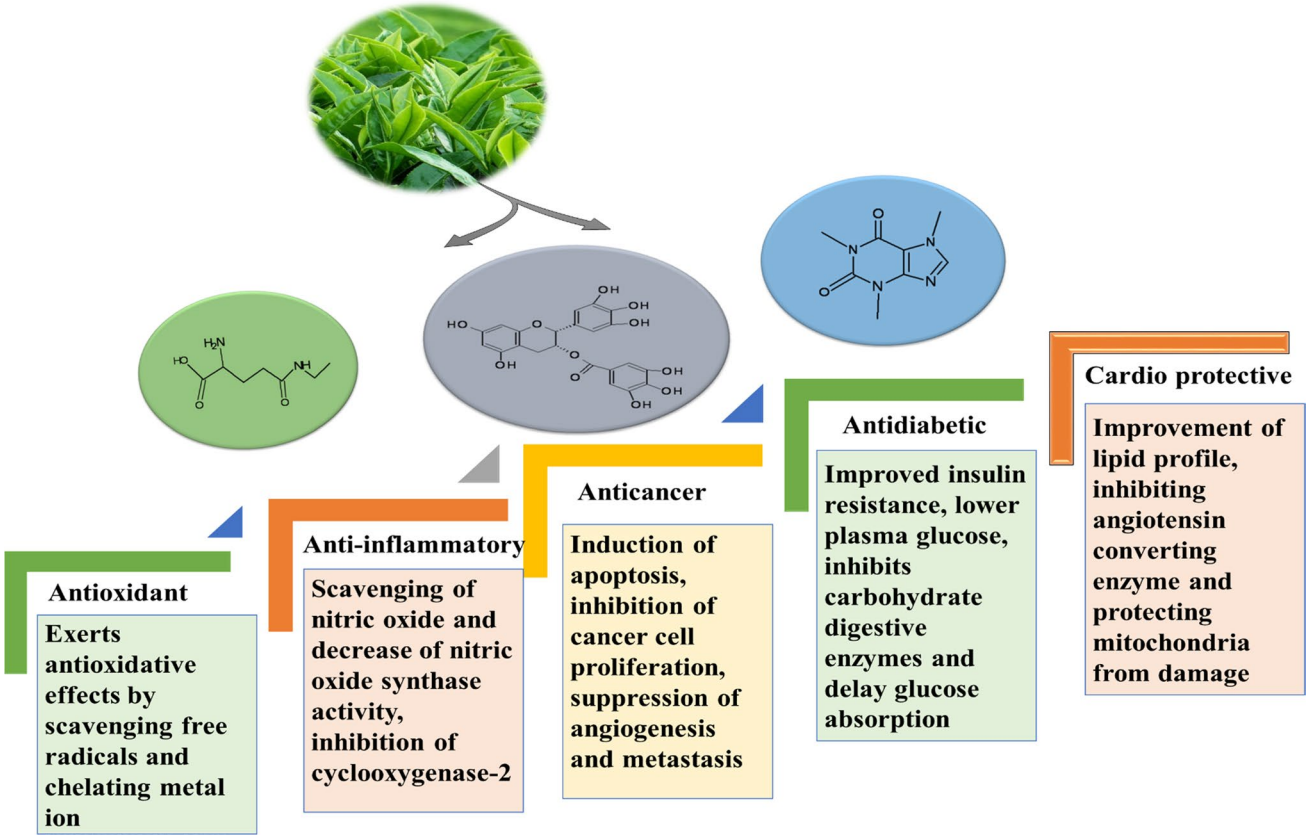

Fig. 1 Major tea constituents and their biological activities as antioxidants, anti-inflammatory, anticancer, antidiabetic, and cardioprotective

themselves. The tea phenolics are well-recognized antioxidant compounds. Numerous research reports illustrate the antioxidant behavior of tea phenolics (Wiseman et al. 1997; Rietveld and Wiseman 2003; Wang et al. 2006; Sharma and Rao 2009; Chu et al. 2017). Catechins are the major polyphenolic antioxidant compounds present in tea with ability to donate proton or hydrogen, due to high conjugation in their molecular structure that makes them potential antioxidant candidate (Sen et al. 2020; Yan et al. 2020).

