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'Exploring the Therapeutic Potential of Camellia sinensis (L.) Kuntze for Metabolic and Endocrine Disorders: A Comprehensive Systematic Review'

Himani Rana*, Meenakshi Malhotra, Ajeet Pal Singh and Amar Pal Singh.
St. Soldier Institute of Pharmacy, Lidhran campus Behind NIT, Jalandhar-Amritsar Byepass, Jalandhar, Punjab 144001

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ABSTRACT: This systematic review aimed to update our understanding of the pharmacological effects of Camellia sinensis, commonly known as tea, on metabolic and endocrine disorders. The review considered both preclinical and clinical studies conducted between 2018 and 2022, focusing on the impact of tea extracts and isolated compounds on hypertension, diabetes, metabolic syndrome, and hypercholesterolemia. The search included English-language publications from PubMed, Science Direct, and Scopus, resulting in 80 reports that met the inclusion criteria out of a total of 1384 studies.

The majority of papers were published in 2018 (29.3%) and 2019(20.6%), with the primary research conducted in China (28.75%), the United States (12.5%), and South Korea (10%). Among the studies, tea extracts, especially green tea, were used in 67.5% of the cases, while isolated compounds, particularly epigallocatechin gallate, were employed in 41.25% of the studies. The main focus of the pharmacological investigations was on diabetes and hypertension with a significant number of in vitro and in vivo studies.

Although some clinical trials demonstrated promising results, their overall number was limited. Therefore, there is a clear need for more extensive clinical research to establish stronger evidence, especially for less explored pathologies such as hypertension, and metabolic syndrome. Furthermore, given the interconnected nature of various endocrine disorders, future studies should also aim to identify a standardized tea dosage or specific bioactive constituents that could be beneficial across these conditions.

Keywords: Camellia sinensis, Tea Extracts,Hypertension,Diabetes, and Metabolic Syndrome

I. INTRODUCTION:

The Rising Tide of Metabolic and Endocrine Disorders: An Alarming Surge in Hypertension and Type 2 Diabetes Mellitus Attributed to Sedentary Lifestyles, Dietary Habits, and Endocrine Disruptors, Among Other Factors. [(1)]By the year 2030, metabolic and endocrine diseases are +projected to emerge as one of the primary global causes of mortality, underscoring the severity of these conditions and their potential impact on public health. [(2)]Camellia sinensis (L.) Kuntze, a tree belonging to the Theaceae family, predominantly thrives in tropical and subtropical climates. The leaves of this tree are used to create tea, making it one of the most widely consumed beverages globally. Teas can be categorized based on their fermentation levels, encompassing green tea (unfermented), white tea and yellow tea (lightly fermented), oolong tea (semi-fermented), black tea (fully fermented), and pu-erh tea (post-fermented).

Notably, black tea holds the title of the most produced and consumed tea worldwide, accounting for 78% of the total tea consumption, particularly prevalent in Western countries. Following closely is green tea, representing 20% of the global tea consumption, with significant popularity in regions like China, India, and Japan. Oolong tea constitutes less than 2% of the overall tea consumption. [(3)] The leaves of Camellia sinensis contain various bioactive compounds, with primary catechins like epigallocatechin gallate (EGCG) being prominent, along with flavonols and their glycosyl derivatives (apigenin, myricetin, quercetin, rutin), teaflavins, and thearubigins. The specific type and quantity of these compounds are influenced by the fermentation level of the leaves during tea processing.

Green tea, being unfermented, predominantly contains high levels of epigallocatechin-3-gallate (EGCG) as its major bioactive compound. In contrast, black tea, due to fermentation during processing, produces theaflavins, which contribute to its characteristic flavor and aroma. [(4,5,6)]Teas derived from Camellia sinensis offer a range of health benefits, including

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antioxidative, anti-inflammatory, anticancer, cholesterol-lowering, and cardiovascular protective properties, among various other advantageous effects. [7,8]

The objective of this updated systematic review is to assess the pharmacological effects of Camellia sinensis (L.) Kuntze on metabolic and endocrine disorders. The disorders under investigation include hypertension, diabetes, metabolic syndrome, and hypercholesterolemia.

II. METHODS:

2.1 SEARCH STRATERGY:

The systematic review encompassed both preclinical and clinical investigations examining the effects of Camellia sinensis on endocrine and metabolic disorders. To identify relevant studies, a comprehensive literature search was conducted across prominent databases such as Pubmed, Science Direct, and Scopus. The search utilized a combination of specific keywords, including "Camellia sinensis," "hypertension," "diabetes," "metabolic syndrome,"and "hypercholesterolemia,". The selected studies were limited to those published between the years 2018 and 2022

2.2 INCLUSION AND EXCLUSION CRITERIA:

The inclusion criteria for this systematic review encompassed both preclinical (in vitro and in vivo) and clinical studies written in English, specifically focusing on the pharmacological effects of isolated compounds and extracts from Camellia sinensis on metabolic and endocrine disorders. To ensure the relevance and quality of the selected studies, certain criteria were excluded, such as case reports, review articles, conference proceedings, and editorial letters. Additionally, studies involving medicinal plant mixtures, galenic formulations, Camellia species other than Camellia sinensis, functional foods with tea, and comorbidities associated with endocrine and metabolic diseases were also excluded.

The literature search was meticulously conducted by two independent researchers, namely E.G.-B. and M.S. The process involved an initial identification of relevant studies in the aforementioned databases, followed by the removal of duplicated works. Subsequently, studies that did not meet the predetermined inclusion criteria for this systematic review were excluded. To ensure the accuracy and consistency of the research, a third reviewer, M.P.G.-S., verified the process using a predefined spreadsheet designed by the authors.

