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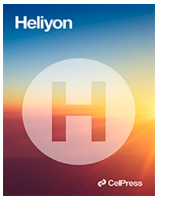

Review article

A mechanistic review of the pharmacological aspects of Kaempferide as a natural compound

Bocui Song [a,*,1], Wenqi Niu [b,1], Shuang Zhang [c], Meihan Hao [b], Yuqi Li [b], Qian Chen [b], Shuang Li [b], Chunyu Tong [b,**]

[a] Heilongjiang Provincial Key Laboratory of Environmental Microbiology and Recycling of Argo-Waste in Cold Region, College of Life Science and Biotechnology, Heilongjiang Bayi Agricultural University, Daqing, Heilongjiang, China
[b] College of Life Science and Technology, Heilongjiang Bayi Agricultural University, Daqing, Heilongjiang, China
[c] Administration Committee of Jilin Yongji Economic Development Zone, Jilin, China

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ABSTRACT

Background: Kaempferide exhibits a range of pharmacological effects, including anti-tumor activity, kidney protection, oxidative stress relief, gastroprotection, and endocrine regulation. The increasing attention surrounding kaempferide, a promising therapeutic agent, has sparked considerable debate, making it a topic of significant interest in recent research.
Purpose: This paper aims to provide a comprehensive review of the clinical applications, pharmacological properties, and underlying molecular mechanisms of kaempferide, while also examining its potential for future therapeutic applications in the field of pharmacology.
Methodology: We used the keywords "kaempferide" and "kaempferide derivatives" to search for relevant articles in Science Direct, PubMed, MEDLINE, and Web of Science databases.
Results: Kaempferide possesses anti-inflammatory, stomach-protective, antioxidant, anti-tumor, and anti-adipogenic activities, and thus has great potential in different systemic therapies. These interactions involve a multitude of pathways that directly or indirectly affect upstream and downstream key molecules.
Conclusions: Although kaempferide has shown promising potential, its practical applications still require further in-depth investigation. Future research should prioritize elucidating its mechanisms of action, identifying specific therapeutic targets, and optimizing the compound to facilitate its translation into drug development.

1. Introduction

The natural compounds found in medicinal plants have shown great potential in modern medical research. The bioactive molecules in medicinal plants are crucial for slowing aging and preventing or treating chronic diseases, and their potential is widely recognized.

* Corresponding author. College of Life Science and Technology, Heilongjiang Bayi Agricultural University, Daqing, Heilongjiang Province, 163319, China.
** Corresponding author. College of Life Science and Technology, Heilongjiang Bayi Agricultural University, Daqing, Heilongjiang Province, 163319, China.
E-mail addresses: songbocui66@163.com (B. Song), tongchunyu@126.com (C. Tong).
[1] These authors contributed to the work equally and should be regarded as co-first authors.

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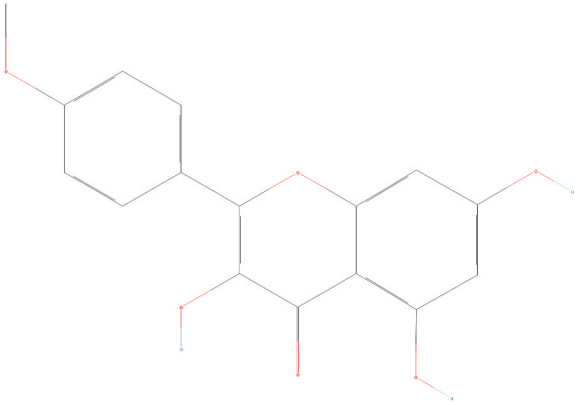

Fig. 1. Chemical structure of kaempferide.

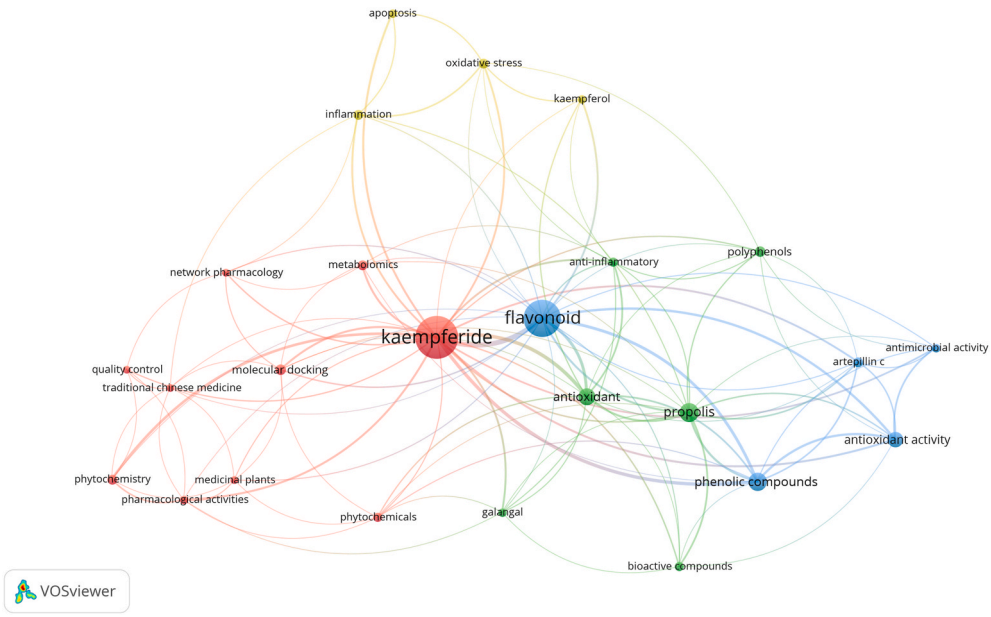

Fig. 2. Network analysis of keywords related to kaempferide bioactivity studies collected from the ScienceDirect database. Irrelevant literature was manually removed.