Numerous epidemiological studies have revealed that tea polyphenols help in the protection of cells and tissue from oxidative damage of reactive oxygen species (Mao et al. 2017; Yan et al. 2020). Due to their free radical scavenging behavior, tea polyphenols can act as a natural and reliable source of potent antioxidant compounds (Yan et al. 2020). Tea consumption is also related to the protection during alcohol intoxication by preventing the reduction of liver glutathione peroxidase, reductase, and catalase activity, which would otherwise deplete the cellular antioxidant defense system, especially in the liver (Luczaj and Skrzydlewska 2004).

Anti-inflammatory activity

Inflammation is the cellular response of our body that involves the influx of defensive cells like leukocytes (neutrophils, monocytes, and eosinophils) to the site of injury (Chaplin 2010). Any disturbance in these cellular mechanisms or prolonged inflammation leads to implications, which could cause cancer and other diseased conditions (Chen et al. 2017). Generation of nitric oxide and prostaglandins by inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 is considered as the most prominent molecular mechanisms involved in inflammation and cancer (Ahmed et al. 2002; Zhong et al. 2012). It was reported that green tea exhibits anti-inflammatory effects by inhibiting the expression of iNOS (Tedeschi et al. 2004).

From the extensive epidemiological data, it has been established that green and black tea polyphenols play a significant role in the suppression of inflammation by inhibition of various transcription factors like tumor necrosis factor-α, granulocyte–macrophage colony-stimulating factor, and cyclooxygenase-2 (Cao et al. 2007; Novilla et al. 2017). However, exact molecular mechanisms explicating

the role of tea polyphenols in inflammation is not very clear till now. It has been recognized that drinking a sufficient amount of tea might be helpful in the prevention of inflammation, which is also responsible for causing various other disease conditions.

Anticancer activity

Cancer is a disease condition wherein the cells of any specific tissue of the body start uncontrolled growth and division (Anantharaju et al. 2016). These cells are recognized as cancerous as they can invade and destroy surrounding healthy cells, tissues, and organs as well (Cooper 2000). A diverse range of research articles are available in the literature reporting that tea and its constituents have positive effects in inhibition of tumorigenesis at various sites in the body, including skin, mammary gland, lung, oral cavity, esophagus, stomach, small intestine, colon, liver, prostate, and pancreas (Yang et al. 2002; Demeule et al. 2002; Boehm et al. 2010). Various clinical trials have been conducted in the past on both human and animal models for the investigation of possible anticancer properties of tea constituents (Demeule et al. 2002; Bettuzzi et al. 2006). Nonetheless, the use of tea polyphenols as therapeutics has to explore its perspectives in prevention and delay of cancer which is among the major killer of millions of people globally (Miyata et al. 2018). Epigallocatechin gallate was reported to induce apoptosis and inhibit cell proliferation in different human cancer cell lines and also showed inhibitory effects on angiogenesis and metastasis (Singh et al. 2011). Epigallocatechin gallate is also found to inhibit the malignant transformation/cell proliferation by targeting transcription factors nuclear factor-kappa B and activator protein-1 and exhibits chemopreventive actions (Surh 2006). Regardless of the large number of research data demonstrating the significant role of tea and its polyphenols against cancer progression, still there is a long way to comprehend the unknown mechanisms behind cancer occurrence (Boehm et al. 2010; Yang and Wang 2011).