III. PHARMACOLOGICAL ACTIVITY, DISCRIPTION OF DATA:

At the beginning of the review process, a total of 1384 studies were initially found across different databases: Pubmed (n = 170), Science Direct (n = 1177), and Scopus (n = 37). To ensure data accuracy, 40 duplicate reports found in multiple databases were removed. Subsequently, 1264 articles were excluded based on evaluations of their titles and abstracts (n = 1237), as well as a thorough examination of their full texts (n = 27). Ultimately, 80 articles met the inclusion criteria and were included in this systematic review (Figure1).

Among the 80 selected articles, five studies conducted both in vitro and in vivo experiments, while one study involved both in vitro investigations and clinical trials. These studies collectively provided valuable insights into the pharmacological activity of Camellia sinensis on metabolic and endocrine disorders.

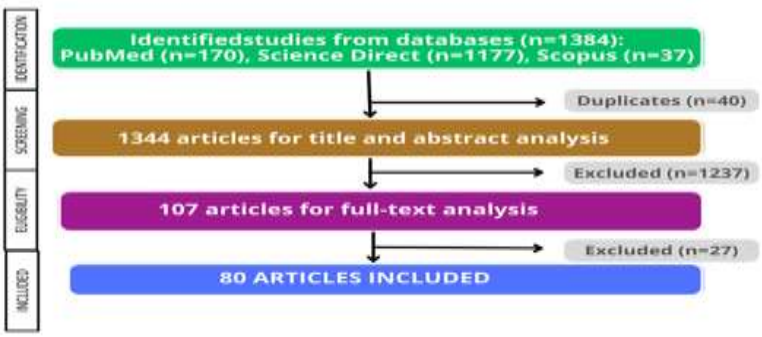

Figure 1: illustrates the flowchart of the literature research conducted on Camellia sinensis, encompassing studies in vitro, in vivo, and clinical trials. The flowchart visually represents the systematic approach used to identify, select, and include relevant studies in this comprehensive review.

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In this systematic review, the included studies were categorized into three appendices. Appendix A (Table A1) contained in vitro pharmacological studies, while Appendix B (Table A2) comprised in vivo pharmacological studies. These studies were grouped based on the disease investigated, the type of extract or isolated compound used, the experimental model employed, the treatments administered, the major findings, and the corresponding references. Additionally, Appendix C (Table A3) provided information on clinical trials, including details such as the study author, year, and country, study design, sample size, study population, type of plant (Camellia sinensis), intervention, treatment duration, and study results.

The majority of papers included in this review were published in 2018 (n = 27, 29.3%) and 2019 (n = 19, 20.6%) (Figure 2A). These studies originated from research groups in 23 different countries, with a significant proportion coming from China (n = 23, 28.75%), the United States (n = 10, 12.5%), and South Korea (n = 8, 10%) (Figure 2B).

Both extracts (n = 54, 67.5%) and isolated compounds (n = 33, 41.25%) from Camellia sinensis were utilized in the studies. Extracts were predominantly investigated in in vivo studies and clinical trials, while isolated compounds were more frequently studied in in vitro experiments.

The focus of the investigations revolved around endocrine and metabolic disorders, with diabetes being the most frequently studied pathologies (n = 35). Hypercholesterolemia (n = 9) hypertension (n = 5), and metabolic syndrome (n = 4) were also subjects of study. Specifically, diabetes was the most commonly studied disease in in vitro studies (n = 16). Notably, some research works examined the effects of extracts and isolated compounds of Camellia sinensis on two different pathologies within the same study. [7,8,9,10,11,12,13,14] This systematic review is structured into four distinct sections, focusing on various pathologies: diabetes, hypercholesterolemia, hypertension, metabolic syndrome. Within each pathology, the pharmacological activities of both isolated compounds and extracts from tea (Camellia sinensis) were categorized into three main aspects: signal transduction, redox system, and changes of biomarkers. Each section presents a comprehensive analysis of the relevant studies, shedding light on the specific effects of tea components on different aspects of these metabolic and endocrine disorders.

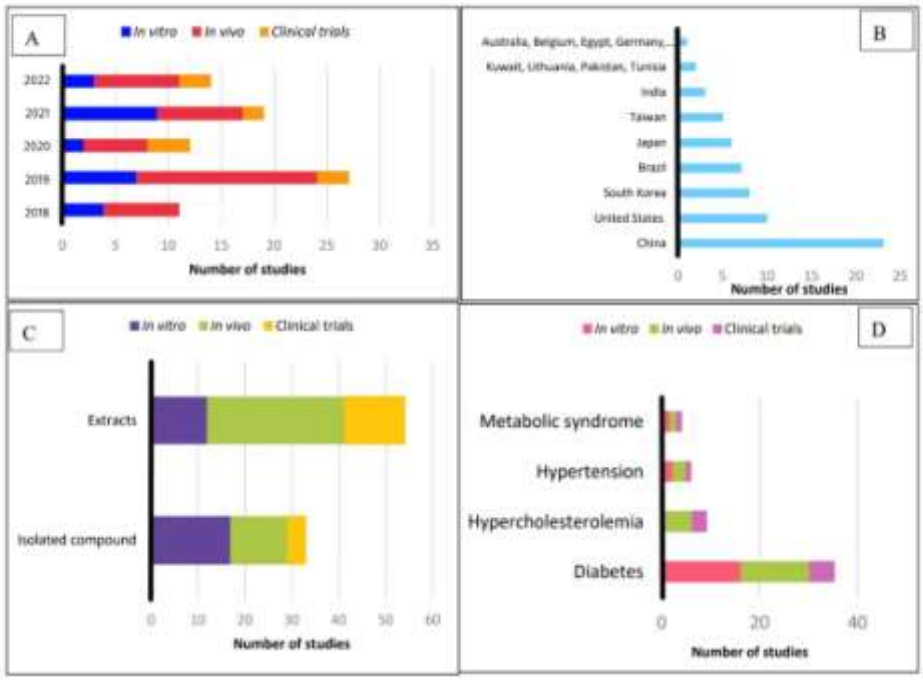

Figure 2: presents the main characteristics of papers focusing on the pharmacological activity of Camellia sinensis. The figure is divided into four sections: (A) Year of publication, (B) Research group country, (C) Part of the plant used for research, and (D) Diseases studied in in vitro, in vivo, and clinical trials studies [1].

