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Review

Genkwanin: An emerging natural compound with multifaceted pharmacological effects

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ABSTRACT

Plant bioactive molecules could play key preventive and therapeutic roles in chronological aging and the pathogenesis of many chronic diseases, often accompanied by increased oxidative stress and low-grade inflammation. Dietary antioxidants, including genkwanin, could decrease oxidative stress and the expression of pro-inflammatory cytokines or pathways. The present study is the first comprehensive review of genkwanin, a methoxyflavone found in several plant species. Indeed, natural sources, and pharmacokinetics of genkwanin, the biological properties were discussed and highlighted in detail. This review analyzed and considered all original studies related to identification, isolation, quantification, investigation of the biological and pharmacological

Abbreviations: ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); AD, Atopic dermatitis; AFSV, African swine fever virusAdjuvant-induced arthritis; AKT, Protein kinase B; ALI, Acute lung injury; AUC, Area under the curve; Bcl-2, B-cell lymphoma-2; Bcl-xL, B-cell lymphoma-extra large; BCRP, Breast cancer resistance protein; CAA, Intracellular antioxidant activity; CC, Column chromatography; CCC, Counter-current chromatography; Cdc2, Cyclin-dependent kinase 2; CLP, Cecal ligation puncture; COX, Cyclooxygenase; CVDs, Cardiovascular diseases; DAD, Diode array detection; DCF, Dichlorofluorescein; DESI-MSI, Desorption electrospray ionization mass spectrometry imaging; DNCB, 2, 4-dinitrochlorobenzene; DPH, 1,6-diphenyl-1,3,5-hexatriene; DPPH, 2,2-diphenyl-1-picrylhydrazyl; DSS, Dextran sulfate sodium; FLSs, Fibroblast-like synoviocytes; FRAP, Ferric reducing antioxidant power; GBE, Ginkgo biloba extract; G-CSF, Granulocyte-colony-stimulating factor; GM-CSF, Granulocyte-macrophage colony-stimulating factor; HPLC, High-performance liquid chromatography; ICAM, Endothelial intercellular adhesion molecule; IFN, Interferon; IgE, Immunoglobulin E; IL, Interleukin; iNOS, Inducible NO; JAK, Janus kinase; LPS, Lipopolysaccharide; MAPK, Mitogen-activated protein kinase; MKP-1, Mitogen-activated protein kinase phosphatase-1; MMP-3, Matrix mettaloproteinase-3; MPP, 1-Methyl-4-phenylpyridinium; MIC, Minimum inhibitory concentration; mTOR, Mammalian target of rapamycin; MyD88, Myeloid differentiation primary response 88; NF-kB, Nuclear factor kappa B; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NO, Nitric oxide; NSCLC, Non-small-cell lung carcinoma; PARP1, Poly [ADP-ribose] polymerase 1; PI3K, Phosphoinositide 3-kinase; ROS, Reactive Oxygen Species; RP-HPLC, Reversed phase-high performance liquid chromatography; SARS-CoV-2, Severe acute respiratory syndrome-coronavirus-2; SIRT1, Sirtuin-1; STAT, Signal transducer and activator of transcription protein; TBARS, Thiobarbituric acid reactive species; TLRs, Toll-like receptors; TNF-α, Tumor necrosis factor-alpha; VEGF, Vascular endothelial growth factor.

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properties of genkwanin. We consulted all published papers in peer-reviewed journals in the English language from the inception of each database to 12 May 2023. Different phytochemical demonstrated that genkwanin is a non-glycosylated flavone found and isolated from several medicinal plants such as *Genkwa Flos*, *Rosmarinus officinalis, Salvia officinalis*, and *Leonurus sibiricus*. *In vitro* and in vivo biological and pharmacological investigations showed that Genkwanin exhibits remarkable antioxidant and anti-inflammatory activities, genkwanin, via activation of glucokinase, has shown antihyperglycemic activity with a potential role against metabolic syndrome and diabetes. Additionally, it revealed cardioprotective and neuroprotective properties, thus reducing the risk of cardiovascular diseases and assisting against neurodegenerative diseases. Furthermore, genkwanin showed other biological properties like antitumor capability, antibacterial, antiviral, and dermatoprotective effects. The involved mechanisms include sub-cellular, cellular and molecular actions at different levels such as inducing apoptosis and inhibiting the growth and proliferation of cancer cells. Despite the findings from preclinical studies that have demonstrated the effects of genkwanin and its diverse mechanisms of action, additional research is required to comprehensively explore its therapeutic potential. Primarily, extensive studies should be carried out to enhance our understanding of the molecule's pharmacodynamic actions and pharmacokinetic pathways. Moreover, toxicological and clinical investigations should be undertaken to assess the safety and clinical efficacy of genkwanin. These forthcoming studies are of utmost importance in fully unlocking the potential of this molecule in the realm of therapeutic applications.

1. Introduction

Oxidative stress and inflammation are essential components of physiological pathways in the occurrence and progression of numerous chronic disorders, including obesity, diabetes, cardiometabolic and neurodegenerative diseases, cancer, or autoimmune diseases, and major factors in the rate of aging [1,2]. Scientific investigations frequently postulated that natural antioxidants may have favorable biochemical effects against various pathologies [3]. Natural products, key sources of bioactive compounds, demonstrated their safety and efficacy in several diseases [4–9].