Medicinal plants and their active components serve as effective therapeutic agents, not only providing reliable efficacy but also offering good tolerance and fewer side effects, making them more appealing and trusted among patients [1–4].

As a flavonoid Kaempferide (3,5,7-Trihydroxy-4′-methoxyflavone) is found in various medicinal plants of the *Zingiberaceae* family. The molecular formula of Kaempferide is $C_{16}H_{12}O_6$. The IUPAC name for kaempferide is 3,5,7-trihydroxy-2-(4-methoxyphenyl)chromen-4-one. Structurally, kaempferide consists of two fused rings and a benzene ring, with a double bond between C-2 and C-3, a carbonyl group at C-4, and no hydroxyl group at C-3, forming a 15-carbon flavonoid skeleton. It also features hydroxyl groups at the 3rd, 5th, and 7th carbon atoms, conforming to the basic structure of flavonoids. Aminomethylation of kaempferide occurs preferentially at the C-6 and C-10 positions, resulting in various kaempferide derivatives [5]. The inhibitory inflammatory action of kaempferide is linked to the unsaturated bonds in the B and C rings [6]. Furthermore, the carbonyl group on C-4 and the double bond between C-2 and C-3 are closely related to the antioxidant and melanogenesis inhibitory activity of kaempferide [7]. The chemical structure of kaempferide is shown in Fig. 1.

Kaempferide has many beneficial biological activities including endocrine modulation [8], mitigation of testicular damage [9], inhibition of oxidative stress [10], gastroprotective [11], anti-tumor [12], and immunomodulatory [13], making it effective in treating diseases involving lung cancer [14], gastric damage [11], Alzheimer's disease [15], and osteoporosis [16]. In addition, kaempferide may slow the progression of chronic diabetes [17].

Medicinal plants containing kaempferide have long been utilized for therapeutic purposes, while the demand for synthetic kaempferide is steadily increasing. For this reason, several methods of synthesizing kaempferide have been developed, making this

Table 1
The sources of kaempferide.

Time	Source of Engeletin	author
1964	heartwood of Prunus domestica linn.	G.R. Nagarajan
1971	leaf tissue in Dillenia	E.C. Bate Smith,
1971	Alpima oficinarum	Giovanni Vidari
1974	A. Japonica, A. Koehnei	Eckhard Wollenweber
1975	Dillenia indica L.	Gowsala Pavanasasivam
1975	Pityrogramma triangularis	Aura E. Star
1978	Balsamorhiza deltoidea	B.A.Bohm
1985	Wyethia bolanderi	Susan McCormick
1991	Trifolium pratense	Chae Youngheum
1993	Agrimonia eupatoria	A.R. Bilia
2000	Carduus micropterus ssp. perspinosus	R. Tundis
2003	Warburgia ugandensis leaves	Lawrence O.Arot Manguro
2004	Brazilian green propolis	L.M.C Simões
2009	Alpinia officinarum	Hisashi Matsuda
2011	Chromoleana odorata	Pascal Wafo
2013	Polygoni avicularis herba	Sebastian Granica
2013	Rosa laevigata Michx	Shuai Zhang
2013	Alpinia oxyphylla	Qing Ya Bian
2017	Myricaria brbrteata Royle	Alexander A. Chernonosov
2017	Kaempferia galanga	Zixian Jiao
2018	Alpinia oxyphylla Miquel:	Qiao Zhang
2019	hromolaena odorata Linn.	Supakanya Kumkarnjana
2021	Tagetes erecta L,	Heng Tang
2021	Camellia nitidissima Chi	Yiwei Chen
2021	alpinae oxyphylla Miq	Muhammad Shoaib Tahir
2022	Mint (Mentha spp.	Tomislav Pavlešić
2023	Ziziphora clinopodioides Lam.	Hongbing Liu
2023	M. tenuiflora propolis	Arthur Alves Sartori
2023	*Tamarindus indica* L	Edinéia Bonin
2023	Vernonia polyanthes Less.	Jordana Damasceno Gitirana de Santana

compound available in the market at reasonable prices [5]. This review aims to overview the latest research findings on kaempferide, to explore its potential applications in disease prevention and therapy, and to discuss future directions for its development. We will begin by reviewing key literature, while also considering relevant supporting studies, to provide a comprehensive and in-depth analysis of high-quality research on kaempferide. The diagram made by VOSviewer is shown in Fig. 2.

2. The source of Kaempferide

The flavonoid kaempferide has been studied for more than two decades. The effect of kaempferide on the metabolism of benzo [a] pyrene by rat liver microsomes was first reported in 1991 [18]. Kaempferide was first extracted from *Agrimonia eupatoria* L. in 1993 by A R. Bilia et al. [19]. In 2002, a study by Daniel E. Frigo et al. demonstrated the presence of kaempferide in fruits, vegetables, and crops. It was found that kaempferide exhibits potent anti-estrogenic activity, which not only reduces E2-mediated gene expression but also inhibits the proliferation of MCF-7 cells. In addition, kaempferide (25 μmol/L), which reduced phorbol myristate acetate-stimulated activity by 91.0 %, modulated the activator protein-1 signaling pathway in endometrial and renal stable cell lines [20]. Hisashi Matsuda noted in 2009 that kaempferide, isolated from *Alpinia officinarum*, remarkably affected the level of tyrosinase, TRP-1, and TRP-2 mRNA in B16 melanoma 4A5 cells [7].