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3.1 Camellia sinensis and diabetes

Diabetes mellitus is a persistent metabolic disorder characterized by elevated blood sugar levels (hyperglycemia). This condition arises from either insufficient insulin production by the pancreas or the body's inability to utilize insulin effectively. [15]Approximately 425 million adults between the ages of 20 and 79 are affected by diabetes mellitus, and projections indicate that this number is expected to rise to 629 million by the year 2025. Diabetes mellitus is particularly widespread in low and middle-income countries, with a significant burden observed in regions like South-East Asia (82 million cases) and the Western Pacific (159 million cases). [16]Diabetes mellitus can be categorized into three main types: type 1, type 2, and gestational diabetes. Type 1 diabetes mellitus, also known as insulin-dependent diabetes, is an autoimmune disorder that primarily affects individuals during childhood. It constitutes approximately 5% of all diagnosed cases of diabetes mellitus. [15,17]Type 2 diabetes mellitus, commonly known as adult-onset diabetes, represents the most prevalent form of diabetes, accounting for approximately 90% to 95% of all diagnosed cases globally. This type of diabetes is primarily linked to factors such as excessive body fat, a sedentary lifestyle, and the natural process of aging. [15]Gestational diabetes mellitus emerges during pregnancy, typically in the second or third trimester, due to impaired glucose tolerance. The main risk factors associated with gestational diabetes mellitus encompass obesity, ethnic background, age at childbearing, and a family history of type 2 diabetes mellitus. [18,19]

The majority of in vitro diabetes studies involving Camellia sinensis focus on the isolated compounds and extracts' capacity to inhibit the activities of α-amylase and α-glucosidase. Additionally, researchers have conducted several in vitro studies using cellular models, with mouse 3T3-L1 pre/adipocytes and HepG2 cell lines being the most frequently employed.

For in vivo investigations, preclinical diabetic animal models such as Kunming mice, Sprague-Dawley rats, and Wistar rats are commonly used to explore the anti-diabetic properties of tea. These studies often induce diabetes in the animals using streptozotocin or alloxan to mimic the diabetic condition. [8,14,20,21]Additionally, researchers have also explored the nematode Caenorhabditis elegans as a diabetic model in their investigations. [22]

Targeting molecular pathways in signalling has proven to be one of the most successful approaches in antidiabetic therapy. [23]Recent research has established that tea and its active metabolites possess therapeutic potential against diabetes by influencing various signalling pathways. Notably, studies conducted on rat islet RIN-5F cell tumour revealed that a type II arabinogalactan (isolated from green tea leaves at a concentration of 200 µg/mL) enhanced glucose-stimulated insulin secretion by targeting the cAMP/PKA signalling pathway. [24]The cAMP/PKA signaling pathway plays a pivotal role in regulating glucose homeostasis by influencing processes such as gluconeogenesis, glycogen synthesis, and glycogen breakdown. [23])Tea polysaccharides derived from green tea (administered at doses of 200, 400, and 800 mg/kg b.w. per day for 4 weeks) have also been found to target the PI3K/Akt signaling pathway. This pathway facilitates GLUT 4 translocation and activation, contributing to the beneficial effects of the polysaccharides in diabetes management.[8]) Furthermore, in L6 skeletal muscle cells, epigallocatechin gallate was observed to enhance glucose uptake by promoting GLUT4 translocation through the activation of the PI3K/AKT signalling pathway.[13]Another strategy to combat hyperglycemia involves inhibiting sodium glucose transporters like intestinal SGLT1 and renal SGLT2, responsible for glucose absorption, while promoting GLUT2 and GLUT4 transporters that facilitate glucose movement across membranes. In a study conducted on Wistar rats fed a high-fat diet, both acute (30 minutes) and chronic (6 weeks) administrations of green tea decoction (50 g/L) and a combination of 4 mg epigallocatechin gallate (EGCG) and 2 mg epigallocatechin (EGC) demonstrated inhibitory effects on SGLT-1 activity. Moreover, these interventions led to increased GLUT2 mRNA levels in the jejunum mucosa and elevated GLUT4 mRNA levels in adipose tissue, thereby showcasing their potential to improve glucose regulation. [10]Furthermore, in 3T3-L1 adipocytes, epigallocatechin gallate was found to inhibit GLUT4-dependent insulin-like growth factor I and II, while simultaneously stimulating glucose transport. [25]

In recent years, there has been extensive research on the ability of various types of teas and their bioactive compounds to inhibit the enzymes α-amylase and α-glucosidase. The enzyme α-amylase, present in saliva and pancreas, plays a role in breaking down glycogen and starch by

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hydrolysing alpha 1–4 bonds to form simple sugars like oligosaccharides and disaccharides. Subsequently, the α-glucosidase enzyme further catalyses alpha 1–4 bonds of oligosaccharides and disaccharides, converting them into glucose in the small intestine. Targeting both of these enzymes has become a therapeutic approach in the treatment of diabetes mellitus. [26]

Yang and Kong (2016) [27])Green tea, black tea, and oolong tea were investigated for their α-glucosidase inhibitory activity, with oolong tea exhibiting the lowest IC50 value (1.38 µg/mL). Additionally, oh et al. (2015) conducted the study. [28]

In a comparative study, the α-glucosidase inhibitory activity of tea water extracts and tea pomace extracts derived from green, oolong, and black tea was investigated. Surprisingly, the research revealed no significant differences between the inhibitory effects of tea water extracts and tea pomace extracts. Among all the tea types examined, green tea exhibited the most potent activity (IC50 = 2040 µg/mL for tea water extracts and IC50 = 1950 µg/mL for tea pomace extracts).

