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REVIEW ARTICLE

Diospyros kaki: A Review of its Pharmacological and Anticancer Properties

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Abstract

Background: Traditional Chinese Medicine (TCM) offers a comprehensive approach to cancer treatment, often complementing conventional therapies. Persimmon or *Diospyros kaki* has long been used in Traditional Chinese Medicine for its potential antioxidant and anti-inflammatory effects. Bioactive compounds found in this plant can be used for cancer treatment and therapy. **Aim:** The study aims to comprehensively review the pharmacological and anti-cancer properties of *Diospyros kaki*, emphasising its phytochemical composition, mechanism of action and its potential application in traditional medicine and modern oncology. **Methods:** Relevant literature published till 2024 was retrieved from various databases including Google Scholar, PubMed, SciSpace, ScienceDirect, IMMPAT 2.0 and PubChem. Keywords such as *Diospyros kaki*, anti-cancer, pharmacological activity, and phytochemicals were chosen for screening. Studies reporting pharmacological properties, particularly those exhibiting anti-cancer activity, were selected. **Result:** *Diospyros kaki* demonstrates significant pharmacological activity across multiple systems. Its fruit, leaves, roots, and calyx contain polyphenols, flavonoids, and triterpenes that exhibit antidiabetic, cardioprotective, neuroprotective, antimicrobial, and anti-inflammatory effects. From an anticancer perspective, compounds such as quercetin, kaempferol, diospyrin, and plumbagin contribute to apoptosis, oxidative stress modulation, and inhibition of tumour proliferation and angiogenesis. Therapeutically, its phytoconstituents support immune modulation, cellular redox balance, and enzyme inhibition, enhancing its potential as a supportive agent in chemotherapy and radiotherapy. **Conclusion:** The broad therapeutic profile of *Diospyros kaki* underlines its role in managing chronic diseases and cancer. Further research should focus on standardising extraction, improving bioavailability, and conducting clinical trials to translate these benefits into clinical use.

Major Findings: *Diospyros kaki* exhibits potent anticancer and pharmacological activities, primarily through apoptosis induction, ROS modulation, and inflammation suppression, validating its traditional medicinal use and modern therapeutic relevance.

Keywords: Anti-cancer Activity, *Diospyros kaki*, Pharmacological Activity, Phytochemicals, Traditional Chinese Medicine

1. Introduction

For thousands of years, Traditional Chinese Medicine (TCM) has been extensively applied to treat a wide range of diseases, including cancer, either alone or in conjunction with alternative approaches. Growing evidence has emphasised the obvious advantages of TCM compared to traditional therapies, including

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lower drug toxicity, fewer side effects and lower economic expenses[1]. Environmental circumstances, farming practices, geographical origin, harvesting methods, initial raw material processing and specialised techniques used for clinical preparation are some of the aspects that affect the medicine quality, distinguished by its multi-constituent nature[2]. Traditional Chinese Medicine offers an extensive repository of documented therapeutic knowledge, comprising two essential components: the TCM theoretical framework and Chinese Herbal Medicine (CHM)[3]. Chinese herbal medicine, which includes both Chinese-patented medicines and sliced herbs, stands out as the extensive application category among traditional Chinese medicine's various branches[4]. The urgent need for discovering novel and potent medicinal drugs persists. Traditional Chinese Medicine has been practised in China, providing valuable insights. Cannabinoids, curcumin, quercetin, resveratrol, and triptolide are examples of some phytochemicals having anticancer properties. Through various novel and distinctive mechanisms, these naturally occurring compounds exert their therapeutic benefits on the human body[5]. Rather than being redistricted to use in the terminal stages of cancer, recent studies suggest that Traditional Chinese Medicine can contribute substantially throughout cancer treatment, including post-operative recuperation and during chemotherapy or radiotherapy[6]. Pattern identification in Traditional Chinese Medicine has proven to be very beneficial in managing cancer symptoms. During symptomatic treatment, this method addresses both localised and systemic issues. Research shows that approximately 70% of patients with advanced cancer report symptom relief and improved quality of life following treatment guided by TCM pattern identification[7].

Persimmon, scientifically known as *Diospyros kaki*, belongs to the plant family Ebenaceae. It is extensively found throughout East Asia, especially in China, Japan, Korea and in parts of South Europe, the United States, Africa and Brazil[8]. The Ebenaceae family has only three genera, with *Diospyros* being the largest, encompassing around 500 species. This species is extensively dispersed over tropical and warm temperate regions globally, with 24 species native to India[9]. In China, the plant is cultivated for regional development in the specialised fruit tree industry because of its edible fruit and potential use in Chinese medicine[10]. While the fruit is frequently consumed for its beneficial properties, the plant's leaves are also commonly used in traditional medicine[11]. *D. kaki* leaves are rich in bioactive compounds such as polyphenols, terpenoids and flavonoids. Ethanol extracts of the leaves contain kaempferol, glycoside, galactoside, galloylated, and quercetin[12]. Anti-tobacco toffees have been made using a combination of jasmine and Japanese persimmon leaf extracts. Ursane, lupine and oleanane are among various triterpenes extracted from plant cells and have strong anti-inflammatory properties.