Furthermore, Lekshmi R. Nath et al. demonstrated in 2015 that kaempferide induced Caspase-dependent apoptosis in cervical cancer models *in vitro*, leading to PARP cleavage, thus exhibiting anticancer effects, while kaempferide was confirmed to be non-toxic and pharmacologically safe by mouse experiments [21]. On this foundation, in recent years, Lekshmi R. Nath conducted a detailed study on the anti-cervical cancer activity of kaempferide, and found that kaempferide is a potential anticancer agent with low cytotoxicity and potent results capable of causing apoptosis in cervical cancer cells [22]. In 2015 Van-Son Nguyen et al. semi-synthesized kaempferide using commercially available naringin, which reduced the cost of kaempferide synthesis and consequently accelerated clinical studies on the compound [5]. In 2018, Zhitao Jiang et al. determined the concentration of kaempferide in plasma after oral administration of *Sedum sarmentosum Bunge* to rats. They found that the plasma concentration of kaempferide reached its maximum value approximately 1.50 ± 0.58 h after administration, with widespread distribution, superior bioavailability compared to kaempferol, and an oral half-life of 3.56 ± 1.06 h [23]. In 2021, Xun He et al. noted that a key ingredient in Xuefu Zhuyu decoction, a prescription for treating baldness, is kaempferide [24]. Additionally, in 2023, Xinliang Wang et al. noted that Wuzi Yanzong Pill, a traditional Chinese medicine prescription for treating reproductive disorders, also contains kaempferide [25]. The chronological sources of kaempferide are shown in Table 1. The potential effects of kaempferide on different diseases are shown in Fig. 3 and Table 2.

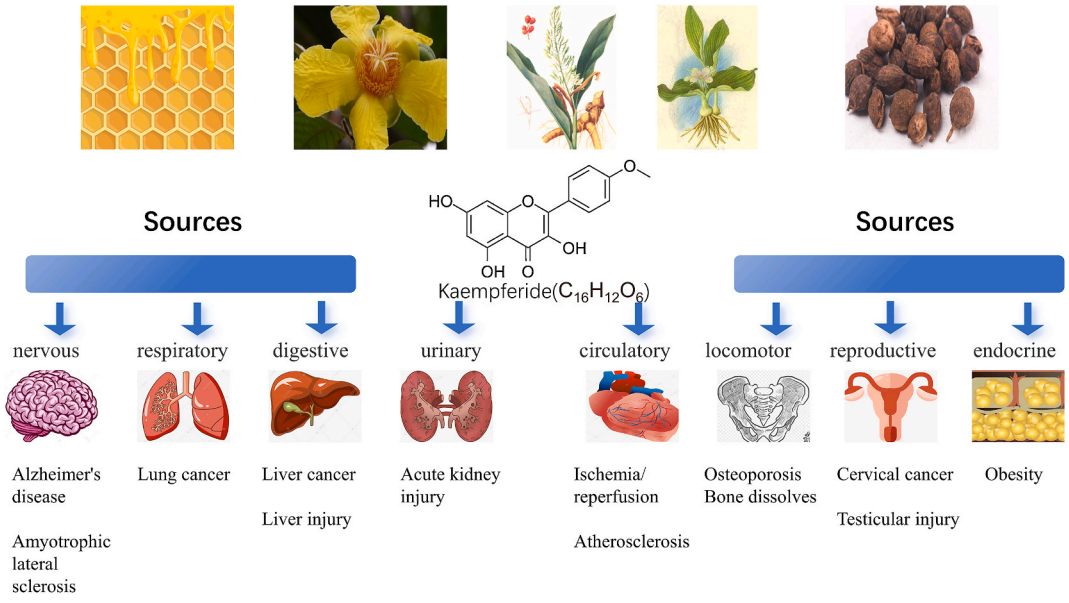

Fig. 3. The potential role of kaempferide in different diseases.

Table 2
The activity and mechanisms of keampferide in different diseases.

System	Event	Key Targets	References	Time
Nervous System	Alzheimer's disease	neurotrophic factor/tropomyosin receptor kinase B/cAMP	Tingxu Yan	2019
	Amyotrophic lateral sclerosis	SOD1	Tomoyuki Ueda	2017
	Nerve cell injury	Nrf2-ARE	Madoka Takashimaa	2019
Respiratory System	Non-Small Cell Lung Cancer (NSCLC)	Akt phosphorylation and Claudin-2	Hiroaki Eguchi	2020
	Lung cancer	MAPK, STAT3, AKT, TGF-β	HongLiang Li	2020
Digestive System	Non-alcoholic fatty liver disease (NAFLD)	Adipogenic protein C/EBPβ, PPARγ, FAS and SCD-1	Fangfang Tie	2021
	ALI Acute Liver Injury	MAPK	Abdullah A. Elgazar	2018
	Hepatotoxicity	CAT SOD TBARS	Muhammad Umar Ijaz	2023
	Liver Cancer	caspase-9	Gopika Chandrababu	2023
	Colon Cancer	VEGFA and AKT1 targets and PI3K-Akt pathway	Yiwei Chen	2021
	Stomach Injury	EGFA, AKT1, EGFR and SRC	Philipe Costa	2018
Circulatory System	Cardiotoxicity (PQ)	Anti-inflammatory/anti-apoptotic	Muhammad Umar Ijaz	2023
	Cardiac damage (DOX)	53BPI	Xuechun Chen	2023
	Myocardial Ischemia/reperfusion	PI3K/Akt/GSK-3β	Dong Wang,	2017
	Atherosclerosis	eNOS, P22phox, gp91phox, and PCSK9.	Hongbing Liu	2023
Endocrine System	Obesity	TLR4/i - κ b α/NF - κ b signaling pathway	Heng Tang	2021
	Dysglycemia	PPARγ/LXRα/ABCA 1/PI 3 K/AKT	Heng Tang	2021
	Obesity	Inhibition of proliferation/apoptosis	Supakanya Kumkarnjana	2019
Reproductive System	Ovarian cancer、Breast cancer	Tumor proteins E6, E7 and MDM2, p53, p21 and pRb/ apoptosis	Van-Son Nguyen	2015
	Cervical cancer	Apoptosis	Lekshmi R Nath,	2023
	Testicular injury	Nrf-2/Keap-1/Bax/Bcl-2	Muhammad Umar Ijaz	2023
Urinary System	Acute kidney injury	Oxidative stress/induced autophagy	Yan-fei Shao	2023
Exercise system	Osteolysis	JNK and ERK signaling pathways	Zixian Jiao	2017
	Osteoporosis	FoxO1/β-catenin	Xiaoli Ma	2021

3. Pharmacological effects of Kaempferide

3.1. Kaempferide and the nervous system

In the nervous system, kaempferide mainly inhibits oxidative stress, reduces nerve cell inflammation, nourishes nerve pathways, and protects nerve function.