Furthermore, the aqueous extract obtained from black tea leaves demonstrated inhibitory effects on α-glucosidase enzyme activity (IC50 = 2400 µg/mL for sucrose and IC50 = 2800 µg/mL for maltase). However, this extract did not show any inhibitory activity against α-amylase. [29])In addition to the above findings, it was observed that black tea and green tea demonstrated inhibitory effects on α-amylase activity, with IC50 values of 589.86 µg/mL and 947.80 µg/mL, respectively. Similarly, both black tea and green tea inhibited α-glucosidase activity, with IC50 values of 72.31 µg/mL and 100.23 µg/mL, respectively.The different chemical compositions of these three teas may account for their varying effects on diabetes-related enzyme activity. Notably, oolong tea contains dimeric flavan-3-ols known as theasinensins, green tea is rich in epigallocatechin-3-gallate as a major catechin, and black tea stands out for its abundance of theaflavins and thearubigins. These distinct compounds in each tea type may contribute to their specific inhibitory activities on the enzymes related to diabetes. [30,31]

Furthermore, variations in the activity of the same type of tea can be attributed to the significant impact of the chemical composition, which is highly influenced by the nature of the green shoots and the specific procedures used to manufacture tea in the producing countries. These factors play a crucial role in determining the unique characteristics and bioactive components present in each tea variant, leading to differences in their effects on diabetes-related enzyme activity. [32])In addition to the studies on black, green, and oolong tea, investigations on various ages of pu-erh tea polysaccharide have shown inhibitory effects on α-glucosidase activity, particularly in 3-year-old and 5-year-old teas, with IC50 values of 0.583 µg/mL and 0.438 µg/mL, respectively. However, no inhibitory activity against α-amylase was observed [37]. In a related study, Xu et al. (2014) conducted research on this topic. [33])The study found that pu-erh tea polysaccharides, aged for 3 years and 5 years, exhibited potent inhibition of α-glucosidase enzyme activity, comparable in potency to acarbose (at 3 years aging) and three times more potent than acarbose (at 5 years aging). Furthermore, the water extract of pu-erh tea showed moderate inhibitory effects on sucrose activity (IC50 = 14.4 µg/mL) and maltase (IC50 = 11.4 µg/mL). Among the compounds tested, epigallocatechin-3-O-gallate demonstrated the highest inhibitory activity, with an IC50 of 32.5 µM against sucrose and an IC50 of 1.3 µM against maltase. [12])In a separate study, the ethyl acetate fraction derived from Qingzhuan tea extracts demonstrated significant α-glucosidase inhibitory potential, with an IC50 value of 0.26 µg/mL. This activity was attributed to the presence of compounds such as epigallocatechin gallate and epicatechin gallate. Specifically, epicatechin gallate exhibited inhibitory effects on α-amylase activity (IC50 = 45.30 µg/mL) and α-glucosidase activity (IC50 = 4.03 µg/mL), while epigallocatechingallate inhibited α-glucosidase with an IC50 value of 19.5 µM. These findings highlight the potential of these tea-derived compounds in managing diabetes-related enzyme activities. [13,34])Furthermore, the isolated compound amelliaone A from YingDe black tea demonstrated a more potent inhibition of α-glucosidase enzyme activity, with an IC50 value of 10.2 µM, compared to the reference compound acarbose, which exhibited an IC50 value of 18.2 µM. This highlights the potential of amelliaone A as a promising candidate for managing and controlling diabetes-related enzyme activity. [35])Moreover, Hua et al. [36] The inhibitory activity of flavone and flavone glycosides of green tea (Lu'anGuaPian) on α-glucosidase and α-amylase enzymes was investigated. Among the compounds tested, 7 kaempferolmonoglycoside exhibited the most potent inhibitory activity against α-glucosidase, with an IC50 value of 40.02 µM, while kaempferoldiglycoside showed the highest

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inhibition against α-amylase, with an IC50 value of 0.09 µM.

Considering the IC50 values of the isolated compounds, epigallocatechin gallate and 7 kaempferolmonoglycoside were identified as the most promising α-glucosidase inhibitory agents, and kaempferoldiglycoside showed significant potential as an α-amylase inhibitor.

It is worth noting that oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and antioxidants, plays a crucial role in the development of diabetes mellitus and its associated complications. To address this, a black tea aqueous extract with a concentration of 2.5% was administered to diabetic rats.

The results showed that the black tea extract effectively reduced lipid peroxidation levels, which is a marker of oxidative stress, in the diabetic rats. Additionally, the extract increased the content of glutathione (GSH), an important endogenous antioxidant, which helps counteract the damaging effects of ROS.

These findings suggest that the consumption of black tea may help alleviate oxidative stress and offer potential benefits in managing diabetes and its related complications. However, further research is required to fully understand the mechanisms and potential therapeutic applications of black tea in combating oxidative stress and its role in diabetes management. [20]In a study conducted on diabetic Kunming mice, tea polysaccharides derived from green tea were administered at different doses (200, 400, and 800 mg/kg b.w. per day) for a period of 4 weeks.

The results of the study showed that the mice treated with tea polysaccharides exhibited significant increases in the activities of two important antioxidant enzymes: superoxide dismutase (SOD) and glutathione peroxidase (GPX). SOD is responsible for neutralizing superoxide radicals, while GPX plays a vital role in reducing hydrogen peroxide and lipid hydroperoxides by using glutathione as a substrate.