Traditionally, the genus has been medically used for curing fever, intestinal worms, sleeplessness, hypertension and joint discomfort[13]. Certain traditional applications have confirmed that extracts from *Diospyros* species have strong anti-cancer and antioxidant properties, contributing to their therapeutic effectiveness[14]. For instance, according to a study, certain chemical constituents of *D. lycioides* showed antimetastatic effects by suppressing cell migration and invasion[15]. Moreover, compounds such as betulinic acid produced by *D. lotus* have shown anticancer activity. A main component, myricitrin, serves as a promising oral therapeutic agent for the treatment and management of pruritus, and its wood extract has anticancer potential, alongside antibacterial, anti-inflammatory, antioxidant, and antitumor activities[16-18]. *D. blancoi* stem bark contains high amounts of antioxidants, significant free radical scavenging properties and has moderate anticancer activity[19]. *D. winitii* has shown anti-cancer property against hepatoma cell line, and *D. rhodocalyx* extract exhibits selective cytotoxicity against prostate cancer cells by inducing apoptosis via BAX/Bcl-2 regulation, MMP reduction, and caspase-3 activation[20,21]. Potent naphthoquinone derivatives found in *D. quercina*, show promising cytotoxic activities, suggesting their potential as anticancer lead molecules[22].

2. Methodology

The methodology for this review involved a systematic search and analysis of the literature published till 2024, focusing on the pharmacological properties of *Diospyros kaki,* particularly its anti-cancer activities. A wide and comprehensive coverage of the available

studies was ensured by the retrieval from several reputable databases, including Google Scholar, PubMed, SciSpace, ScienceDirect, IMMAPT 2.0, PubChem and Web of Science. The search strategy utilised targeted keywords such as *D. kaki,* anti-cancer, pharmacological activity, phytochemicals and TCM. To ensure relevance and quality, articles were screened in two steps: beginning with reviewing titles and abstracts, followed by an in-depth examination of full texts. Studies describing the pharmacological characteristics of *D. kaki* with emphasis on those investigating its anti-cancer effects through *in vitro*, *in vivo* or clinical models. Unrelated topics and unavailable full papers were excluded. The extracted data included identified phytochemicals, mechanisms of action, experimental models, and therapeutic insights, which were subsequently analysed to highlight significant findings (Figure 1).

3. Botany

Diospyros kaki is a deciduous tree with a round and open canopy that can grow up to 6 meters tall. It may have several stems or just one spreading wider than 4.5 to 6 meters that can be erect, semi-erect, willowy or crooked[23]. The leaves are simple, alternate and can be elliptic, oblong or ovate. They usually measure 2.8-9 cm in width and 5-18 cm in length with a cuneate base and complete margins. The leaf apex is either acuminate or obtuse. Lighter green leaves

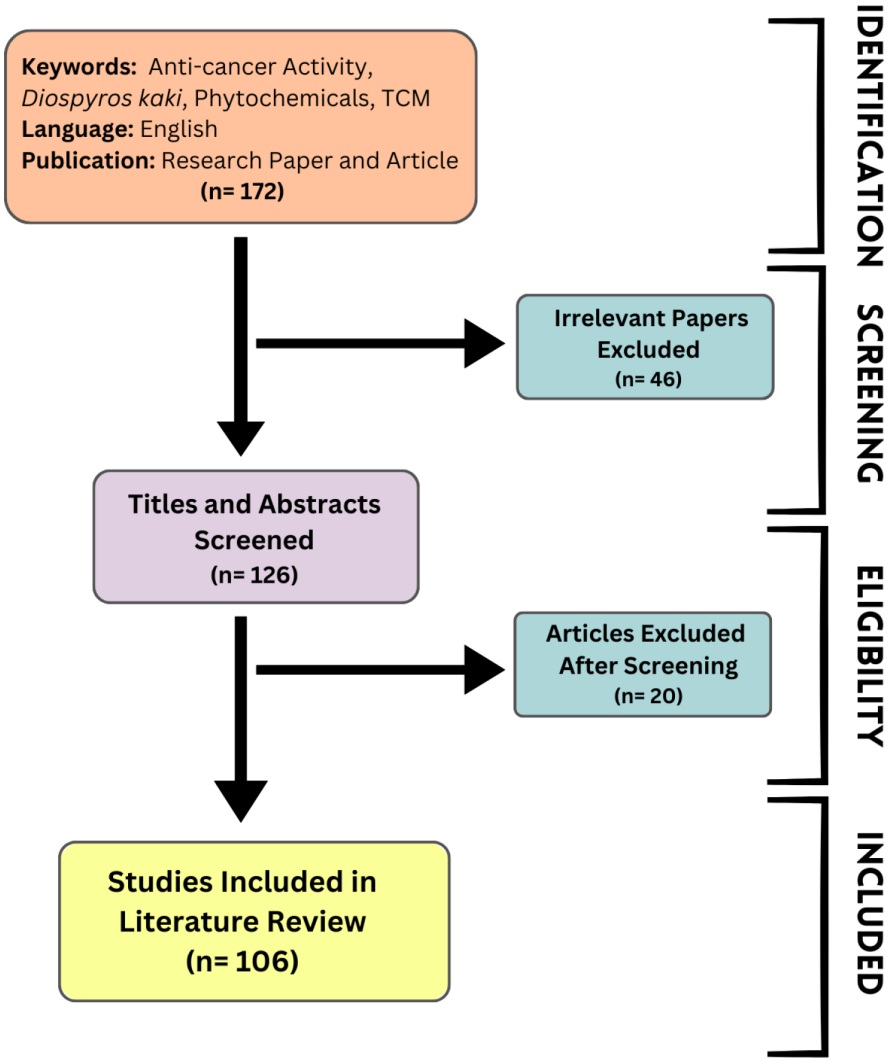


Figure 1. PRISMA flow chart displaying the results of the screening and identification process for exclusion and inclusion studies.

have a velvety touch due to little pubescence and dark green primary veins with pubescence along them[24]. Usually, *D. kaki* produces cymose inflorescences with hermaphrodite male and female flowers. Male cymes generally bear three to five flowers, including a central flower and 2-4 lateral flowers, whereas female cymes often have a central flower with undeveloped lateral flowers. Hermaphrodite flowers derived from female flowers usually produce smaller fruits compared to those formed from female flowers[25]. Persimmon fruit can be spherical or slightly flattened in shape. The flesh of young fruits exhibits a yellowish-orange hue, mature fruits are orange, and unripe fruits are green (Figure 2). The pulp has a smooth and fibrous texture without any grittiness. Tannin content makes the flesh sweet and a bit spicy, which can be diminished by soaking the fruit in lime water[26].