Polyphenols, a major class of natural products, belong to plant secondary metabolites and are linked with a wide spectrum of health-promoting effects due to their potent antioxidative, anti-inflammatory, anti-carcinogenic, or enzyme inhibitory activities [10] Among polyphenols, flavonoids have received increased attention for their health-promoting benefits and have been exploited for their medicinal and neutraceutical properties [11] They are divided into many sub-classes, such as anthocyanins, flavonols, flavanones, isoflavones, and flavones [12].

Nutraceuticals are nutritional supplements that are used to improve health, postpone aging, fend against disease, and support normal bodily functions. Due to its potential for both nutrition and treatment, nutraceuticals are currently receiving a lot of attention. They are classed as dietary supplements and herbal bioactive substances based on their origins [13]. In this sense, flavonoids present a wide range of structural variations and are the main ingredients responsible for the organoleptic qualities of plant-based meals and beverages, in particular, their color and flavor. They also enhance the nutritional value of vegetables and fruit [14]. This multifunctional class of compounds has significant properties that can be used in the development of medicines for a number of chronic disorders. A wide variety of pharmacological properties, including anti-oxidant, anti-tumor, anti-viral, anti-allergic, anti-inflammatory, and anti-viral activities, have been discovered in flavonoids. The phenolic structure of these compounds is primarily responsible for these beneficial biological effects [15].

Genkwanin is a non-glycosylated flavone and is found and extracted from several plant matrices, among others *Genkwa Flos* [16,17], *Rosmarinus officinalis* [18–22], *Salvia officinalis* [23,24], and *Leonurus sibiricus* [23]. Biological investigations exposed that genkwanin possesses various biological activities, such as antioxidant [25], anti-inflammatory [26], neuroprotective [27], anticancer [28], antibacterial [29,30], and antidiabetic activities [31]. Indeed, genkwanin has been shown to be a potential anti-inflammatory agent due to its effective action against pro-inflammatory mediators, including TNF-α, IL-1β, IFNγ, and IL-6 cytokines, inhibition of the generation of reactive oxygen species (ROS) [32], or down-regulation of microRNA-101, p38- and JNK-mediated AP-1 signaling pathway [4]. On the other hand, flavones have the ability to inhibit a number of protein kinases, including the dual-specificity tyrosine phosphorylation regulated kinase 1 A (DYRK-1A), cyclin-dependent kinases (CDKs), glycogen synthase kinase-3 (GSK3), and others that are connected to the growth of cancer [33]. By influencing cell growth, metastasis, and the tumor microenvironment (TME), these biomolecules have been demonstrated to have both pro-tumor and antitumor effects in cancer [34]. In this context, studies have revealed that genkwanin exerted anticancer effects by inducing apoptosis of MCF-7 human breast cancer, HepG-2 human hepatocellular carcinoma [28], human HT-29, HCT-116, and SW-480 colon cancer cell lines [35] through inhibition of PARP1, Bcl-2, and Bcl-xL proteins and by enhancing host immunity and reducing inflammatory factor level. In a rat model, genkwanin and other flavones decreased arthritis via antioxidant and hemorheological modulatory mechanisms [36].

Moreover, in vitro studies have shown that genkwanin could present a potential antioxidant activity by scavenging oxidative radicals, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and 2,2-dipenyl-1-picrylhydrazyl (DPPH) [25], and controlling thiobarbituric acid reactive species (TBARS) [37]. The antidiabetic effects of genkwanin are related to its capacity to inhibit enzymes involved in the metabolism of carbohydrates and lipids, as well as the signaling pathways involved in metabolism regulation [31,38,39].

To the best of our knowledge, this is the first comprehensive review of genkwanin. It has been designed to explore all previously published articles relating to genkwanin in terms of origin and analyses of biological and pharmacological processes. Thus, this review can guide further studies to develop optimized methods for identifying, isolating, and testing this flavonoid. The structure-activity relationships and the action mechanisms data can assist in future potential applications in pharmaceutical industries and medical applications.

2. Methods

This comprehensive review study was conducted using relevant electronic databases, including PubMed/Medline, Embase, and employing search terms applicable to specific databases. Binary logical Boolean operators (AND and OR) and the following keywords: genkwanin, chemistry, antioxidant, inflammation, aging, and diseases were applied in the search strategy.

Our review analyzed and considered all original studies related to identification and/or quantification, investigation of the biological activities by in vitro, in vivo, and *in silico* experiments, and published in peer-reviewed journals in the English language from the inception of each database to 12 May 2023. We omitted abstracts, editorials, reviews, comments, opinions, letters, and duplicate studies. The included studies

are presented in Table 1. Of the total of 120 studies, 35 were conducted in China, 28 in European countries, and 8 in the USA.

3. Chemistry

Flavonoids are naturally-occurring polyphenols widely distributed in plant tissues. Phenylalanine, biosynthesized in plants via the Shikimate pathway, is the starting molecule used in the synthesis of flavonoids. They are comprised of 15 carbon atoms (C6-C3-C6) and consist of two phenyl rings (A and B) and a heterocyclic ring (C) containing the embedded oxygen. Flavonoids can accomplish various functions, including plant pigments, defending against pathogens and herbivores, guarding against harmful sunlight radiation, assist plant metabolism, and, according to their chemical structure, are divided into several classes [132]. Flavones, one of these classes, are based on the backbone of 2-phenylchromen-4-one (2-phenyl-1-benzopyran-4-one) and present a double bond between the C2 and C3 positions. Flavones are common in foods, some vegetables, and fruits [133].