The elevation of SOD and GPX activities indicates an enhancement in the antioxidant defense system of the diabetic mice, which can effectively combat and neutralize reactive oxygen species (ROS) and oxidative stress. This finding suggests that tea polysaccharides from green tea have the potential to mitigate the detrimental effects of oxidative stress in diabetes and contribute to improved antioxidant status in the body.

Further investigation is warranted to elucidate the specific mechanisms through which tea polysaccharides exert their antioxidant effects and to determine the optimal dosage for achieving the maximum benefits in managing diabetes-associated oxidative stress. [8]

In a separate research study, epigallocatechin-3-gallate (EGCG) was found to exhibit significant reductions in lipid peroxidation and protein oxidation, along with a decrease in superoxide levels in diabetic rats. Moreover, EGCG supplementation was shown to enhance the activity of antioxidant enzymes and increase the levels of glutathione (GSH) content in these diabetic rats. These findings suggest that EGCG possesses potent antioxidant properties that may be beneficial in mitigating oxidative stress and associated complications in diabetes. [21]

In rigorously conducted clinical trials, the hypoglycaemic effects of green tea (predominantly) and black tea were evaluated through randomized, double-blind, and placebo-controlled methodologies. These studies encompassed patients of various genders, with the exception of one trial focusing on overweight women, and ages ranging from 30 to 80 years.

The treatment durations in these trials varied from weeks to months, and the daily doses administered also differed across each study. The doses ranged from 1 g/day of green tea dry extract to 2.5 g/three times a day of black tea. Other dosage regimens included 560 mg of tea polyphenols taken twice a day and 200 mg of tea extract per day.

The measured parameters encompassed a wide range of factors, including blood glucose levels and various markers of oxidative stress. Notably, doses of 1 g of green tea dry extract and 2.5 g/three times a day of black tea administered over a 12-week period were found to be highly effective in improving glycemic control, surpassing the efficacy of the reference drug, metformin. These findings suggest that green tea and black tea extracts have promising potential as natural alternatives for managing blood glucose levels in patients with varying degrees of effectiveness. [37])Furthermore, significant antioxidant effects were observed in two different treatment regimens: 560 mg of tea polyphenols administered twice a day for a duration of 20 weeks, and 200 mg of tea extract taken daily for a period of 9 to 18 months. In both cases, these interventions led to an increase in superoxide dismutase activity, an important antioxidant enzyme, and a reduction in lipid

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peroxidation, indicating a decrease in oxidative stress. These findings highlight the potential of tea polyphenols and tea extracts in promoting antioxidant defences and combating oxidative damage. [43]

3.2. Camellia sinensis and hypercholesterolemia

More than 39% of the global population is affected by hypercholesterolemia, a condition characterized by elevated blood cholesterol levels exceeding 200 mg/dL. Among the continents, Europe and America show the highest prevalence rates of this condition. [37]

In vivo studies have shown that green tea extracts exhibit a capacity to reduce levels of total cholesterol, LDL (low-density lipoprotein), and triglycerides. [11,14,38]The reduction in total cholesterol, LDL, and triglycerides observed in these in vivo studies is primarily attributed to the presence of epigallocatechin gallate and flavonols in green tea extracts. [39,40]) Furthermore, studies on Chungtaejeon aqueous extracts, a Korean fermented tea, have demonstrated its ability to reduce hepatic cholesterol, total serum cholesterol, and LDL cholesterol levels in high fat atherogenic Wistar rats. These findings suggest that Chungtaejeon tea may have potential benefits in managing cholesterol-related issues in experimental animal models. [41]

Randomized, double-blind, and placebo-controlled clinical trials were conducted to investigate the anti-hypercholesterolemic properties of black tea and green tea in patients with high cholesterol levels. These trials evaluated the cholesterol-lowering effects of tea extracts by assessing biochemical parameters, such as LDL content, total cholesterol, and antioxidant levels.

The clinical studies on black tea demonstrated its effectiveness in reducing the LDL/HDL ratio, total cholesterol, apolipoprotein B, and oxidative stress in patients with high cholesterol levels. In one of these trials, the effective dosage consisted of 2.5 g of black tea along with a phytosterol mixture containing 1 g of plant sterols, which was administered for a duration of 4 weeks. These findings highlight the potential benefits of black tea in managing cholesterol-related issues and oxidative stress in individuals with elevated cholesterol levels. [42]

In the mentioned study, the dosage for black tea was not specified; rather, participants consumed five cups of black tea per day during two 4-week treatment periods.

Conversely, another study evaluated the impact of consuming "Benifuuki" green tea, which is abundant in methylated catechins. Participants in this study consumed 3 g of green tea extract three times daily for a duration of 12 weeks. The results revealed that the "Benifuuki" green tea consumers experienced significant reductions in serum total cholesterol and serum LDL cholesterol levels compared to individuals who consumed "Yabukita" green tea or barley infusion (placebo tea). These findings suggest that the specific composition of green tea, particularly its higher content of methylated catechins, may play a crucial role in its cholesterol-lowering effects. [44,45]

3.3. Camellia sinensis and Hypertension

1. Hypertension, defined as having a blood pressure of equal to or greater than 130/85 mm Hg, is a prevalent cardiovascular condition that affects a significant number of individuals worldwide, totaling around 1.13 billion people. However, not all cases of hypertension are solely due to lifestyle or genetic factors. In some cases, hypertension can be linked to endocrine disorders, which result from hormone imbalances within the body.Endocrine hypertension occurs when there is an abnormality in the production or regulation of hormones, leading to an elevation in blood pressure. Several examples of endocrine disorders that can cause hypertension include Cushing syndrome, primary aldosteronism, and pheochromocytoma.Cushing Syndrome: This condition arises when the body produces excessive levels of the hormone cortisol. Cortisol plays a vital role in managing stress and metabolism, but excessive amounts can lead to hypertension among other health issues.
2. Primary Aldosteronism: In this disorder, the adrenal glands produce too much aldosterone, a hormone responsible for regulating salt and water balance in the body. Elevated aldosterone levels can cause increased sodium retention and potassium loss, leading to high blood pressure.
3. Pheochromocytoma: Pheochromocytoma is a rare tumor that develops in the adrenal glands, causing them to release excess adrenaline and noradrenaline. These hormones can dramatically increase heart rate and blood pressure, resulting in hypertension.