3.1.1. Kaempferide and Alzheimer's disease (AD)

AD is a major reason for the memory loss in older adults, with the extracellular deposition of amyloid β peptide (Aβ) leading to the generation of neuritic plaque regarded as the primary causative factor of the disease [26]. In a rat model of AD induced by the injection of Aβ1-42, Tingxu Yan et al. demonstrated that kaempferide exerted neuroprotective effects by increasing cAMP response elements (CREB) protein phosphorylation and inhibiting Aβ, and by increasing brain-derived neurotrophic factor (BDNF) expression in AD model mice; in addition, neural plasticity and longer retention of memories can be affected by kaempferide through a number of cytokines and signaling pathways, such as BDNF, CREB, tropomyosin receptor kinase B [15]. Oxidative stress is associated with attention deficit disorder and cognitive decline, thus oxidative stress contributes to the etiopathogenesis of AD [27; 28]. Madoka Takashimaa et al. found kaempferide to be protective against oxidative stress-induced cell death, contributing to the basis for the utilization of kaempferide in the treatment of AD [29]. However, both studies failed to provide detailed pharmacokinetic and pharmacodynamic relationships of kaempferide, nor did it do toxicological studies on kaempferide, so kaempferide is only a novel drug in the research and development stage.

3.1.2. Kaempferide and amyotrophic lateral sclerosis

Tomoyuki Ueda et al. found that kaempferide reduced intracellular aggregation of Superoxide Dismutase 1 (SOD1) mutants by inducing inhibition of SOD1 mutant-induced cell death and mitochondrial superoxide mutation in an Amyotrophic Lateral Sclerosis model, thus preventing neurotoxicity induced by SOD1 mutation. It also induces autophagy through the AMPK-mTOR pathway and inhibits the aggregates formed of mutant SOD1 proteins [29]. Based on previous studies, Madoka Takashimaa found that kaempferide has strong hydroxyl radical scavenging activity and its antioxidant activity is involved in neuroprotection against SOD1-related neurotoxicity in mutant SOD1. Additionally, kaempferide promotes ARE activation and inhibit SOD1-induced superoxide in mutant SOD1, as shown by ESR analysis. This suggests that kaempferide prevents neuronal cell death associated with oxidative stress [30].

3.2. Kaempferide and the respiratory system

In the respiratory system, kaempferide primarily promotes the apoptosis of lung cancer cells, restricts their proliferation, inhibits cell migration, and enhances the chemosensitivity of A549 lung adenocarcinoma cells, making it a promising agent for lung cancer therapy.

Lung cancer is one of the deadliest malignant tumors, and NSCLC accounts for about 85 percent of all lung cancer cases [31]. Through a study on A549 cells, Hong-Liang Li et al. found that kaempferide had a significant killing effect on lung cancer cells through the regulation of mitochondria-dependent apoptosis by Bcl-2 family proteins, inhibited the AKT signaling pathway, prevented the cells from passing through the cell cycle checkpoints, and limited the proliferation of A549 cells. In addition, kaempferide limited the emigration of lung cancer cells by modulating TGF-β/β-catenin pathway and restricting cellular activity. In conclusion, kaempferide stimulated reactive ROS production and inhibited the proliferation of A549 cells by mediating MAPK, AKT, STAT3, NF-κB, and TGF-β pathways or targets [14]. However, only *in vitro* data were provided in this paper, and further investigation using animal models is needed to confirm these findings.

Hiroaki Eguchi et al. also found, through an *in vitro* study on A549 cells, that kaempferide increased the responsiveness of lung cancer cells to chemotherapeutic compounds. This enhancement may be related to the presence of the 2,3-double bond in the C-ring of kaempferide. The 2,3-double bond in its C-ring inhibits the phosphorylation of AKT, which reduces the expression of Claudin-2 and lowers the paracellular barrier for small molecules, therefore increasing the paracellular permeability of chemotherapeutic drugs. Furthermore, kaempferide reduces hypoxic stress as well as enhances the intracellular accumulation of chemotherapeutic agents [32]. However, the study has some shortcomings: first, the molecular mechanism of kaempferide-induced decrease in Claudin-2 expression is not fully explained. Second, it is unclear how kaempferide reduces hypoxia levels, but this does not prevent kaempferide from providing important theories about its therapeutic role during lung cancer. Further research is needed to elucidate its underlying mechanisms.

3.3. Kaempferide and the digestive system

As a potent compound, kaempferide modulates apoptosis, lipid accumulation, inflammation, autophagy, and oxidative stress, and has been involved in the pathophysiology of a variety of digestive disorders, such as nonalcoholic fatty liver disease (NAFLD) [33], hepatitis [34], liver injury [35], hepatocellular carcinoma (HCC) [36], gastric ulcers [11], and colorectal cancer (CC) [37].

3.3.1. Kaempferide and NAFLD

NAFLD is one of the common forms of liver disease, which is mainly characterized by lipid accumulation without heavy alcohol consumption[38; 39]. Fangfang Tie et al. found that kaempferide inhibited intracellular lipid accumulation by downregulating the expression of enhancer binding proteins β, peroxisome proliferator-activated receptor γ (PPARγ), fatty acid synthase, and stearoyl-CoA desaturase-1 (SCD-1). It could attenuate the expression of Nrf2 and HO-1 to alleviate oxidative stress in HepG2 cells [33]. It can also inhibit intracellular lipid accumulation by directly acting on the structural proteins of lipid droplets. Among them, kaempferide exhibited a concentration-dependent increase in the inhibition of lipid accumulation, and these studies found that kaempferide inhibited the expression of a number of proteins associated with adipogenesis, such as lipogenic and lipotropic proteins, lipid droplet proteins, and oxidative stress-related proteins, and thus could be used for the treatment of NAFLD. Nonetheless, this paper merely provides preliminary *in vitro* results, which will still need to be confirmed *in vivo*.