Genkwanin (4′,5-dihydroxy-7-methoxyflavone) is an O-methylated flavone with methylation on one hydroxyl group (Fig. 1). The genkwanin biosynthesis pathway is represented in Fig. 2.

3.1. Natural sources of genkwanin

Genkwanin was found and described in many plant matrices (Table 2). It was the single most important compound isolated in the leaf chloroform extract of *Vernonia fasciculata* collected from the United States [40], stem parts of hydromethanolic extract of *Eremanthus elaeagnus* [41], flower of *Daphne genkwa* collected from China [43,56,66, 79] and Korea [119]. Also, propolis (*Apis mellifera* honeybees) was distinguished by its abundance in genkwanin [44].

Other studies mentioned different plant matrices for the richness in the genkwanin compound, such as *Ocimum basilicum* leaves [45], aerial parts of *Baccharis trimera* from Brazil [47], stems of *Daphne gnidium* collected in Italy [16,17], seeds of *Salvia officinalis* from Portugal [23, 24] and Tunisia [80]. Also, flowers, leaves, roots, and stems of aqueous and methanolic extracts of *Rosmarinus officinalis* from Spain [18–22], *Artemisia afra* collected in Germany [51] and South Africa regions [61], as well as Iranian species of *Nepeta* leaves [50] were characterized by the richness in genkwanin.

In addition, genkwanin is the major compound in methanolic extract of aerial parts of *Artemisia iwayomogi* from Korean regions [53], hydromethanolic extract of leaves and roots of *Rumex induratus* collected in Portugal areas [57], *Alnus glutinosa* seeds from U.K. [58], *Combretum erythrophyllum* leaves from South Africa [63], *Sidastrum micranthum* aerial parts [72], *Aquilaria crassna* leaves collected in Japan districts [75], *Phegopteris decursive-pinnata* leaves [91], and whole plant methanolic extract of *Tinospora crispa* from Bangladesh [98].

Genkwanin is a major compound of various species of Lamiaceae family, such as *Leonurus sibiricus* [23], *Coleus forskohlii* [82], *Salvia aegyptiaca* [83], *Leonurus artemisia* [84], *Teucrium ramosissimum* [85], *Mentha piperita* [95], and *Callicarpa americana* [96], Asteraceae family including *Gochnatia pulchra* [29], *Vernonia fasciculata* [31], *Artemisia* ssp. [51,53,61], and *Moquiniastrum floribundum* [97], or Thymelaeaceae family involving *Daphne* ssp. [3,4,29–33], and *Aquilaria ssp.* [50,51,57].

3.2. Extraction, isolation, and purification of genkwanin

Several studies revealed the isolation and purification of genkwanin from plants (Table 1). A leaf chloroform extract of *Vernonia fasciculata* was subjected to column and preparative thin-layer chromatography in order to isolate genkwanin. NMR, I.R., U.V., and M.S. spectral analyses have been performed, and the results have been compared to data for closely related substances [40]. Analysis by high-performance liquid chromatography (HPLC), 13 C NMR, ESI-MS, and 1 H-, counter-current chromatography (CCC) and Macroporous resin column chromatography, HPLC with diode array detection (DAD), chromatography on column with Sephadex gel L.H. 20 HPLC analysis, column HPLC with U.V. absorption and mass spectrometry (M.S.) detection, reversed phase-HPLC (RP-HPLC) with DAD, desorption electrospray ionization mass spectrometry imaging (DESI-MSI), and spectroscopic analyses, one-dimensional NMR, HRESIMS and was confirmed by single-crystal X-ray diffraction were employed for the elucidation of the structure of genkwanin purified and extracted from parts of various plants, such as *Leonurus sibiricus* [23], *Gochnatia pulchra* [29], *Aquilaria crassna* [75], *Coleus forskohlii* [82], *Salvia aegyptiaca* [83], *Leonurus artemisia* [84], *Teucrium ramosissimum* [85], *Aquilaria sinensis* [134], *Mentha piperita* [95], *Callicarpa americana* [96], and *Moquiniastrum floribundum* [97].

4. Biological and pharmacological properties

Due to their polyphenolic structure, flavonoids possess free-radical scavenger potential and act as strong antioxidant agents. *In vitro* and in vivo studies indicated that diets rich in flavonoids and flavones have health-beneficial effects [135].

Numerous findings confirmed the health-promoting effects of genkwanin. This natural flavone demonstrated beneficial effects against many diseases, including type 2 diabetes, cardiometabolic diseases, cancer, and neurodegenerative disorders (Fig. 3). The favorable effects of genkwanin have been attributed to its ability to control oxidative stress and inflammation, cellular cycle arrest, and regulation of apoptosis.

4.1. Antioxidant activities

In the last decades, the research focused on finding novel, effective, and safe antioxidants from natural products since oxidative stress has become increasingly one of the leading causes of various chronic ailments [136].

It is believed that the antioxidant potency of flavonoids is related to the B-ring substitution more than the A-ring substitution; a hydroxyl group located in the B-ring, especially in position C4', warrants scavenging potential [137].