4. Pharmacological Activity

Diospyros kaki, a traditional Chinese medicine used for over 600 years, is known for its cold, slightly bitter, and astringent nature. It is traditionally used to improve blood circulation, regulate Qi, prevent bleeding, and alleviate asthma. Its primary active ingredient, flavonoids, exhibits various biological activities, including improving endothelial function, dilating cerebral arteries, relieving vasospasm, and enhancing cerebral blood flow and oxygen supply[29].

It is a seasonal fruit available only during a short period of time each year, usually from October to December. The high nutrient content and natural antioxidants make it extremely popular for preparing fruit-based beverages. Vitamins, fibres, carbohydrates, minerals and phenolics, proteins and carotenoids are abundantly present in persimmons. The fruit peel has higher levels of copper, calcium, iron, manganese, magnesium, potassium and zinc except sodium. Polyphenols, ascorbic acid and tannins are also present in the fruit, which contribute to the management of cholesterol, cardiovascular diseases, diabetes and other health issues[30]. Its leaves and fruits have historically been utilised to manage high blood pressure and atherosclerosis due to their antiproliferative and anti-inflammatory properties[31].

Amino acids, choline, carotenoids, Vitamin C and essential minerals like calcium, iron, and zinc are present in persimmon leaves in large amounts, due to which they have long been used in Chinese medicine. Extracts including flavonoids, polyterpenoids and terpenoids have antibacterial, antioxidative, antidiabetic, haemostatic and hypolipidemic properties[32]. Studies conclude that the severity of radiation-induced liver damage, hyperglycemia, hypoinsulinemia and dyslipidemia can be alleviated by the therapeutic application of these leaves[33]. Its leaves are commonly used in Asia as a tea infusion and traditional medicine, and also recognised as a safe and effective immunomodulatory agent with potential to reverse immune suppression in cancer[34]. Its alcoholic extract demonstrates anticancer activity against E705 and SW480 colorectal cancer cell lines by



(a) (b)

Figure 2. **(a).** Picture of plant form of *Diospyros kaki*[27] and **(b).** Fruiting branch[28].

inducing oxidative stress, mitochondrial dysfunction, and apoptosis. The extract also inhibits the Warburg effect, offering potential for colorectal cancer (CRC) therapy[35]. In HCT116 colon cancer cells, PLF induced apoptosis, potentially by modulating the redox balance and increasing intracellular ROS levels, whereas a study shows that 24-HUA significantly reduces the tumorigenic potential of HT-29 colon cancer cells by activating AMPK, leading to the suppression of COX-2 production. By cleaving caspase-3 and PARP and phosphorylating p53 at Ser15 in HT-29 cells, this activation promotes apoptosis[36,37]. Pectic polysaccharide DL-3B_2 extracts can help in stimulating LPS-induced B lymphocyte proliferation[38]. The leaves extract of persimmon indicates potent antioxidant activity by showing a reduction in ROS and MDA production with a rise in GSH levels, SOD and CAT activities[39]. Phospholipid complex of flavonoids from persimmon leaves enhances the therapeutic efficacy of PLF against atherosclerosis by offering greater protection against oxidative stress-induced endothelial dysfunction, making it a promising candidate for the treatment and management of atherosclerosis and related cardiovascular conditions[40].

Flavonoids extracted from *D. kaki* leaves are major components of a patented and authorised Chinese medicine, NaoXingQing (NXQ), which is used for treating stroke and apoplexy syndrome. It improves the outcomes for ischemic stroke patients with minimal side effects[41]. NQX protects nerve cells from oxidative stress injury by upregulating Bcl-2 and improving the cellular redox state and shows potential for preventing and treating ischemia/reperfusion injuries, excitotoxic glutamate-induced injury, hypoxia-induced damage and neurodegenerative diseases[42,43]. NXQ significantly mitigated oxidative stress and protected the cells from H_2O_2-induced damage, suggesting its potential for preventing and treating stroke or apoplexy[44].

Phytochemicals present in the roots of *D. kaki* show excellent anti-inflammatory, analgesic and sedative effects[45]. 5-Hydroxy-2-methyl-1,4-naphthoquinone, 2-Hydroxy-1,4 naphthoquinone, 2-Methyl-1,4-naphthoquinone2-Bromo-1,4-naphthoquinone, and 5-Hydroxy-1,4-naphthoquinone are some compounds found in root extracts. 5-Hydroxy-2-methyl-1,4-naphthoquinone and some derivatives can be used as an alternative to insecticides for controlling some rice insect pests[46]. Catechol is present in the roots and shows antimicrobial activity against harmful intestinal bacteria with negligible effects on essential bacteria, indicating its therapeutic potential[47].

The extract from the stem is used for medically treating nocturnal enuresis, vomiting and hiccups due to the presence of tannins contributing to its anti-inflammatory properties[48].