3.3.2. Effects of Kaempferide on hepatitis

The early stage of liver injury is usually characterized by hepatic inflammatory lesions [40]. Therefore, inhibiting the production of inflammatory factors is an effective treatment for slowing down the progression of liver injury, and drugs to ameliorate hepatitis still need to be explored.

Abdullah A. Elgazar et al. utilized the Lipopolysaccharides-induced HepG2 cell to produce the ALI model noting that kaempferide reduces the levels of inflammatory factors such as TNF-α, IL-1β and IL-6 through the MAPK pathway. The anti-inflammatory effects of kaempferide work through interaction with p38α MAPK [34]. Although this study showed that kaempferide was effective against hepatitis, the *in vitro* experiments primarily revealed differences in inflammatory factor expression. Further experimental studies are required to demonstrate the suppressive effect of kaempferide on p38α MAPK proteins, for which there is not much external evidence.

3.3.3. Effect of Kaempferide on cadmium-induced hepatotoxicity

Cadmium can cause serious health problems in humans and animals, and it can lead to a decrease in the content of antioxidant enzymes, an increase in the level of inflammatory factors, an increase in apoptotic signals, and an increase in histopathological damage. Muhammad Umar Ijaz et al. found that the antioxidant activity of kaempferide scavenges free radicals produced and accumulated by cadmium exposure, restores the Catalase (CAT) and SOD activities, decreases Thiobarbituric Acid Reactive Substances and H_2O_2 levels, and reduces oxidative stress after treatment with kaempferide. Kaempferide exhibited hepatoprotective effects by mitigating liver tissue damage and decreasing plasma levels of functional markers, It also alleviated apoptosis in rat hepatocytes by inhibiting caspase-3 activation and elevating anti-apoptotic markers. Kaempferide manifested its anti-inflammatory role by decreasing the levels of inflammatory factors such as TNF-α, IL-6, IL-1β and modulating NF-κB [35]. In conclusion, the present findings suggest that kaempferide was effective against oxidative stress markers, hepatic serum markers, apoptotic markers, and the level of inflammatory indices, as well as hepatic histopathological abnormalities. The role of kaempferide in hepatotoxicity would be better demonstrated if it were studied in depth and clinical data were used to illustrate the effect of kaempferide on cadmium-induced hepatotoxicity.

3.3.4. Effects of Kaempferide on HCC

HCC is a primary malignant tumor of the liver closely related to inflammation and metabolic syndrome. Currently, available treatments for HCC do not achieve satisfactory results. The study by Gopika Chandrababu et al. demonstrated that kaempferide induces caspase-mediated apoptosis *in vitro*. In murine models, kaempferide exhibited significant therapeutic effects, including tumor volume reduction, increased caspase-9 levels, and downregulation of TGF-β1 expression [41]. These findings highlight the anticancer potential of kaempferide; however, further *in vivo* analyses are required to validate kaempferide as a therapeutic candidate for HCC.

3.3.5. Effect of Kaempferide on CC

CC is the second deadliest malignant tumor globally, causing at least 600,000 deaths annually [42]. Yiwei Chen et al. found that kaempferide modulates VEGFA, AKT1, EGFR, and SRC proteins to restrain the activity of colon cancer cells by using web-based pharmacological analysis [37]. Although this study shows that kaempferide is effective against colon cancer, the findings are derived solely from web-based pharmacological analysis and require validation through well-designed experimental studies.

3.3.6. Effects of Kaempferide on the stomach

Gastric ulcer is a disease that is estimated to affect 5–10 % of the world's population [43]. Philipe Costa et al. found that kaempferide inhibited gastric acid secretion, reduces gastric ulcer size, lowers the gastric ulcer index, restores gastric mucosal SOD activity, decreases lipid hydroperoxide levels, increases gastric mucin levels, alleviates histological damage, and exhibits gastroprotective activity [11]. While the study demonstrates the efficacy of kaempferide in these areas, it focuses solely on its effects on the stomach and does not delve into the molecular mechanisms underlying its gastroprotective effects.

3.4. Kaempferide and the circulatory system

There are many studies on the role of kaempferide in cardiovascular events, with a focus primarily on its effects on the heart. Kaempferide demonstrates considerable potential for the treatment of atherosclerosis (AS) [44], myocardial injury [45], and cardiotoxicity [46] through its anti-inflammatory, tissue damage-reducing, anti-apoptotic, and antioxidant effects.

3.4.1. Effect of Kaempferide on the cardiotoxicity caused by paraquat

Exposure to paraquat damages several organs, and cardiovascular damage is one of the obvious complications of paraquat poisoning. Paraquat produces a large amount of ROS, significantly reduces the activity of antioxidant enzymes, raises the level of oxidative stress, and the levels of inflammatory cytokines are all significantly elevated, and the expression of anti-apoptotic marker genes is reduced, which promotes apoptosis, leading to cellular damage and histopathological damage. Treatment with kaempferide increased the activity of antioxidant enzymes, elevated GSH levels, and decreased the levels of ROS, H_2O_2, and Malondialdehyde (MDA). It is hypothesized that its ability to scavenge ROS may be related to the multiple hydroxyl groups and conjugated double bonds in its structure. Kaempferide exhibited its anti-inflammatory effects by decreasing the expression of inflammatory factors such as TNF-α, IL-6, IL-1β, and COX-2, as well as its anti-apoptotic effects by decreasing the levels of pro-apoptotic markers and elevating anti-apoptotic markers. Kaempferide was able to decrease the concentrations of Creatine Kinase (CK), lactate dehydrogenase, CK-MB, and troponin I markers of myocardial injury suggesting that kaempferide administration restored the histopathological damage of

paraquat, modulated the abnormalities of antioxidant enzymes, cardiac function markers, apoptosis, and inflammatory markers, and alleviated paraquat-induced cardiotoxicity [46]. However, further clinical trials are essential. Building on previous research, Xuechun Chen et al. found that kaempferide was equally therapeutic in the face of doxorubicin-induced cardiotoxicity, and that kaempferide not only reduced foci but also ameliorated doxorubicin-induced reduction of ATP levels in H9c2 cells as well in a concentration-dependent approach. Kaempferide not only reduced the aggregation of proteins indicative of DNA damage in screening experiments, but was also shown to attenuate the doxorubicin-induced decrease in cardiomyocyte viability [47].