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Identifying and managing endocrine hypertension is crucial to control blood pressure levels effectively. Proper diagnosis and treatment of the underlying endocrine disorder can significantly improve hypertension management and reduce the risk of cardiovascular complications. Therefore, medical professionals must consider the possibility of an endocrine cause when evaluating and treating patients with hypertension. [46,47]

Angiotensin I-Converting Enzyme (ACE) is responsible for converting angiotensin I into angiotensin II, which possesses vasoconstrictor properties and can contribute to hypertension. Researchers conducted experiments using infusions and decoctions of four different black tea samples, namely Door's tea, Siliguri tea, Guwahati tea, and Nilgiri tea, each at a concentration of 15 µg/mL. The purpose was to investigate their potential to inhibit ACE activity.

In this study, the researchers found that decoctions, which involve boiling the tea leaves in water, exhibited higher ACE inhibitory activity compared to infusions, where tea leaves are steeped in hot water. Notably, among all the tea samples tested, Nilgiri tea displayed the most potent inhibitory activity against ACE.

The antihypertensive properties observed in these black tea samples can be attributed mainly to the presence of compounds such as thearubigin and theaflavin. These bioactive compounds are abundant in black tea and have been associated with various health benefits, including potential antihypertensive effects.

In conclusion, the study suggests that consuming black tea, particularly Nilgiri tea, may offer potential antihypertensive benefits due to its ability to inhibit ACE activity, which can help in managing hypertension and promoting cardiovascular health. Thearubigin and theaflavin are believed to play a significant role in conferring these beneficial properties to black tea. [48]

In a separate laboratory study, researchers found that pre-treating cultured rat aortic endothelial cells with black tea extract (at concentrations ranging from 0.3 to 5 µg/mL) and theaflavin-3,3'-digallate (at concentrations ranging from 0.03 to 0.5 µg/mL) for 30 minutes resulted in improved relaxation responses of the endothelium. This was particularly significant in cells that had been treated with homocysteine, a known inducer of endoplasmic reticulum stress.

In addition to this in vitro study, a research team led by San Cheang explored the effects of black tea extract administered at a dose of 15 mg/kg/day for 2 weeks in a rat model subjected to angiotensin II. The findings revealed that the black tea extract successfully prevented the elevation of plasma homocysteine levels and downregulated markers of endoplasmic reticulum stress.

Furthermore, Nomura et al. conducted research to investigate the protective properties of three different cultivars of Camellia sinensis (specifically, "Yabukita," "Sofu," and "Sunrouge") in a rat model of hypertension induced by a high salt diet. Notably, all three tea cultivars demonstrated the ability to reduce urinary nitric oxide metabolites. Additionally, "Yabukita" and "Sofu" cultivars were found to increase the expression of soluble guanylate cyclase, which is a positive indicator of endothelial function.

These studies collectively suggest that black tea extract and certain cultivars of Camellia sinensis have potential protective effects on endothelial function and may offer benefits in conditions associated with endothelial dysfunction, such as hypertension and elevated homocysteine levels. [49,50]

One clinical trial focused on investigating the impact of tea compared to coffee on blood pressure. The study involved 1352 participants aged between 18 and 69 years, who were categorized into three groups based on their tea or coffee consumption habits: non-consumers, those consuming up to 3 dL/d (deciliters per day), and those consuming more than 3 dL/d of tea or coffee.

The results of this trial revealed that individuals who consumed 1 dL/day of tea experienced lower systolic blood pressure, with a reduction of 0.6 mm Hg, as well as lower pulse pressure, with a decrease of 0.5 mm Hg. These findings suggest that tea consumption might have a favorable impact on blood pressure levels compared to coffee consumption in this particular population. [51]

3.4. Camellia sinensis and Metabolic Syndrome

Metabolic syndrome refers to a grouping of metabolic disorders, including obesity, hypertension, hypercholesterolemia, and diabetes, which collectively contribute to an increased risk of developing cardiovascular diseases. The prevalence of this syndrome is significant, affecting approximately one billion people globally. [52,53,54]

In a study conducted by Yang et al. [55] in 2014, it was shown that green tea extract, at concentrations ranging from 0.2% to 0.5% (w/v), effectively inhibited lipid accumulation in 3T3-L1 preadipocytes during the process of adipogenesis.

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This inhibitory effect was achieved by reducing the expression of transcription factors C/EBPα and PPARγ, which are known to play crucial roles in adipocyte differentiation and fat storage.