The peels, seeds, and calyx of *D. kaki* are reported to be rich in polyphenols and effective in treating intractable hiccups. In particular, 70% ethanol extracts from *D. kaki*'s calyx lower cyclin D1 levels via suppressing Wnt signalling, which inhibits its transcription, and encouraging its breakdown through phosphorylation that is dependent on ERK1/2, p38, and GSK3β[49]. Fisetin, found in persimmon, plays a role in reducing ischemia-induced brain damage and exhibits potential as a neuroprotective agent and cancer preventive compound[50]. These pharmacological effects are consolidated in Table 1.

4.1 Quercetin

It is an important flavonoid with health advantages such as anti-inflammatory, antioxidative, and anti-apoptotic properties. It is found in various plants, including *D.kaki* and protects cells from oxidative stress produced by various xenobiotics[71]. Extensive research has demonstrated that quercetin can inhibit cell cycle and cell growth in both androgen-independent and androgen-dependent prostate cancer cells through various signalling pathways, including the stimulation of the P38-MAPK signalling pathway and inhibition of PI3K/AKT, ERK1/2, and IGF pathways. Furthermore, quercetin has been observed to suppress proliferation and trigger apoptosis in PC-3 cells by promoting oxidative stress and initiating mitochondrial apoptotic pathways (Figure 3)[72]. Quercetin and kaempferol are closely related phytochemicals that are partially responsible for NaoXingQing's effects associated with the free radical scavenging and inhibition of intracellular ROS generation[73]. It is a well-known vasodilator and exhibits various vascular effects, including antiplatelet activity, inhibition of smooth muscle proliferation and pro-apoptotic effects within both systemic and coronary circulation. It does not circulate in the blood in its form but conjugates with glucuronide and is released into tissues following deconjugation. It functions as a classic

pan-inhibitor of the TGF-β pathway and MAPKs. It also downregulates the survivin expression in several cancer cells by decreasing the survivin promoter activity quercetin[74]. The pharmacological activities of quercetin have been shown to inhibit various human tumours, including oral and breast cancer, while also reducing angiogenesis[75]. It can regulate fasting blood glucose/lipid levels, reduce fat accumulation in the liver, alleviate renal fibrosis, and contribute to the AMPK-dependent autophagy process[76].

4.2 Kaempferol

Kaempferol is abundantly found in numerous fruits, vegetables and Chinese herbal remedies. It lowers the

Table 1. Therapeutic role of various Phytochemicals of *Diospyros kaki* (IMPPAT | IMPPAT: Indian Medicinal Plants, Phytochemistry and Therapeutics)

Super Class	Plant Part	Phytochemical Name	Activity	References
Benzenoids	Root	Plumbagin	Acaricidal, Immunologic, Antinematodal, Antineoplastic, Anticoagulant, Contraceptive, Cardiotonic	51, 52
		Diospyrin	Antimycobacterial, Anticancer	53, 54
		Neodiospyrin	Antimycobacterial	55
		8-Hydroxy-2-(8-Hydroxy-6-Methyl-1,4-Dioxonaphthalen-2-Yl)-6-Methylnaphthalene-1,4-Dione	Unknown	
		5-Hydroxy-8-(4-Hydroxy-7-Methyl-5,8-Dioxonaphthalen-1-Yl)-2-Methylnaphthalene-1,4-Dione	Unknown	
	Leaf	Eugenol	Toothache, Anti-Infective	56
Organic Acids and Derivatives	Fruit	Citric Acid	Anticoagulants	57
Organic Oxygen Compounds	Fruit	Chlorogenic Acid	Antidiabetics, Anti-obesity	58, 59
Organoheterocyclic Compounds	Fruit	Ascorbic Acid	Antioxidant	60
Phenylpropanoids And Polyketides	Fruit	Delphinidin	Anticancer	61
		Epigallocatechin Gallate	Anti-Oxidative, Anti-Inflammatory, Anti-Tumour	62
	Leaf	Kaempferol	Antitumor, Antioxidant, Anti-Inflammatory	63
		Quercetin	Antitumor, Antioxidant, Antimicrobial	64
		5,7-Dihydroxy-2-(4-Hydroxyphenyl)-3-((2R,3S,4S,5S,6R)-3,4,5-Trihydroxy-6-Methyltetrahydro-2H-Pyran-2-Yloxy)-4H-Chromen-4-One	Unknown	
		Isoquercitrin	Anticancer, Antidiabetic, Antiviral, Anti-osteoporotic	65, 66
		Astragalin	Anti-Inflammatory, Antioxidant, Antidiabetic, Anticancer, Antimicrobial	67, 68
		Trifolin	Anticancer	69
	Root	11-Methylgerberinol	Unknown	
	Wood	Gerberinol	Anticancer, Antimicrobial, Anti-Inflammatory, Antitumor	70