Genkwanin has shown good antioxidant effects using different in vitro models. Sroka et al. [25] demonstrated that genkwanin exhibited anti-ABTS and anti-DPPH radical scavenging properties. Moreover, as indicated by ferric reducing antioxidant power (FRAP), genkwanin employed ferric ion reduction potential; however, compared to quercetin and kaempferol, strong antioxidant flavonoids, genkwanin was less active. Furthermore, genkwanin extracted from *Rosmarinus officinalis* displayed an inhibitory effect against TBARS in a membrane-based system [37]. It also showed a higher quenching effect of 1, 6-diphenyl-1,3,5-hexatriene (DPH), revealing that genkwanin could promote membrane stabilization and inhibit radical propagation through its electron donor ability and thereby preventing the membranes from oxidative damage. Bouzaiene et al. assessed the intracellular antioxidant activity (CAA) of genkwanin isolated from *Teucrium ramosissimum* by inhibiting dichlorofluorescein (DCF) production using ABAP-induced peroxyl radicals in splenocytes. The investigation exposed that genkwanin may be absorbed into splenocytes and exhibits an antioxidant effect. At a concentration of 40 M, genkwanin prevented splenocytes from producing DCF [138].

4.2. Anti-inflammatory activities

In recent years, the scientific interest in natural anti-inflammatory molecules increased exponentially due to the low efficacy and serious adverse effects of conventional drugs. In fact, the long-term administration of these drugs, either steroidal or non-steroidal anti-inflammatory compounds, can induce excessive side effects.

Natural bioactive compounds, including flavones, are generally safe

Table 1
Characteristics of the selected studies.