3.4.2. Effect of Kaempferide on myocardial ischemia/reperfusion injury (I/R)

Acute myocardial infarction caused by ischemia and hypoxia is a disease with a high mortality rate [48]. During myocardial ischemia/reperfusion, kaempferide mainly reduces oxidative stress, inhibits the level of inflammatory factors to reduce cardiomyocyte apoptosis, and decreases myocardial infarct size to protect cardiac function. I/R injury is a complex process involving multiple mechanisms. Dong Wang et al. used ligation of rat coronary artery with 0.5 h and reperfusion for 2 h to establish a rat myocardial I/R injury model, revealed that kaempferide alleviated myocardial I/R injury through activation of the PI3K/Akt/GSK-3β pathway [45]. The study demonstrated that kaempferide protects cardiomyocyte activity to alleviate myocardial infarction and post-ischemic cardiac insufficiency, providing a theoretical basis for the potential therapeutic value of kaempferide in ischemia-reperfusion injury.

3.4.3. Effects of Kaempferide on AS

AS, caused by a combination of factors such as lipid metabolism disorders, endothelial dysfunction, inflammation, and oxidative stress, is an important cause of death [49; 50]. Naoki Ohkura et al. found that Brazilian green propolis, which contains a high concentration of kaempferide, was able to reduce the tendency of thrombosis in mice [51]. Hongbing Liu et al. found that kaempferide has the potential to regulate the level of inflammatory factors and lipid metabolism for the treatment of AS [44]. Although specific studies directly addressing kaempferide's effects on AS are lacking, these findings highlight its potential therapeutic benefits and offer insights for future research on the biological effects of kaempferide in AS.

3.5. Kaempferide and the endocrine system

Obesity is a dangerous factor for heart disease, fatty liver, atherosclerosis, diabetes, and even psychological disorders[52; 53]. Supakanya Kumkarnjana et al. used the 3T3-L1 cell line, an *in vitro* model of adipogenesis, and found that kaempferide exhibited significant, concentration-dependent anti-adipogenic activity during the initial phase of adipogenesis. Further studies revealed that kaempferide exerted its anti-adipogenic activity by inhibiting mitotic clonal expansion, delaying cell proliferation at early stages, inhibiting PPARc expression and inducing apoptosis [54]. While this study elucidated the restraining role of kaempferide on adipogenesis *in vitro*, adipogenesis and accumulation are influenced by several factors, and thus the effect of kaempferide on adipogenesis *in vivo* is still unknown. In addition, this research was unable to clearly illustrate the mechanism of action of kaempferide on mitotic clonal amplification. Follow-up experiments are needed to verify the effects of kaempferide on adipogenesis *in vivo*. Constructing an obese mouse model through a high-fat diet, Heng Tang et al. found that kaempferide reduced obesity and lipid metabolism disorders *in vivo* and *in vitro*, improved glucose metabolism abnormality and insulin sensitivity, and suppressed blood glucose elevation, as well as reduced the state of abdominal obesity and alleviated hyperlipidemia, hyperglycemia, and insulin resistance in mice. Its mechanism of action is achieved by activating PPARγ-mediated Cholesterol LXRα/ABCA1/PI3K/AKT signaling pathways. Kaempferide is a PPARγ activator, and the hypolipidemic effect of kaempferide is achieved by activating the PPARγ-LXRα-ABCA1 signaling pathway, and the hypoglycemic effect of kaempferide is achieved by activating the PPARγ-PI3K/AKT signaling pathway [8]. This research provides original evidence for the simultaneous weight loss, hypolipidemic and hypoglycemic effects of kaempferide as a natural molecule and reveals the underlying mechanisms of kaempferide's pharmacological activity, but the interaction of kaempferide with PPARγ is not known. In addition, the pharmacokinetics and pharmacodynamics of kaempferide were not described.

In another study by Heng Tang et al. on an obese mouse model, kaempferide was found to alleviate oxidative stress and glucolipid metabolism disorders in obese mice via TLR4/IκBα/NFκB signaling pathway. Kaempferide inhibited the activation of TLR4 to promote the level of IκB and further suppressed the level of NF-κB, reduced the release of inflammatory factors such as IL-6 and TNF-α, and increased the activity of SOD enzyme and the GSH levels, thereby alleviating inflammation and oxidative stress damage[17; 55]. This study provides new insights into the anti-obesity mechanism of kaempferide, but the specific mechanism of interaction between kaempferide and TLR4 was not clearly elaborated, and whether anti-inflammatory, antioxidant, and anti-obesity effects interact was not explicitly addressed. Therefore, further work is necessary to elucidate the potential of kaempferide as a novel and potent natural-based treatment for obesity, diabetes and other metabolic diseases.

3.6. Kaempferide and the genitourinary system

Kaempferide, known for its anticancer activity, has demonstrated a significant killing effect on cervical cancer cells [22], breast ductal cancer cells [5], and ovarian cancer cells, preventing tumor cell proliferation and metastasis, thus inhibiting reproductive system tumors. Its unique activity is effective in mitigating testicular damage [9].