risk of atherosclerosis (AS) by influencing a variety of physiological processes such as lipid droplet deposition, oxidative damage, and vascular inflammation. By blocking the Piezo1 channels and Ca^{2+} influx, it controls CD36-mediated mitochondrial ROS production. Subsequently, modulating downstream MAPK/NF-κB and Nrf2/HO-1 pathways helps in the prevention of foam cell formation (Figure 3)[77]. It is a naturally occurring flavonoid which has many pharmacological activities, including anticancer, anti-apoptotic, anti-inflammatory, antioxidant and cardioprotective properties. In human umbilical vein endothelial cells, it has been reported to mitigate oxidised Low-density lipoprotein-induced apoptosis by promoting autophagy through PI3K/Akt/mTOR pathway inhibition. Additionally, it has been found to decrease ox-LDL-induced apoptosis in Human Aortic Endothelial Cells (HAECs) by upregulating miR-26a-5p through the suppression of the TLR4/NF-κB signalling pathway[78]. It also inhibits the expression of angiogenesis-related signals, thereby protecting the gut vascular barrier[79]. It has shown significant health benefits such as cervical, ovarian, oesophageal, liver cancer and leukaemia mainly due to its antioxidant properties. Preclinical research has demonstrated that, in combination with other polyphenols, kaempferol can show better anticancer activity, especially in breast cancer cell lines. However, its low bioavailability is a major problem which can be addressed through various approaches, such as the formation of kaempferol-based nanoparticles or metallodrugs like copper-kaempferol complexes. Additionally, under Cu- Fenton conditions, it exhibits antioxidant properties, indicating that it can be used for preventing and treating oxidative stress-related conditions, including neurological conditions like Alzheimer's and Menkes diseases that are associated with disrupted redox metal metabolism[80]. By activating the mitochondrial pathway and cell surface death receptors, it can cause the death of colon cancer cells. It promotes the expression of miR-326 in colon cancer cells, which suppresses the glycolysis process by directly targeting the 3'UTR of PKM2 to suppress its expression or blocking the selective splicing factor of PKM mRNA indirectly, thus suppressing glycolysis and potentially reversing colorectal cancer cell resistance to 5-FU (Figure 3). Therefore, kaempferol may play a crucial role in overcoming 5-FU treatment resistance by modulating the miR-326-hnRNPA1/A2/

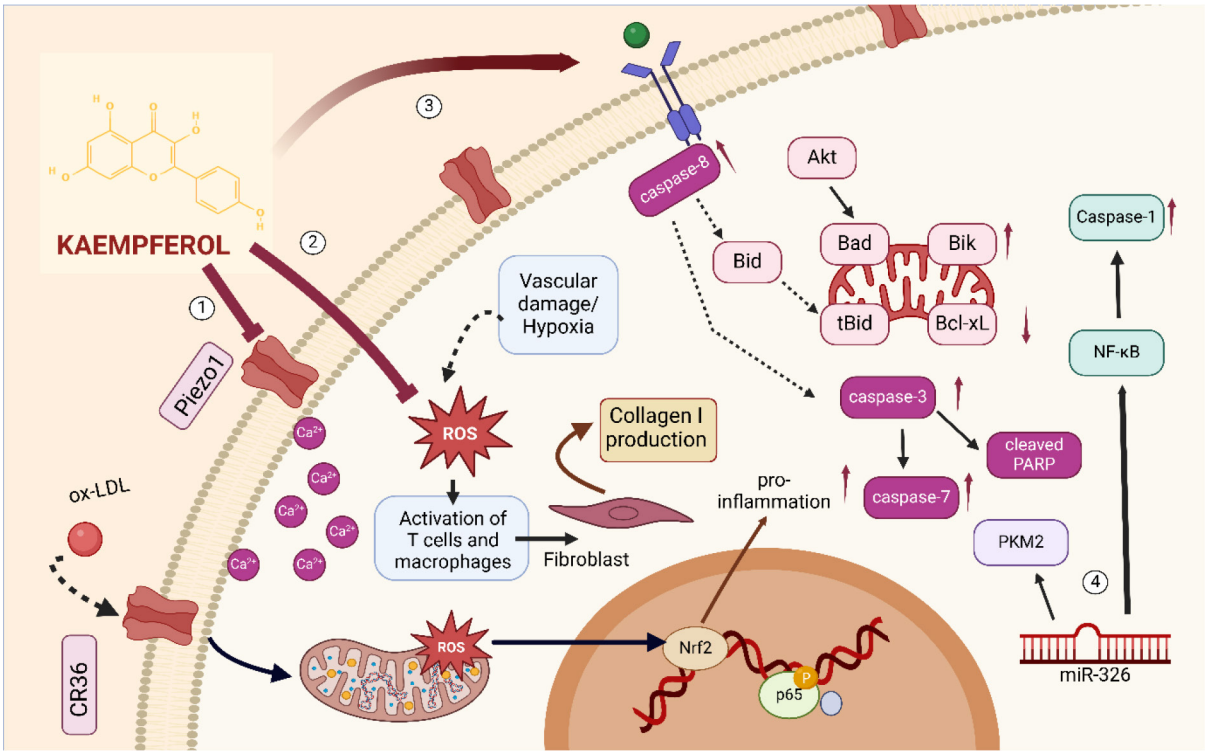


Figure 3. Role of Kaempferol[1].

PTBP1-PKM2 axis. It downregulates the anti-cancer apoptotic protein Bcl-xL, and upregulates the pro-apoptotic protein Bik and other apoptotic proteins, including caspase-9, caspase-7, PARP and caspase-3. It influences the Akt signalling by reducing its activity and enhancing mitochondrial Bad levels (Figure 3). In pancreatic cancer cells, it effectively targets the SNU-213, Pac-1 and MIA PaCa-2 cells, causing apoptosis in a concentration-dependent manner[81]. It has been seen that kaempferol inhibits collagen production by reducing oxidative stress, inflammation and cellular oxidative damage. Studies suggest that it can serve as a potential alternative for skin sclerosis in patients with systemic skin sclerosis (SSc) and may also be effective in managing vasculopathy due to its association with oxidative stress (Figure 3)[82]. By inhibiting the iNOS and ICAM-1 signalling pathways, kaempferol mitigates CLP-induced acute lung injury. The impact is likely achieved through the inhibition of tissue oxidative damage, the reduction of neutrophilic inflammation, and the enhancement of antioxidant defences[83].