Olanzapine, an atypical antipsychotic drug, is known to be linked with significant metabolic side effects due to its interactions with various receptors. These effects are attributed to its antagonistic actions on the H1 receptor, 5-HT2C receptor, D2 receptor, and muscarinic (M3) receptor. These interactions can lead to metabolic disturbances and contribute to the development of metabolic side effects in individuals taking olanzapine. (56,57)

In a study involving adult male Wistar rats treated with olanzapine, the administration of green tea aqueous extract at doses of 25, 50, and 100 mg/kg/day for 11 days demonstrated beneficial effects. The green tea extract effectively reduced body weight gain, alleviated hypertension, and lowered hyperleptinemia. Furthermore, it led to a reduction in blood glucose, triglycerides, total cholesterol, and LDL cholesterol levels, while increasing HDL cholesterol levels in the olanzapine-induced metabolic condition. These findings suggest that green tea extract may offer potential therapeutic benefits for mitigating the metabolic side effects associated with olanzapine usage in this rat model. (58) In a separate animal study conducted by Xu et al. in 2018, the researchers examined the impact of large yellow tea produced in the Anhui Province of China on metabolic syndrome in C57BL/6 mice treated with a high-fat diet. The findings of this study indicated that consumption of yellow tea led to improvements in metabolic abnormalities, including positive changes in lipid profile, reduced hyperglycemia, and decreased body weight in the mice subjected to the high-fat diet. These results suggest that yellow tea may have potential therapeutic benefits in addressing metabolic disturbances associated with a high-fat diet in this experimental model. (59)

During a clinical trial, patients diagnosed with metabolic syndrome were given decaffeinated green tea extract capsules containing 500 mg of green tea extract, which provided 400 mg of catechins. The participants were instructed to take two capsules twice a day for a total of 12 weeks. At the end of the trial, it was observed that the patients who received the decaffeinated green tea extract capsules had lower levels of adiponectin and visfatin concentrations compared to the control group, who received water. These findings indicate that the green tea extract supplementation might have influenced the levels of these metabolic markers in patients with metabolic syndrome. (55)

IV. CONCLUSION

This systematic review aimed to consolidate existing research on the pharmacological effects of teas derived from Camellia sinensis leaves and its isolated compounds concerning metabolic and endocrine disorders. The majority of the studies included preclinical in vitro and in vivo investigations focused on diabetes and hypertension. Although clinical trials have shown promising outcomes, their numbers are limited. Green tea and epigallocatechin gallate have been extensively studied among the various teas and compounds, respectively. Research has predominantly explored the impact of these teas and compounds on different signalling pathways, oxidative stress, and relevant biomarkers for each specific pathology. The variation in pharmacological actions among tea types may be attributed to their distinct chemical compositions. Additionally, discrepancies in the effects of the same tea type can be observed due to differences in the chemical composition influenced by the green shoots' nature and tea manufacturing procedures in producing countries.The differences in activity observed in clinical trials can be explained by varying doses, treatment durations, and the characteristics of the subjects included in each study. For future research, it is crucial to generate more clinical evidence for less explored pathologies such as hypertension and metabolic syndrome. Given the interconnectedness of endocrine disorders, determining a standardized dose of tea or its bioactive constituents that can be beneficial for all these conditions would be of significant interest.

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Appendix A

TABLE A. In vitro pharmacological studies of camellia sinensis.[1]

Disease	Extract/isolated compound	Experimental model	Treatments	Major findings
Diabetes	Amelliaone A	A-glucosidase model	-	α-glucosidase inhibition: IC_{50}= 10.2ug/ml
	Arainogalacton	Rat islet tumor RIN-5F cells	50 or 200ug/ml,2h	↑insulin secretion
	Black and green teas	Mouse 3t3-L1 preadipocytes	10ug/ml,24h	↑SOD,CAT,andGPx activities ↓protienglycation ↓α-amylase and α-glucosidase activities
	Black tea aqueous extract	A-glucosidase model A-amylase model Caco-2 cells	-	↓α-glucosidase activity No effect on GLUT2 and SGLT1 uptake
	Black,green,and dark tea extracts	Human liver hepG2 cancer cells	-	↓ α-Glucosidase, aldose reductase, advanced glycation end-products ↑ Glucose uptake (dark tea extracts)
	Epicatechin gallate	α-amylase model α-glucosidase models	- -	↓α-amylase activity (IC_{50}= 45.30ug/ml) ↓α glucosidase activity (IC_{50}= 4.03ug/ml)
	Epigallocatechin gallate	Mouse 3t3-l1 adipocytes	20Um,2h	↓ IGF-I and IGF-II stimulation.
	Epigallocatechin-3-o-gallate	Rat skeletal muscle L6 cells	0,20,40,50, and 60Um,48h	↓α glucosidase activity (IC_{50}= 19.5Um)
	Flavanols	α-glucosidase model	-	↓sucrase activity and maltase activity
	Flavone and flavone glycosides	α-glucosidase model α-amylase model	- -	↓α-glucosidase activity ↓α-amylase acivity
	Green tea polyphenols green, black, oolong tea extracts	α-glucosidase model	-	↓α-glucosidase activity (green tea polyphenols IC_{50}= 2.33UG/ML
HYPERTENSION	Black tea Taqueous extracts Thearubigin, theaflavin, catechin, epicatechin, epigallocatechin gallate, gallic acid, caffeine	Angiotensin converting enzyme model	Aqueous tea extract (15 µg/mL) Isolated compounds (37 µM)	↑ ACE inhibitory activity (Thearubigin, theaflavin, catechin)
METABOLIC SYNDROME	Green tea extracts	Mouse 3T3-L1 preadipocytes	Green tea extract (0.2%–0.5%, w/v),2 days	↓ Adipogenesis induced lipid accumulation ↓ C/EBPα and PPARγ expression

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APPENDIXB

TABLE: In vivo pharmacological studies for Camellia sinensis. [1]