Antidiabetic activity

Diabetes is a disease state wherein the blood glucose level of the patient is higher than the normal level (Musman et al. 2019). This situation may usually arise due to the inability of the body to pick up extra glucose from the bloodstream or inability in glucose metabolism. Studies have found that diabetes has emerged as one of the leading cause of global deaths that occurs annually (Tripathy 2018). In the last two decades, various studies have found that tea, especially green tea, plays a significant role in the prevention of diabetes (Miura et al. 2005; Islam and Choi 2007). Various investigators reported the preventive and curative properties of tea polyphenols against diabetes (Chacko et al. 2010; Jankun et al. 2012). The documented research data showed that the consumption of tea is correlated with the prevention of diabetes.

Obesity is one of the main causes of insulin resistance that leads to the production of various pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin 1, and interleukin 6, which eventually inhibits insulin signaling (Al-Goblan et al. 2014). Earlier studies revealed that tea and its constituents showed insulin-enhancing activity, lower plasma glucose level, and inhibit the level of inflammatory cytokines (Liu et al. 2013; Anderson et al. 2002; Suzuki et al. 2016; Molina et al. 2015). Sharma et al. (2019) reported that green tea catechins increase insulin secretion, control blood glucose levels, and also help in improving insulin resistance in type 2 diabetes mellitus patients. Tea catechins were also reported to inhibit the enzymes involved in carbohydrate digestion and decrease glucose absorption in the intestine (Sharma et al. 2019). These factors are directly linked with the occurrence of diabetes; therefore, it is stipulated that tea consumption helps in the prevention of diabetes. There is still a lack of sufficient data in support of proper cellular and molecular mechanisms related to the prevention of diabetes in humans by tea constituents.

Cardioprotective effects

Cardiovascular diseases are the ailment of the heart and blood vessels and are generally distinguished as coronary heart diseases, cerebrovascular diseases, hypertension, and heart failure (Beyer 2016). These causes are directly associated with our diet and lifestyle responsible for the elevated occurrence of cardiovascular diseases among populations (Buttar 2005). The major reasons for the high prevalence of cardiovascular diseases are high blood pressure, high cholesterol, diabetes, extensive smoking, and family history (Buttar 2005; Hajar 2017). Tea and its polyphenols have been recognized as a potent and reliable source to fight against cardiovascular diseases (Yan et al. 2020). A large number of research data have been available supporting tea and its constituents and their role in the prevention of these disease conditions. The tea polyphenols could act as possible cardioprotective candidates due to their potent antioxidant capacity (Yan et al. 2020). They induce antioxidative effects by scavenging reactive oxygen species and chelating metal ions (Velayutham et al. 2008). It has been found that free radicals play a key role in the occurrence of cardiovascular disorders by causing oxidative stress (Aron and Kennedy 2008). Due to the repetitive induction of cellular oxidative stress, there occurs induced cellular resistance to consequent exposure to reactive oxygen species. This could be inhibited by galloyl group in tea polyphenols (Stangl et al. 2007). The galloyl group may be interfering by modifying kinase activities in multiple pathways of signal transduction in

cardiovascular relevant cells which could play a crucial role in the prevention and treatment of cardiovascular diseases (Stangl et al. 2007). Tea catechins were reported to improve blood lipid profile by inhibiting the main enzymes involved in the biosynthesis of lipids (Velayutham et al. 2008). Tea flavan-3-ols were reported to decrease blood cholesterol levels and avoid the accumulation of cholesterol in the liver and heart in rat models with hypercholesterolemia (Velayutham et al. 2008). Earlier studies reported that consumption of green tea catechins is associated with a reduction in total and low-density lipoprotein (Kim et al. 2011). Endothelial dysfunction is substantially correlated to the pathogenesis of cardiovascular diseases (Hadi et al. 2005). Earlier findings suggest the beneficial effect of tea catechins in patients with cardiovascular diseases by improving endothelial dysfunction (Widlansky et al. 2007; Babu et al. 2008). Thus, tea polyphenols have a huge perspective to be used as preventive therapeutics against cardiovascular disorders.