It inhibits macrophage foam cell formation induced by oxidised Low-Density Lipoprotein (ox-LDL), protecting against atherosclerosis by regulating the formation of LDL-induced foam cells via the Piezo1/MAPK/NF-κB signalling pathways and the HO-1/Nrf2 axis[2]. Vascular injury-induced hypoxia may elevate the production of ROS, which can activate T cells, fibroblasts, and macrophages, enhancing collagen production by fibroblasts. Kaempferol injection significantly reduces the ROS levels in lesional skin, the presence of myofibroblasts, T cells, and pro-inflammatory and pro-fibrotic cytokines such as IL-6, TGF-β, and TNF-α[3]. Kaempferol induces apoptosis by modulating key regulators, including caspases, Bik, PARP, and Bcl-xL[4]. It upregulates miR-326 by targeting PKM2, thereby inhibiting glycolysis and overcoming drug resistance. It further lowers oxidative stress indicators and affects genes linked to apoptosis through multiple pathways, NF-κB signalling mediated inflammasome activation and ROS-dependent apoptosis via the Akt/mTOR pathway.

4.3 Diospyrin

Diospyrin is an active bisnaphthoquinonoid product found in the *Diospyros* genus that has been used in Chinese Medicine, ancient Ayurveda, and numerous African and Latin American folklore systems. The plant has been widely used in the treatment of skin rashes, fever, parasitic infestations, renal diseases, dental problems, diarrhoea, pneumonia, and syphilis and has anti-tubercular, anti-cancer and anti-leishmanial activity[84,85]. It has been shown to regulate the extensive production of RANTES, MCP-1, IL-10, LIF, IL-6, MIP-1β and VEGF in LPS-induced RAW 264.7 cells. Thus, it can be used for treating bacterial infectious diseases such as bacterial pneumonia and meningitis. Studies suggest that diospyrin can reduce the calcium release and production of inflammatory cytokines and downregulate the mRNA expression of C/EBP homologous protein and macrophage in cells. It inhibits the phosphorylation of p38 MAPK, a crucial signalling molecule involved in inflammatory responses (Figure 4)[85]. It inhibits the catalytic activity of DNA topoisomerase I of Leishmania donovani proastigotes and the topoisomerase reaction of gyrase[86,87]. A study found that diospyrin derivative- Diospyrin diethyl ether treatment in MCF7 cells caused oxidative stress, leading to calcium release from the ER and activating pathways for apoptosis. This included the calpain-caspase12 pathway for ER-related cell death and the mitochondrial apoptosis pathway, suggesting that D7 has strong potential as an agent to induce cancer cell death and could be a promising candidate for preclinical cancer therapy research (Figure 4)[88].

4.4 Plumbagin

Plumbagin is a secondary metabolite exhibiting anti-atherosclerotic, anticancer, anti-inflammatory, antimicrobial, contraceptive, cardiotonic, immunosuppressive, and neuroprotective activities. According to a study, plumbagin induces intracellular ROS inside cells through multiple mechanisms and inhibits Glutathione Reductase (GR) activity necessary for maintaining intracellular redox balance. GR facilitates the NADPH-dependent reduction of oxidised glutathione (GSSG) to reduced glutathione (GSH). Inhibition of this enzyme leads to GSSG accumulation, GSH depletion and ROS production[89]. It suppresses Epithelial-Mesenchymal Transition (EMT) in human Tongue Squamous Cell Carcinoma (TSCC) cells through a ROS/p38 MAPK-mediated pathway[90]. Its treatment results in the downregulation of multiple differentially expressed (DEGs) genes related to

humoral immune responses[91]. Plumbagin induces apoptosis in colonic cancer cells by upregulating TNF-α expression and activating the TNF-α mediated pathway, which involves Caspase-3 activation and Cytochrome C release[92]. It has been seen that plumbagin inhibits the development of prostate cancer associated with the loss of phosphatase and tensin homolog (PTEN). It decreases the cell viability and proliferation of the Oesophageal Squamous Cell Carcinoma (ESCC) cells through the inhibition of STAT3 activation. It was also observed that plumbagin suppresses the growth of A549 lung cancer cells by inactivating the c-Jun N-terminal kinase signalling pathway[93]. It reduces the level of PI5K-1B, resulting in increased ROS generation, which contributes to its cytotoxic effects in human breast cancer cells (Figure 4)[94]. A study revealed that plumbagin interacts with TrxR1 by targeting its Sec residue, increasing the production of superoxide and NADPH oxidation and generating SecTRAPs that lead to cell death (Figure 4)[95]. It exhibits anti-tumour activity against hepatocellular carcinoma (HCC) by suppressing the mTOR signalling pathway and downregulating SIVA by promoting apoptosis, causing cell arrest and inhibiting proliferation, independent of p53[96]. It acts through the VEGF/VEGFR2-mediated Ras/MEK/ERK signalling pathways for inhibiting tumour angiogenesis. It disrupts endothelial cell migration and cytoskeletal remodelling by inhibiting Rac1 activity and its downstream targets, such as PAK1, LIMK1, and cofilin. It inhibits VEGFR2 phosphorylation, hindering VEGF-induced proliferation and survival (Figure 4)[97].

It has anti-inflammatory properties which inhibit the LPS-stimulated macrophage's production of MCP-1, MIP-1β, IL-6, VEGF, and RANTES. The ER-stress-induced Calcium-p38, MAPK/CHOP/Fas signalling pathway mediates these effects[3]. Plumbagin targets the Sec residue of TrxR1 and inhibits cell growth[4]. It targets Ras signalling pathways in endothelial cells to prevent tumour angiogenesis. It may prevent endothelial cell migration through the Ras-dependent Ra-Rac-cofilin pathway by blocking VEGFR2 activation. Furthermore, it disrupts the Ras-mediated cascades of the Ras/MEK/JNK and Ras/MEK/ERK pathways for inhibition of endothelial cell development[5]. It also contributes to the cytotoxicity of human breast cancer by reducing PI5K-1B levels, resulting in increased production of ROS[6]. Quercetin inhibits the inflammation and proliferation of tumour cells.