3.6.1. Kaempferide and reproductive cancers

Vaccines are currently the primary method of preventing cervical cancer. Despite the rapid approval of Merck's Gardasil in many countries, its high cost renders it unaffordable for many HPV carriers, who are at higher risk of developing cervical cancer. Although

various chemotherapeutic drugs have been developed for cervical cancer treatment, they often come with serious side effects or are too expensive for patients to afford. This underscores the need for affordable treatments with fewer side effects. A study found that kaempferide extracted from the leaves of *Chromolaena odorata* has strong anticancer effects. Van-Son Nguyen et al. developed an artificial semi-synthesis method for kaempferide using naringenin and investigated its activity. Their research demonstrated kaempferide's cytotoxic effects against HeLa cells, HCC1954 cells, and SK-OV-3 cells [5]. Lekshmi R. Nath et al. on the basis of previous studies found that kaempferide induces apoptosis by activating the caspase cascade reaction, which leads to the cleavage of PARP. Meanwhile, kaempferide was found to be pharmacologically safe through acute toxicity study and chronic toxicity study [21]. However, this study only verified the killing effect on cancer cells from *in vitro* experiments, and its effect *in vivo* has not been verified; furthermore, it is not clear whether other mechanisms of action exist for the effect of kaempferide on cervical cancer. Further research by Lekshmi R. Nath et al. demonstrated that kaempferide significantly reduced tumor size in a xenograft mouse model of human cervical cancer. Kaempferide significantly increased the production of ROS, which dramatically reduced the activity and growth of cervical tumors, and it also induced apoptosis in cervical cancer cells by down-regulating the tumor-regulating proteins E6 and E7, up-regulating p53 and pRb, and phosphorylating and glucolipid metabolism disorders [22]. This study, complementing previous findings, highlights the anti-tumor potential of kaempferide and supports its consideration as a candidate drug molecule for cervical cancer treatment.

3.6.2. Kaempferide and testicular injury

Muhammad Umar Ijaz et al. found that kaempferide exhibited a mitigating role against PE-MPs-induced testicular toxicity in rats. Kaempferide enhances the activity of antioxidant enzymes (SOD, CAT, and GSR) by increasing the expression of Nrf2 and decreasing the expression of Keap-1, leading to a reduction in ROS and MDA levels. It also elevates steroidogenic enzyme levels and alleviates structural damage caused by varicocele. In addition, kaempferide promotes sperm production by increasing follicle-stimulating hormone, luteinizing hormone and testosterone levels. It reduces the level of inflammatory markers by modulating the NF-κB signaling pathway, and enhances sperm count and survival by decreasing the levels of Bax and Caspase-3, which ultimately results in the alleviation of testicular damage [9]. These findings suggest that kaempferide could potentially enhance the quality of life for men suffering from testicular injury.

3.6.3. Effects of Kaempferide on acute kidney injury (AKI)

AKI is a relatively common side effect of various medications, and there remains a significant need to develop and study drugs for its treatment. An animal model study of cisplatin-induced AKI suggests that kaempferide exerts therapeutic effects through its anti-inflammation properties, inhibition of oxidative stress, and induction of autophagy [56]. Although this study demonstrated that kaempferide was effective against acute kidney injury in mice, we only established that kaempferide protects renal cells from death both *in vivo* and *in vitro* models. However, the direct target of kaempferide in alleviating oxidative stress, along with many other detailed mechanisms, remains unknown. Further experimental studies are therefore required to elucidate these mechanisms.

3.7. Kaempferide and the locomotor system

3.7.1. Kaempferide and periprosthetic osteolysis

Total joint replacement is considered to be the most effective therapy for patients with end-stage arthritis, and periprosthetic osteolysis is a crucial factor influencing the outcome of the procedure [57; 58]. Osteoclast activation leads to periprosthetic osteolysis, resulting in the aseptic loosening of titanium particle-induced prostheses. Therefore, osteoclast inhibitors can be used to treat titanium particle-induced osteolysis. Kaempferide dose-dependently suppressed osteoclast differentiation by inhibiting the RANKL-induced JNK and ERK signaling pathways, and the bone resorption assay demonstrated that kaempferide inhibits the bone resorption function of osteoclasts [59]. In conclusion, this study provides a theoretical foundation for kaempferide as a potential drug for the prevention of titanium particle-induced osteolysis *in vivo*, though feasibility studies are necessary to assess its clinical application.

3.7.2. Kaempferide and osteoporosis (OP)

OP is characterized by bone microarchitectural deterioration and decreased bone mass, which leads to increased bone fragility and a higher risk of fractures, particularly among older adults[60; 61]. Kaempferide has been shown to promote osteogenic differentiation by inducing GSK-3β phosphorylation for activating FoxO1/β-catenin or β-catenin/TCF1/Runx2 signaling pathways. Additionally, kaempferide ameliorates H_2O_2-inhibited osteogenic differentiation by increasing antioxidant capacity. Therefore, kaempferide can be used as a possible means for the therapy of OP [16]. However, further studies are required to determine the optimal dosage of kaempferide for osteoporosis and to validate the interaction between kaempferide and GSK-3β.

3.8. Kaempferide and skin

The skin, the largest organ in the body, serves as a protective barrier against harmful factors such as viruses and toxins. Excessive UV exposure can cause skin aging. Jong-Kyu Choi et al. found kaempferide as a potential anti-photo-aging agent for modulating skin abnormalities caused by photoaging, with modulating effects on collagen loss, decreasing metalloproteinase activity, and elevated levels of pro-inflammatory cytokines. In addition, it inhibits UVB-induced ROS elevation and the phosphorylation of MAPKs and AKT, thereby exhibiting anti-photoaging activity [62]. Excessive UV irradiation also causes melanocytic tumors, and kaempferide concentration-dependently inhibited the level of tyrosinase, TRP-1, and TRP-2 mRNA in B16 melanoma 4A5 cells, and kaempferide

Table 3
The cytotoxic of Kaempferide.