Studies	Country	Study Type	Characterization and/or Activity	Main Findings
Narain 1976 [40]	USA	*In vitro*	Phytochemistry	Genkwanin spectral data
Le Quesne et al. 1978 [41]	USA	*In vitro*	Phytochemistry	Phenolic compounds identified in *Eremanthus elaeagnus*
Fraga et al. 1987 [42]	Argentina	*In vitro* *In situ*	Antioxidant	Inhibition of mouse liver chemiluminescence
Tang & Eisenbrand 1992 [43]	Germany	*In vitro*	Phytochemistry	Chemistry, pharmacology of *Daphne genkwa*
Garcia-Viguera et al. 1993 [44]	Spain	*In vitro*	Phytochemistry	Flavonoids identification in propolis
Grayer et al. 1996 [45]	UK/Germany	*In vitro*	Phytochemistry	Flavones identification in sweet basil
Zahir et al. 1996 [46]	France	*In vitro*	Anticancer	Cytotoxicity against human nasopharynx carcinoma cells
Nakasugi et al. 199 [47]	Japan	*In vitro*	Phytochemistry	Antimutagenic activity of carqueja extracts
Cottiglia et al. 2001 [48]	Italy	*In vitro*	Antibacterial	Antimicrobial activity of *Daphne gnidium* extract
Santos-Gomes et al. 2002 [24]	Portugal	*In vitro*	Phytochemistry	Phenolic compounds identified in sage extracts
Köhler et al. 2002 [49]	Germany	*In vitro*	Anticancer	Antiplasmodial activity of *Calea tenuifolia* extracts
Jamzad et al. 2003 [50]	UK	*In vitro*	Phytochemistry	Flavonoids identifications in *Nepeta* ssp.
Kraft et al. 2003 [51]	Germany	*In vitro*	Phytochemistry	Antiplasmodial activity of *Artemisia afra* and *Vernonia colorata* compounds
del Baño et al. 2004 [20]	Spain	*In vitro*	Phytochemistry	Flavonoids identification in *Rosmarinus officinalis*
Deiana et al. 2003 [17]	Italy	*In vitro*	Phytochemistry	Phytochemical analysis and antioxidant activity of *Daphne gnidium* extracts
Ibañez et al. 2003 [52]	Spain	*In vitro*	Antioxidant	Antioxidant compounds from rosemary plants
Kim et al. 2004 [53]	Korea	*In vitro*	Phytochemistry	Peroxynitrite scavenging activity of *Artemisia iwayomogi* compounds
Boalino et al. 2004 [54]	Barbados	*In vitro*	Phytochemistry	Phytochemical identification from *Leonurus sibiricus*
Martini et al. 2004 [55]	South Africa	*In vitro*	Anti-inflammatory Antibacterial	Good antibacterial and anti-inflammatory activities of flavonoids from *Combretum erythrophyllum*
P é rez-Fons et al. 2006 [37]	Spain	*In vitro*	Phytochemistry	Good antioxidant activity of genkwanin from rosemary
Park et al. 2006 [56]	Korea	*In vitro*	Phytochemistry	Flavonoid isolation from *Daphne genkwa* flower buds
Ferreres et al. 2006 [57]	Spain	*In vitro*	Phytochemistry	19 compounds identified in *Rumex induratus* leaves
Kumarasamy et al. 2006 [58]	UK	*In vitro*	Phytochemistry	Antibacterial and antioxidant activities of flavonoids *Alnus glutinosa* seeds
Sadhu et al. 2006 [59]	Bangladesh	*In vitro*	Phytochemistry	*Cistus laurifolius* compounds showed prostaglandin inhibitory and antioxidant activities
Jones et al. 2007 [60]	USA	*In vitro*	Anticancer	Citotoxic activity of compounds from *Callicarpa americana*
de Almeida et al. 2008 [23]	Brazil/Italy	*In vitro*	Phytochemistry	Biological activities of *Leonurus sibirucus* compounds
Avula et al. 2009 [61]	USA	*In vitro*	Phytochemistry	Flavonoids identification in *Artemisia afra*
Henchiri et al. 2009 [62]	France	*In vitro*	Phytochemistry	Sesquiterpenoids and flavonoids identified in *Teucrium ramosissimum*
Regnier et al. 2009 [63]	South Africa	*In vitro*	Phytochemistry	Compounds from *Combretum erythrophyllum* inhibited *Candida albicans*
Androutsopoulos et al. 2009 [64]	Greece	*In vitro*	Anticancer	Genkwanin inhibited MDA-MB-468 human breast adenocarcinoma
Brožič et al. 2009 [65]	Slovenia	*In vitro*	Anticancer	Flavonoids inhibited 17beta-hydroxysteroid dehydrogenase type 1
Jordán et al. 2010 [21]	Spain	*In vivo*	Phytochemistry	Diet rosemary leaves increased goat milk poliphenol content
Li et al. 2010 [66]	China	*In vitro*	Phytochemistry	Genkwanin produced from *Daphne genkwa* flowers by combination of macroporous resin and counter-current chromatography
Devkota et al. 2010 [67]	Japan	*In vitro*	Phytochemistry	13 flavonoids isolated from *Diplomorpha canescens*
Bai et al. 2010 [68]	USA	*In vitro*	Phytochemistry	15 compounds isolated from *Rosmarinus officinalis* leaves
P é rez-Fons et al. 2010 [37]	Spain	*In vitro*	Antioxidant	Rosemary compounds presented antioxidant activity
Xie et al. 2011 [69]	China	*In vitro*	Phytochemistry	Luteolin, apigenin, 3′-hydroxygenkwanin, genkwanin isolated from *Daphne genkwa*
Lee et al. 2010 [70]	Korea/USA	*In vitro*	Antibacterial	Bactericidal activity and antilipopolysaccharide effects of flavonoids on *Escherichia coli*
Mizuochi et al. 2011 [71]	Japan	*In vitro*	Phytochemistry	10 compounds isolated from *Linaria canadensis*
Gomes et al. 2011 [72]	Brazil	*In vitro*	Phytochemistry	7 compounds isolated from *Sidastrum micranthum*
Sghaier et al. 2011 [73]	Tunisia	*In vitro*	Antioxidant	Antioxidant activity of 4 compounds isolated from *Teucrium ramosissimum* leaves
Maia et al. 2011 [74]	Brazil	*In vitro*	Antibacterial	6 compounds isolated from *Praxelis clematidea* modulated bacterial drug resistance
Ito et al. 2012 [75]	Japan	*In vitro*	Phytochemistry	8 phenolics isolated from *Aquilaria crassna*
Escandón-Rivera et al. 2012 [76]	Mexico	*In vivo*	Antidiabetic	Compounds from *Brickellia cavanillesii* attenuated postprandial hyperglycemia in diabetic mice
Falcao et al. 2013 [77]	Brazil	*In vitro*	Phytochemistry	11 compounds isolated from *Hyptis pectinate* leaves
Song et al. 2013 [78]	China	*In vivo*	Pharmacokinetic	Genkwanin was poorly absorbed in rats following oral and intravenous administration
Borrás-Linares et al. 2014 [18]	Spain/Serbia	*In vitro*	Phytochemistry	Bioactive compounds isolated from *Rosmarinus officinalis* leaves
Shu et al. 2014 [79]	China	*In vitro*	Phytochemistry	Genkwanin isolated from *Daphne genkwa* flowers by normal-phase flash chromatography
Farhat et al. 2014 [80]	Tunisia	*In vitro*	Phytochemistry	Antioxidant activity of *Salvia officinalis* compounds
Gao et al. 2014 [4]	China	*In vitro*	Anti-inflammatory	Genkwanin exerted anti-inflammatory effect through miR-101/MKP-1/MAPK pathway regulation
Komape et al. 2014 [30]	South Africa	*In vitro*	Antibacterial	Acacetin as the main antibacterial compound from the leaves of *Combretum vendae*
Jiang et al. 2014 [81]	China	*In vivo*	Pharmacokinetic	Genkwanin transported by passive diffusion and multidrug resistance protein-mediated efflux mechanisms
Awasthi et al. 2015 [82]	India	*In vitro*	Phytochemistry	Cytochrome P450 genes isolation from *Coleus forskohlii* roots
Farhat et al. 2015 [83]	Tunisia/Spain	*In vitro*	Phytochemistry	*Salvia aegyptiaca* phenolics with antioxidant capacity
Sroka et al. 2015 [25]	Poland	*In vitro*	Antioxidant	Flavonols had stronger antioxidant activity than flavones with the exception of luteolin
Lucarini et al. 2015 [29]	Brazil	*In vitro* *In vivo*	Anti-inflammatory Antibacterial	Anti-inflammatory activity of *Gochnatia pulchra* compounds through inhibition TNF-α, IL-1β, MCP-1

(*continued on next page*)

Table 1 (*continued*)