DISEASE	Extract /isolated compound	Experimental model	Treatments	Major finding
	Black tea aqueous extract	GK rats	Group 1: black tea31.3,62.5, and 250mg/kg Group 2: acarbase 0.1,0.3, and 3.0mg/kg Group 3: acarbose 0.3mg/kg+ black tea 31.3mg/kg	↓Plasma glucose levels
	Black tea aqueous extract	Alloxan-induced diabetic rats	Group1: control Group2: alloxan Group3: black tea extract (1ml/100g bodyw/d for 10 days before alloxan injection and 35 days after alloxan injection) Group4: black tea extract (35 days) Group5: diabetic insulin group	↑plasma antioxidant potential ↓lipid peroxidantion level ↑GSH levels
Diabetes	Green tea extract	Nematode Caenorhabditis elegans	0.1 percent,48 h	↓glucose induced damage
	Epigallocatechin-3-gallate	Wistar rats Streptozotocin -nicotinamide-induced diabetic rats	Group 1: control Group 2: EGCG (2MG/KG BODY WT) Group3: diabetic control group Group4: diabetic control group+EGCG 1 month	↓ glucose, glycosylated hemoglobin,HOMA-IR and lipid profile level
Hypercholesterolemia	Green tea ethanol extracts	Sprague-Dawley rats	Group 1: hypercholesterolemic rats Group 2: hypercholesterolemic rats + diet containing green tea extracts 5% Group 3: hypercholesterolemic rats + diet containing tea powder 10% 8 weeks	↓ LDL ↓ Triglycerides ↓ Cholesterol
	Green tea extracts	Rat model High sodium diet	Group 1: high sodium diet Group 2: high sodium diet + 2 g green tea extract in kg diet Group 3: high sodium diet + 4 g green tea extract in kg	↓ Total cholesterol, LDL, cholesterol serum concentrations

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			diet 6 weeks	
Hypertension	Black tea extract	Sprague-Dawley rats Angiotensin II induced	Group 1: control Group 2: angiotensin II (50 ng/kg/min) Group 3: angiotensin II + black tea extract (15 mg/kg/day, 14 days)	↑ Endothelium-dependent relaxations ↓ Endoplasmic reticulum stress markers levels ↓ ROS production
	Green tea from three cultivars "Yabukita", "Sofu" and "Sunrouge"	Hypertensive rats High salt diet	Group 1: high salt water Group 2: high salt water + Yabukita Group 3: high salt water + Sofu Group 4: high salt water + Sunrouge	↓ Urinary NO metabolite ↑ Soluble guanyilatecyclase expression (Yabukita and Sofu)
Metabolic Syndrome	Green tea aqueous extract	Olanzapine induced Wistar rats	Group 1: control Group 2: olanzapine (5 mg/kg/day) Groups 3, 4, and 5: green tea aqueous extract (25, 50, and 100 mg/kg/day) + olanzapine Groups 6, 7, and 8: green tea aqueous extract (25, 50, and 100 mg/kg/day)	↓ Body weight gain ↓ Average food and water intake Improved changes in lipid profile ↓ Hyperleptinemia and hypertension
	Yellow tea	C57BL/6 male mice High fat diet	Group 1: low fat diet Group 2: high fat diet Group 3: high fat diet + 2.5% yellow tea Group 4: high fat diet + 0.5% yellow tea 12 weeks	↓ Body weight, liver weight, and adipose tissue weight ↓ Serum glucose, TC, TG, LDL-C, and HDL-C ↓ Glucose intolerance and insulin resistance

Appendix C

Table A3. Clinical trials for Camellia sinensis. [1]

STUDY (AUTHOR, YEAR, COUNTRY)	STUDY DESIGN	SAMPLE SIZE	POPULATION	TYPE OF PLANTS	INTERVETION	DURATION OF TREATMENT	RESULTS
			DIABETES				
Alves Ferreira et al., 2017 Brazil	Randomized, double-blind, placebo-controlled study	120	Women (20–45 years) abnormal glucose values	Green tea capsules	Group 1: control (cellulose) Group 2: green tea (1 g) Group 3: metformin (1 g) Group 4:	12 Weeks	Improving glycemic and lipid profile ↓ Fasting glucose ↓ Total cholesterol

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					green tea (1 g) + metformin (1 g)		and LDL
Vaz et al., 2018 Brazil	Randomized, double-blind, placebo-controlled study	60	Patients with diabetes	Green tea extract	Group 1: green tea extract (two capsules/day, containing 560 mg of polyphenols/each) Group 2: cellulose (two capsules/day)	20 Weeks	No effect on total antioxidant capacity, glycemic control markers, and renal function ↑ SOD activity
			HYPERCHOLESTEROLEMIA				
Imbe et al., 2016 Japan	Randomized, double-blind, placebo-contro	155	Healthy volunteers High LDL cholesterol levels Aged 20–80 years	"Benifuuki" green tea	Group 1: "Benifuuki" Group 2: "Yabukita" Group 3: barley infusion drinker	12 weeks	↓ LDL cholesterol levels ↓ Lectin-like oxidized LDL receptor-1 containing LAB level
Orem et al., 2017 Canada	Randomized, double-blind, placebo-controlled study	125	Subjects 25–60 years hypercholesterolemia	Black tea	Group 1: placebo Group 2: instant black tea Group 3: functional black tea	4 weeks	Functional black tea: ↓ Total cholesterol ↓ LDL ↓ Oxidative stress index ↑ Total antioxidant status
			HYPERTENSION				
Alkerwi et al., 2015 Luxembourg	National cross-sectional stratified sample	1352	18–69 years	Tea	Group 1: nonconsumers Group 2: ≤ 3-dL/d consumers (tea/coffee) Group 3: > 3-dL/d consumers (tea/coffee)	-	↓ Systolic BP and pulse pressure
			METABOLIC SYNDROME				

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Yang et al., 2014 China	-	134	Metabolic syndrome	Green tea	Group 1: green tea extract (500 mg). Two capsules/time/ day Group 2: control (water)	45 days	↑ Adiponectin serum concentrations ↓ Visfatin levels

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