Author	cell line	cytotoxicity
Gopika Chandrababu	HepG2	IC50 = 27.94 ± 2.199 μM
	Huh7	IC50 = 25.65 ± 0.956 μM
	N1S1	IC50 = 15.18 ± 3.68 μM
Lekshmi R. Nath	HeLa	IC50 = 16 μM
	Normal Fibroblast	IC50 > 100 μM
Van-Son Nguyen	HCC1954	IC50 = 36.27 ± 3.26 μM
	SK-OV-3	IC50 = 39.80 ± 0.04 μM
Zi-Xian Jiao	Osteoclast	IC50 = 159.8 ± 15.6 μM (48 h)
		IC50 = 90.72 ± 10.3 μM (72 h)
		IC50 = 43.13 ± 8.7 μM (96 h)
Xiao-Li Ma	MC3T3-E1	IC50 = 217.4 μM
Shuai Jin	N2a cells	No toxicity was observed at 50 μM
Heng Tang	Hepatocyte	No toxicity was observed at 30 μM
Arthur Alves Sartori	PBMC	IC50 > 200 μM
Hisashi Matsuda	B16 Melanoma 4A5 cells	IC50 = 16 μM
Yen Siew Loh	KMS-11	IC50 = 26 μM
Hong-Liang Li	A549	IC50 = 22.5 ± 1.35 μM
	NCI-H460	IC50 = 29.1 ± 1.5 μM
	NCI-H23	IC50 = 26.2 ± 1.4 μM
	IMR90	No significant toxicity at therapeutic concentrations
	GES-1	No significant toxicity at therapeutic concentrations
	L-02	No significant toxicity at therapeutic concentrations
Jong-Kyu Choi	NIH-3T3	protective effect
Yan-Fei Shao	HK-2	protective effect

suppressed theophylline-stimulated melanogenesis in B16-4A5 melanoma cells by suppressing the expression of MITF [7]. It is speculated that the 2,3-double bond of kaempferide is essential for melanogenesis inhibitory activity.

4. The toxicity and adverse effects of Kaempferide

Kaempferide exhibits significant selectivity in terms of cytotoxicity. In studies on different liver cancer cell lines, the half-maximal inhibitory concentrations (IC50) of kaempferide for HepG2, Huh7, and N1S1 cells were 27.94 ± 2.199 μM, 25.65 ± 0.956 μM, and 15.18 ± 3.68 μM, respectively, indicating a potent cytotoxic effect on liver cancer cells. Additionally, kaempferide showed low micromolar IC50 values against HeLa, HCC1954, SK-OV-3, KMS-11, A549, NCI-H460, NCI-H23, and B16 melanoma 4A5 cells, suggesting broad-spectrum antitumor activity. In other cell lines, kaempferide's IC50 values for A549, NCI-H460, and NCI-H23 were 22.5 ± 1.35 μM, 29.1 ± 1.5 μM, and 26.2 ± 1.4 μM, respectively, while the IC50 for B16 melanoma 4A5 cells was 16 μM, demonstrating effective inhibition in these cell lines as well. Moreover, kaempferide showed lower cytotoxicity toward normal cells, with IC50 values of 159.8 ± 15.6 μM for osteoclasts, 217.4 μM for MC3T3-E1 fibroblasts, and greater than 100 μM for normal fibroblasts, indicating a higher safety margin. Studies on PBMCs revealed no cytotoxicity at a concentration of 200 μM, and no significant toxicity was observed in IMR90, GES-1, or L-02 cells. Furthermore, kaempferide has shown protective effects on HK-2 and NIH-3T3 cells. In mice, the safe dose of kaempferide is generally considered to be 20 mg/kg. There is no toxicity-related data available for other animal species. These data suggest that kaempferide holds potential therapeutic value while maintaining low toxicity to normal cells, which is a critical consideration in drug development. The toxicity of kaempferide to various cells is shown in Table 3.

5. Conclusions

Kaempferide, found in plants such as Kaempferia galanga and Alpinia officinarum, exhibits a wide range of beneficial properties, including anti-inflammatory, antioxidant, anti-apoptotic, antitumor, and immunomodulatory effects, indicating its potential for treating various diseases affecting the circulatory, respiratory, reproductive, endocrine, nervous, and musculoskeletal systems. Despite its demonstrated therapeutic effects on certain diseases in these systems, and its low cytotoxicity and good safety profile, most research on kaempferide's pharmacological effects remains in the early stages. For instance, studies on kaempferide's role in the urinary system are limited, underscoring the need for further exploration of its nephroprotective effects. Currently, most studies on kaempferide are conducted *in vitro*, with only a few using mouse models for *in vivo* experiments. More research and clinical trials are needed to determine its efficacy and safety in humans, thereby providing a robust theoretical and experimental foundation for translating kaempferide's therapeutic potential into clinical applications, contributing to the advancement of human health.

Future research on kaempferide should be more comprehensive, not limited to its effects on specific diseases or signaling pathways, but rather focused on deeply exploring its mechanisms of action and targets, particularly at the cellular and molecular levels. Additionally, the combination of kaempferide with other drugs or its use in complex formulations will significantly expand its medical potential. Furthermore, given its remarkable antioxidant and anti-inflammatory properties, kaempferide could become an ideal ingredient for functional foods, health supplements, and cosmetics. This opens new avenues for its application, offering broad prospects in the health and beauty industries.

CRediT authorship contribution statement

Bocui Song: Writing – review & editing, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Wenqi Niu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Shuang Zhang:** Supervision, Resources, Project administration, Conceptualization. **Meihan Hao:** Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yuqi Li:** Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Qian Chen:** Formal analysis, Conceptualization. **Shuang Li:** Formal analysis, Data curation, Conceptualization. **Chunyu Tong:** Writing – review & editing, Visualization, Validation, Supervision, Software.

Declaration of competing interest

No potential conflict of interest was reported by the authors.

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