Studies	Country	Study Type	Characterization and/or Activity	Main Findings
Wang et al. 2015 [35]	China	*In vitro* *In vivo*	Anticancer	Genkwanin inhibited HT-29 and SW-480 human colorectal cancer cells proliferation and IL-8 secretion
Qiu et al. 2015 [39]	China	*In vitro*	Antidiabetic	*Ginkgo biloba* extract with diabetic nephropathy effects
Fan et al. 2016 [84]	China	*In vitro*	Phytochemistry	Genkwanin from *Leonurus artemisia* promoted uterine contractions
Nasr-Bouzaiene et al. 2016 [85]	Tunisia	*In vitro*	Antioxidant Anti-inflammatory Anticancer	*Teucrium ramosissimum* compounds had anti-inflammatory activity
Jung et al. 2016 [86]	Korea	*In vitro*	Dermato-protective	Methoxyflavonoids could inhibit UV-B-induced skin photo-damage
Wei et al. 2016 [87]	China	*In vivo*	Pharmacokinetic	Pharmacokinetics of 4 *Wikstroemia indica* ingredients after oral administration to rats
Liu et al. 2017 [88]	China	*In vitro*	Phytochemistry	Bioactive compounds identified in *Plagiochasma appendiculatum*
Li et al. 2017 [89]	China	*In vitro* *In vivo*	Pharmacokinetic	Genkwanin nanosuspensions showed citotoxicity against cancerous cells
Kiyekbayeva et al. 2018 [90]	Kazakhstan	*In vitro*	Phytochemistry	Compounds isolated from *Echinops albicaulis*
Watanabe et al. 2018 [91]	Japan	*In vitro*	Phytochemistry	6 compouds isolated from *Phegopteris decursivepinnata* leaves
Li et al. 2018 [92]	China	*In vitro*	Neuroprotective	Beneficial effects of *Ginkgo biloba* compounds in dementia
Tao et al. 2018 [93]	China	*In vitro*	Pharmacokinetic	Vinegar-processing could enhance bioavailability of genkwanin, 3′-hydroxygenkwanin, apigenin, and luteolin
Zhang et al. 2018 [94]	China	*In vitro*	Anticancer	Flavonoids caused cell cycle arrest at G2/M phase and induced apoptosis and autophagy in human breast cancer cells
Freitas et al. 2019 [95]	Brazil	*In vitro*	Phytochemistry	Spatial distribution assessment of key flavonoids in peppermint leaves
Porras et al. 2019 [96]	USA	*In vitro*	Phytochemistry	Description of genkwanin in *Callicarpa americana*
Tamayose et al. 2019 [97]	Brazil	*In vitro*	Phytochemistry	11 phenolics isolated from *Moquiniastrum floribundum*
Rakib et al. 2019 [98]	Bangladesh	In silico	Anti-inflammatory	*Tinospora crispa* compounds reduced pyrexia, MDA levels and increased SOD levels
Bao et al. 2019 [99]	China/USA	In vivo	Anti-inflammatory	Genkwanin exerted anti-rheumatoid arthritis effects on rats through inhibiting JAK/STAT, NF-κB signaling pathways
Baek et al. 2019 [100]	Korea	In vitro	Neuroprotective	Compounds isolated from *Prunus padus* leaves can inhibit monoamine oxidase
El-Wassimy et al. 2019 [28]	Egypt	*In vitro*	Anticancer	Flavonoids from *Artemisia sieberi* had anticancer potential
Fan et al. 2019 [101]	China	*In vitro* *In vivo*	Anticancer	11 flavonoids inhibited breast cancer resistance protein
Hakobyan et al. 2019 [102]	Armenia	*In vitro*	Antiviral	Genkwanin inhibited African swine fever virus infection
Sun et al. 2020 [32]	China	*In vitro*	Anti-inflammatory	*Daphne genkwa* flavonoids inhibited NO, iNOS, TNF-α, IL-6, and NF-κB pathway
Jo et al. 2020 [103]	Korea	*In vitro*	Anti-inflammatory Dermato-protective	Compounds from *Stellera chamaejasme* with anti-inflammatory and antiallergic activities
Leu et al. 2020 [104]	Taiwan	*In vitro*	Anticancer	Hydroxygenkwanin from *Daphne genkwa* suppressed cancer cell viability
Gecibesler & Aydin 2020 [105]	Turkey	*In vitro*	Anticancer	Flavonoids had anti-proliferative activity
Khan et al. 2020 [106]	China	*In silico*	Antiviral	42 compounds had better docking score than Remdesivir
Arroo et al. 2020 [107]	UK/Turkey	*In vitro*	Dermato-protective	5 flavones tested showed lower tyrosinase inhibitory effect compared to kojic acid
Ao et al. 2020 [108]	China	*In vitro* *In vivo*	Pharmacokinetic	Hydroxygenkwanin nanosuspensions showed good inhibition against MCF-7 breast tumor cells
Castillejos-Ramírez et al. 2021 [109]	Mexico	*In vitro*	Phytochemistry	*Baccharis heterophylla* compounds demonstrated antinociceptive and anti-inflammatory properties
Cortés-Chitala et al. 2021 [110]	Mexico	*In vitro*	Phytochemistry	62 compounds including genkwanin identified in Mexican oregano
Zhou et al. 2021 [111]	China	*In vitro*	Anti-inflammatory Anti-angiogenic	Among 14 flavonoids from *Daphne genkwa*, genkwanin was the most active anti-rheumatoid arthritis compound
Li et al. 2021 [27]	China	*In vitro*	Anti-inflammatory	Genkwanin attenuated neuroinflammation and neurotoxicity by inhibiting TLR4/MyD88/NLRP3 inflammasome pathway
Zeng et al. 2021 [112]	China	*In vitro*	Neuroprotective	Genkwanin from *Ginkgo folium* had the greatest number of anti-Alzheimer's disease targets
Xu et al. 2021 [113]	China	*In vitro*	Neuroprotective	4 flavones inhibited the aggregation of human islet amyloid polypeptide
Wei et al. 2021 [114]	China	*In vitro*	Anticancer	Genkwanin inhibited proliferation, migration, invasion of A549 and H69AR lung cancer cells by inhibiting the PI3K/Akt pathway
Elhady et al. 2021 [115]	Saudi Arabia/ Egypt	*In vitro*	Anticancer	*Thymelaea hirsuta* compounds exhibited cytotoxic activity against cancer cells
Manilal et al. 2021 [116]	Ethiopia	*In vitro*	Antibacterial	Genkwanin, camphor, endo-borneol, alpha-terpineol, hydroxyhydrocaffeic acid from *Rosmarinus officinalis* showed antimicrobial activity
Nouadi et al. 2021 [117]	Morocco	*In vitro*	Antiviral	Taxol, rutin, genkwanin, luteolin-glucoside had good affinity with ACE2 and 3CLpro-SARS-CoV-2
Yin et al. 2021 [118]	China	*In vivo*	Pharmacokinetic	Genkwanin-loaded self-nanoemulsifying drug delivery system formulation exhibited good oral bioavailability and anti-colitis-associated colorectal cancer efficacy
Kim et al. 2022 [119]	Korea	*In vitro*	Phytochemistry	Apigenin 7-O-glucuronide, genkwanin 5-O-primeveroside, and genkwanin increased during *Daphne genkwa* bud growth
Nguyen et al. 2022 [120]	Vietnam	*In vitro*	Phytochemistry	Genkwanin among 7 polyphenols isolated from *Aquilaria crassna* that inhibited α-glucosidase activity
Duan et al. 2022 [121]	China	*In vitro*	Phytochemistry	Types of flavonoid-related metabolites differed between 2 *Chrysanthemum* species
Chen et al. 2022 [26]	China	*In vivo*	Antioxidant Anti-inflammatory	Genkwanin reduced oxidative stress and proinflammatory cytokines production, improved mitochondrial function and upregulated SIRT1 expression
Muhammad et al. 2022 [31]	Nigeria	*In vitro* *In silico*	Antioxidant Antidiabetic	*Aframomum melegueta* extracts had antioxidant and antidiabetic properties
Xu et al. 2022 [122]	China	*In vitro* *In vivo*	Antioxidant Antibacterial	Genkwa flos exhibited anti-*Listeria monocytogenes* potency