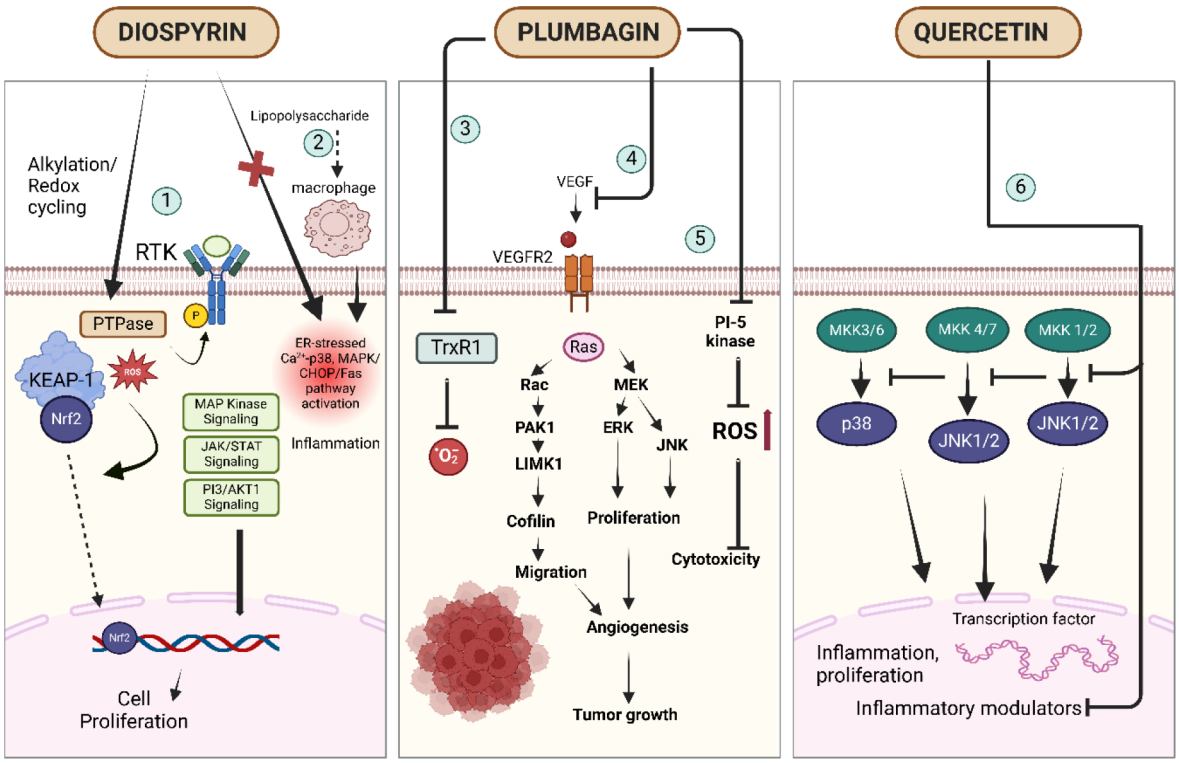


Figure 4. Anticancer properties of Diospyrin[2].

5. Traditional Chinese Medicine Formulations Using *D. kaki*

Unripe *D. kaki* fruits are used for TCM formulations due to their anti-obesity effects and capacity to inhibit pancreatic lipase. It was found that *D. kaki,* in combination with *Citrus unshiu* peel, significantly lowers serum lipid levels and visceral fat, indicating that it can be used for treating obesity and related conditions. Further, it has been seen that high molecular weight tannins enhance lipid metabolism, prevent hepatic steatosis, oxidative stress, and have anti-diarrheal and hemostatic properties, and antioxidant-rich peel is used for skin care products[98]. It has been observed that dried pulp of *D. kaki* reduces triglycerides and plasma glucose levels while inhibiting digestive enzymes. Its leaves can block pancreatic alpha-amylase activity. Triterpenoids extracted from leaves demonstrated inhibitory effects on PTP1B, and proanthocyanidins from the peel were found to influence α-glucosidase and α-amylase enzymes[99]. By increasing the excretion of faecal lipids, persimmon leaf powder improves plasma and hepatic lipid levels. Persimmon vinegar is a traditional fermented product used both in traditional medicine and culinary applications. Its leaves are commonly included in tea formulations for hypertension management. Further, dietary persimmon showed effectiveness in reducing the risk of stroke attributed to its strong radical scavenging capabilities and ability to inhibit lipid peroxidation[100].

The active compounds and crude extract derived from the fruit and leaves of the persimmon make it a valuable ingredient for various dermatological and cosmetic applications. Tannins have been used in medicine for centuries and have gained significant attention for their role in dermatology due to their astringent properties. These compounds are effective in managing superficial skin conditions, such as weeping, inflammation, and itching. The cosmetic cleanser formulation that contains DPC extract includes a notable decrease in oil content, pore size, and pore count. Additionally, it removes solidified sebum and may help eliminate Demodex mites, which are linked to skin disorders like rosacea and seborrheic dermatitis[101].

Traditional extraction techniques and modern scientific adaptations are as follows.

5.1 Supercritical CO_2 Extraction

For extracting lipophilic compounds with greater purity and preserving thermolabile components, a modern technique uses supercritical CO_2[102].