Antimicrobial activity

Antimicrobial behavior is the ability of tea polyphenols to act against harmful microorganisms such as bacteria, fungi, and viruses and inhibit their progression. The role of tea polyphenols in the growth inhibition of various infectious microorganisms has been thoroughly reported in numerous earlier reports (Liu et al. 2005; Friedman 2007). The tea polyphenols regulate the gene expression in *Escherichia coli*, inhibits cellular division in some species of bacteria, and also inhibit human immunodeficiency virus-1 replication in the human body by targeting at various steps in the life cycle of human immunodeficiency virus-1 which is the major causative agent of acquired immunodeficiency syndrome (Liu et al. 2005). Tea polyphenols also act synergistically with selective antibiotics and show benefits against multidrug resistance. Earlier, Tiwari et al. (2005) reported the synergistic activity of tea extracts with chloramphenicol and other antibiotics like methicillin, nalidixic acid, and gentamycin against various strains of enteropathogens. In another study, Betts et al. (2013) found synergistic antifungal effects of black tea theaflavin and green tea epicatechin against *Candida albicans* in combination. Thus, it is evident that tea and its constituents have a good perspective to be used as antimicrobials.

Therapeutic delivery of tea constituents

A plethora of in vitro studies revealed the potential therapeutic benefits of tea catechins in the prevention of various ailments (Baldi et al. 2020). The majority of pharmacological properties of tea constituents are associated with the antioxidant behavior of tea catechins due to the presence of phenolic groups (Yan et al. 2020). This polyphenolic nature of catechins is concomitant with the low efficacy and bioavailability of tea catechins (Bhushani et al. 2016; Son et al. 2016; Cai et al. 2018a, b). It also affects the therapeutic application of tea catechins. Thus, low bioavailability, poor bioaccessibility, and inconsistent systemic release of tea catechins, especially epigallocatechin gallate, have restricted their clinical applications (Bhushani et al. 2016; Son et al. 2016). To overcome these shortcomings, considerable work is done in recent past for processing of tea constituents for enhancing their bioavailability, cell permeability, and inhibition of gastrointestinal degradation (Fig. 2). Various matrix-assisted encapsulation techniques have been used in the recent past to overcome this issue (Table 1). Generally, carbohydrate (chitosan, cellulose polymers, starch-based materials, gum arabic, and sodium alginate), protein, lipids, and gelatin derivatives are widely employed for encapsulation of tea constituents (Cai et al. 2018a, b).

In a recent study by Ahmad et al. (2019), starch-based nanoparticles were prepared for nanoencapsulation of catechin. Results showed that during simulated gastrointestinal digestion, the biological properties of catechins were retained in encapsulated catechin compared to free catechin. In another study, chitosan was used for the nanoencapsulation of catechin that exhibited good surface topography and emulsion stability (Kailaku et al. 2014). Encapsulation of green tea catechins in γ-cyclodextrin and coating with hydroxypropylmethylcellulose phthalate were reported to increase their digestive stability up to 65% and 58%, respectively (Son et al. 2016). Bovine serum albumin, a globular protein, was efficiently used as an effective carrier for encapsulation of epigallocatechin gallate. It was reported that the stability of epigallocatechin gallate was enhanced when bound to bovine serum albumin compared to free one (Yi et al. 2017). Moreover, chitosan-coated bovine serum albumin–epigallocatechin gallate nanoparticles improved the absorption of epigallocatechin gallate. It was showed that chitosan-coated BSA–epigallocatechin gallate nanoparticles showed higher permeability compared to the free form of epigallocatechin gallate (Li et al. 2014). Thus, it is clear that matrix encapsulation of tea constituents helps in enhancing their stability and bioaccessibility.