(*continued on next page*)

Table 1 (*continued*)

Studies	Country	Study Type	Characterization and/or Activity	Main Findings
Ni et al. 2022 [123]	Taiwan	*In vivo*	Anti-inflammatory	Genkwanin protected against acute lung injury by inhibiting NF-κB pathway activation and p38 MAPK phosphorylation
Qin et al. 2022 [124]	China	*In vivo*	Anti-inflammatory	Genkwanin reduced lung edema and inflammation in mice by regulating NF-κB signaling pathway
Ijaz et al. 2022 [125]	China/ Pakistan	*In vivo*	Anti-inflammatory	Genkwanin ameliorated hepatic damages induced by aflatoxin B1 in rats
Fu et al. 2022 [126]	China	*In vivo*	Anti-inflammatory	Genkwanin attenuated osteoclast differentiation
Khandagale et al. 2022 [127]	India	*In silico*	Neuroprotective	Quercetin, cirsimaritin, genkwanin and genistein showed high binding affinity and interaction with acetylcholinesterase and butyrylcholinesterase
Lim et al. 2022 [128]	Korea	*In vitro*	Anticancer	Laetanine and genkwanin inhibited matrix metalloproteinase-9
Kausar et al. 2022 [129]	Saudi Arabia	*In silico*	Antidiabetic	Bromelain, cholecalciferol, luteolin, and neohesperidin demonstrated good binding interactions with alpha-glucosidase
Gaspersz et al. 2022 [38]	Indonesia	*In silico*	Antidiabetic	Genkwanin and sakuranetin from Chromolaena odorata leaves inhibited alpha-amylase
Yan et al. 2023 [130]	China	*In vitro*	Phytochemistry	12 components from *Ziziphus jujube* seeds acted against insomnia
Soltani et al. 2023 [131]	Tunisia/France	*In vitro* *In silico*	Antidiabetic	Hypolaetin 8-O-β-D-galactopyranoside from *Thymelaea tartonraira* leaves inhibited α-amylase and α-glucosidase

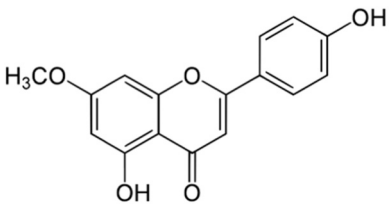

Fig. 1. Chemical structure of genkwanin.

and have proven actions against inflammation. They can regulate the expression of important inflammatory signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), nuclear factor erythroid 2-related factor 2 (Nrf2), and signal transducer and activator of transcription (STAT) [139].