5.2 Water and Alcohol Extraction

Making herbal teas and infusions by decoction or water extraction is a popular method. This technique captures water-soluble substances like flavonoids and tannins. Alcohol extraction is often used for triterpenoids and flavonoids, which are less soluble in water. In order to accomplish a wide range of chemical extraction for antioxidants and anticancer characteristics, ethanol-water mixtures are frequently employed[102, 103].

5.3 Steam Distillation

This method is useful for collecting volatile chemicals like terpenes, which are used for the extraction of essential oils from *Diospyros* leaves. The antibacterial and antioxidant properties of these oils are studied[103].

5.4 Traditional Formulations

Diospyros is processed into powders and pills, often in combination with other herbs, for holistic treatments for ailments like hypertension, diabetes, and oxidative stress[103].

5.5 Fermentation Processes

It is one of the methods used for preparation in which certain microbes are used to digest *Diospyros* leaves and fruits[104].

5.6 Microwave-Assisted Extraction (MAE)

This technique is used increasingly due to its effectiveness in extracting substances like polyphenols and flavonoids while reducing time and use of solvent[104].

6. Role of *Diospyros kaki* in Cancer Management

Diospyros kaki has gained considerable attention for its possible use in the treatment of cancer. These include flavonoids, tannins, carotenoids, and phenolic acids, which have a number of biological properties, such as anti-inflammatory, antioxidative, and anticancer

effects. Its phytochemical profile and ability to interact with essential molecular pathways are associated with critical molecular pathways linked to tumorigenesis.

The chemopreventive potential of *D. kaki* lies in its ability to intervene early in the carcinogenic process. Consuming persimmons or their extract has been associated with a lower risk of cancer, particularly when adhering to diets rich in fruits and vegetables. This effect is mainly due to the synergistic action of phytochemicals, which target several pathways implicated in the development and spread of tumours. Its carotenoids help to upregulate detoxifying enzymes, assisting in the removal of carcinogens and eliminating the risk of DNA damage. Its polysaccharides show immunomodulatory effects. These compounds increase the activity of macrophages and Natural Killer (NK) cells, which play critical roles in detecting and destroying cancer cells. The immune-stimulating impact is particularly beneficial in preventing cancer from recurrence and improving the overall efficacy of immunotherapy. Oxidative stress, caused by an imbalance between ROS production and antioxidant defences, is one known factor in the development and spread of cancer.

It has a high antioxidant capacity that protects cellular DNA and reduces oxidative stress. The probability of mutations that could result in cancerous changes is decreased by this preventive action. Polysaccharides can boost immune responses, which is crucial for detecting and eliminating cancerous or precancerous cells. These antioxidant properties improve the effectiveness of traditional cancer therapies in addition to preventing carcinogenesis. Persimmon extracts may help in alleviating and improving patients' outcomes by lowering oxidative damage caused by treatments like chemotherapy and radiation. This dual role as a protective and supportive agent underscores its potential as a complementary therapy in oncology. The methanolic extract of *D. kaki* has been a focal point in colorectal cancer (CRC) research. A study demonstrates that its extract is abundant in kaempferol and quercetin derivatives, specifically targeting cancer cells while preserving healthy mucosal cells. This mitochondrial dysfunction is achieved through the production of ROS, which causes oxidative stress and cellular damage, effectively impairing cancer cell viability. In comparison to traditional chemotherapy, which frequently lacks specificity and damages healthy tissues, this selective mechanism offers a substantial advantage[105].

Flavonoids derived from persimmon have demonstrated the ability to inhibit angiogenesis, a critical mechanism for tumour growth and metastasis, by inhibiting Vascular Endothelial Growth Factor (VEGF) signalling. This is particularly relevant in the context of aggressive cancers, where limiting blood supply can significantly reduce tumour proliferation. According to research, persimmon tannins are also essential for disrupting cancer cell adhesion and invasion, critical steps in the metastatic cascade[105,106].

Chronic inflammation is a risk factor recognised for its various cancers, as it promotes a microenvironment conducive to immune evasion and tumour growth. Its extracts exhibit strong anti-inflammatory effects by modulating the expression of pro-inflammatory cytokines and enzymes, such as interleukin-6 and cyclooxygenase-2. Persimmon compounds aid in the suppression of tumour-promoting mechanisms and the restoration of immune surveillance by reducing these inflammatory pathways[106].

7. Conclusion

The pharmacological versatility and potential of *D. kaki* highlight its contribution to Traditional Chinese medicine. Rich in bioactive compounds such as flavonoids, tannins, and polyphenols, it exhibits various health benefits, including antioxidant, anticancer, antidiabetic, neuroprotective, and anti-inflammatory activities. TCM, in combination with new scientific findings, underscores its value in diabetes, cancer and cardiovascular disease management. Modern research has further clarified its mechanism of action, like enhancement of lipid metabolism, modulation of oxidative pathways, and inhibition of enzymes like β-glucosidase and alpha-amylase.

Furthermore, the plant's multifaceted applications extend beyond medicine. Its extracts are used in dietary supplements, cosmetic formulations and dermatological products. The integration of *D. kaki* into innovative therapeutic and commercial goods emphasises its applicability in the modern health and wellness industries. Future studies should focus on standardising extraction techniques, maximising its

bioavailability, and conducting comprehensive clinical trials to fully understand its medicinal potential.

8. Author Contribution

Bhawana Yadav, Vijay Jagdish Upadhye, Madhulika Esther Prasad, Shiva Prasad Kollur, Chandan Shivamallu, and Pallavi Singh contributed to conceptualising the review, data collection and analysis, providing feedback, and drafting and finalising the manuscript. All authors have read and agreed to the published version of the manuscript.

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