Perspectives

Numerous epidemiological research evidence in recent years indicated that regular consumption of tea and its constituents could help in the prevention and delay of various diseases such as diabetes, obesity, hypertension, cardiovascular disorders, and cancer. Since tea is an inexpensive and sustainable bioresource to obtain these highly valuable natural antioxidants, there is an immense need to intensify the research efforts to cope with the issues of poor stability, efficacy,

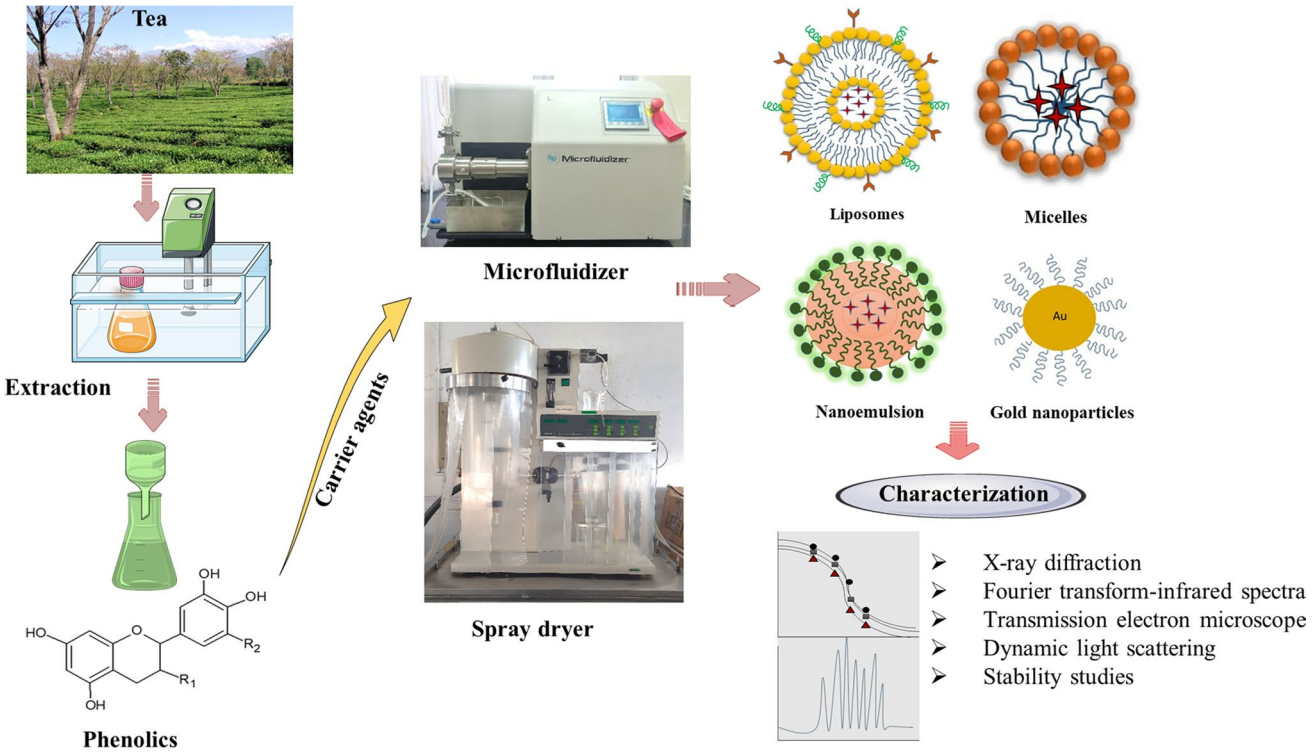

Fig. 2 Tea phenolics extraction and encapsulation utilizing various carriers using a spray drier and high-pressure homogenizer. The micro- and nanoencapsulates can be characterized using various techniques

and bioavailability of tea constituents. The outcome of these research studies will open new horizons for exploration and valorization of tea constituents as therapeutics against miscellaneous health ailments.

Conclusions

Tea is undoubtedly a health-promoting beverage, which constitutes a diverse array of bioactive molecules. The tea shoots are processed for the preparation of various types of teas (green, black, oolong, and white) with different manufacturing processes. These teas constitute a wide array of volatile and non-volatile chemical compounds and impart unique taste and aroma. Various research studies have revealed the role of different teas and their chemical constituents in the prevention and delay of metabolic ailments at the cellular and molecular levels. Contrariwise poor bioavailability, low bioaccessibility, and incongruous systemic release of tea constituents due to their large molecular weight and number of phenolic groups limit their therapeutic applications. Hence, new and sustainable techniques to resolve the issue of poor stability and bioefficacy of tea constituents for extensive clinical applications are indeed necessary for their applications in the development of new functional foods, pharmaceuticals, and nutraceuticals.

Table 1 Encapsulation approaches to improve the bioefficacy of tea constituents

Nanoparticle/ liposomes/nanoe-mulsion	Main matrix	Bioactive molecule/extract	Nature of study	Key findings	References
Casein micelles	Milk serum, milk whey, and skim milk	Epigallocatechin gallate	In vitro	Epigallocatechin gallate–casein complex decreases the proliferation of human colorectal adenocarcinoma cells (HT-29) alike free epigallocatechin gallate	Haratifar et al. (2014)
Nanoemulsion	Soy protein isolate	Catechins	In vitro	Nanoemulsions based on soy protein improved the stability, bioaccessibility, and permeability of tea catechins	Bhushani et al.(2016)
–	Rice bran protein isolate	Catechins	In vitro	Binding catechins to rice bran protein isolate resulting in improved stability of tea catechins	Shi et al. (2017)
Emulsions	Sodium caseinate	Epigallocatechin gallate	In vitro	Sodium caseinate-stabilized emulsions can be employed for effective delivery of epigallocatechin gallate	Sabouri et al. (2017)
Liposomes	Soy lecithin	Green tea extract	In vitro	Improved bioavailability and stability of tea catechins	Dag and Oztop (2017)
Nanoparticles	Maltodextrin, gum arabic, egg-yolk l-alpha-phosphatidylcholine, and stearylamine	Epigallocatechin gallate	In vitro	Effective delivery of epigallocatechin gallate	Gomes et al. (2010)
Nanoparticles	Starch from horse chestnut, water chestnut, and lotus stem	Catechins	In vitro	Helped in retaining biological properties of catechin during simulated gastrointestinal digestion	Ahmad et al. (2019)
Nanoparticles	Chitosan	Catechins	In vitro	Catechin-loaded folate-conjugated chitosan nanoparticles exhibited antiproliferative effects in a concentration-dependent manner for breast cancer cells (MCF-7)	Liu et al. (2017)
Nanoparticle	Gold(III) chloride trihydrate ($HAuCl_4 \cdot 3H_2O$)	Epigallocatechin gallate	In vitro	Epigallocatechin gallate gold nanoparticles showed more apoptosis in cancer cells compared to epigallocatechin gallate	Chavva et al. (2019)
Nanoparticle	Soya lecithin	Epigallocatechin gallate	In vitro	Epigallocatechin gallate-loaded nanoparticles showed higher cytotoxicity against epithelial breast cancer (MDA-MB 231) and human prostate cancer cells (DU-145) compared to free epigallocatechin gallate	Radhakrishnan et al. (2016)
Nanoparticles	β -chitosan	Catechins	In vitro	Improved the antibacterial activity against *Escherichia coli* and *Listeria innocua*	Zhang et al. (2016)
Nanoparticles	–	Epigallocatechin gallate	In vivo	Epigallocatechin gallate–gold nanoparticles controlled growth of tumor cell by apoptosis	Hsieh et al. (2011)
Nanoparticles	Chitosan, polyaspartic acid	Epigallocatechin gallate	In vivo	Nanoformulation of epigallocatechin gallate had greater activity against atherosclerosis	Hong et al. (2014)

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