The NF-κB pathway activates the expression of genes implicated in inflammation, apoptosis, proliferation, or cell survival, and it leads to chronic inflammation, tumor development, or tumor cell proliferation [140].

Nrf2 is a transcription factor that regulates inflammation and displays important antioxidant and anti-stress roles. During inflammatory states, the Nrf2 pathway interacts with the NF-κB signaling pathway to modulate the cellular redox balance [141]. It suppresses the NF-κB pathway by several mechanisms, such as controlling the release of ROS induced by NF-κB, inhibiting the transcription of NF-κB-dependent pro-inflammatory genes, or preventing the nuclear translocation of NF-κB [142]. STAT pathway is implicated in the regulation of the immune response, proliferation, differentiation, and apoptosis. It regulates the expression of genes involved in inflammation and can induce the production of inflammatory cytokines, including TNFα and IL-1β [143].

Several in vitro and in vivo studies exposed the promising anti-inflammatory effects of genkwanin treatments (Table 3).

In a study using C57BL/6 male mice as a model, Chen et al. [26] investigated the anti-inflammatory effects of genkwanin on dextran sulfate sodium (DSS)-induced colitis. As a result, oral genkwanin treatment reduced weight loss, colon length restriction, and histological abnormalities in DSS-induced colitis. Moreover, genkwanin suppressed the generation of ROS as well as pro-inflammatory chemicals like tumor necrosis factor (TNF)-α, interleukin (IL)−1β, interferon (IFN)-γ, and IL-6 cytokines. Genkwanin has also been shown to enhance mitochondrial function in human enterocytes. The molecular mechanisms underlying these events were mainly explained by the ability of genkwanin to activate Sirtuin-1 (SIRT1) genes, thereby preventing oxidative stress and mitochondrial dysfunction [26]. Moreover, Sun et al. investigated the anti-rheumatoid arthritis activity of genkwanin extracted from *Daphne genkwa* on lipopolysaccharide (LPS)-induced RAW264.7 macrophages, concluding that genkwanin significantly suppressed in a dose-dependent manner the production of IL-6 cytokines, TNF-α, nitric oxide (NO), IFN-γ, IL-2 and inducible NO (iNOS) [32]. Deciphering the mechanisms by which genkwanin inhibited the pro-inflammatory cytokines, the authors examined the impact of genkwanin on the NF-kB activity and the mRNA expression levels of iNOS, IL-6, and cyclooxygenase-2 (COX-2) in RAW264.7 cells. The results showed that genkwanin exhibited an anti-rheumatoid arthritis effect by targeting the NF-κB pathway via down-regulating IKK, IκB, and NF-κB phosphorylation levels, as well as the expression levels of iNOS, COX-2, and IL-6. Additionally, genkwanin treatment suppressed the aberrant proliferation of rheumatoid arthritis fibroblast-like synoviocytes (FLSs) and its NO and levels of IL-6 secretion [32]. A therapeutic approach targeting the NF-κB signal transduction pathway is a pivotal step toward the treatment of

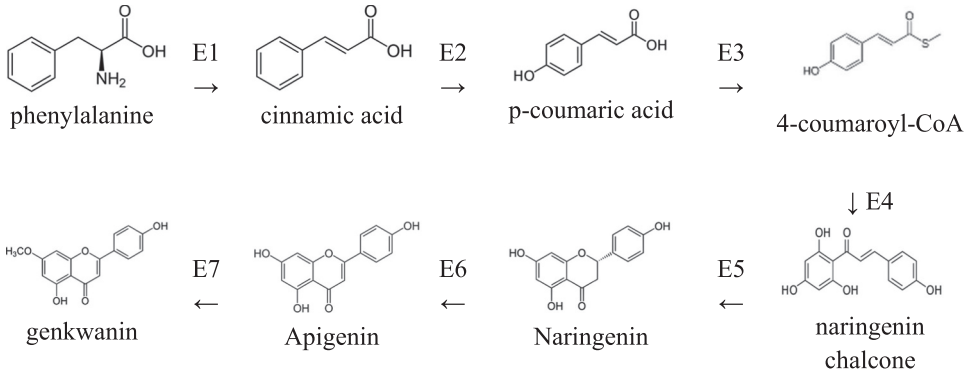

Fig. 2. Schematic representation of the genkwanin biosynthesis pathway. E1: phenylalanine ammonia lyase; E2: cinnamic acid 4-hydroxylase; E3: 4-coumarate—CoA ligase; E4: chalcone synthase; E5: chalcone isomerase; E6: flavone synthase; E7: flavonoid-7-*O*-methyltransferase.

Table 2
Genkwanin sources, extraction, isolation, and purification methods.

Source	Family	Plant matrix	Extraction methods	Isolation & purification methods	Ref.
Daphne gnidium L.	Thymelaeaceae	Stems	Maceration	HPLC	[16,17]
Rosmarinus officinalis L.	Lamiaceae	Roots, stems, flowers, leaves	Infusion	HPLC	[18–21]
Leonurus sibiricus L.	Lamiaceae	Leaves	Ultrasonic	HPLC^{1}H and^{13}C NMR	[23]
Salvia officinalis L.	Lamiaceae	Seeds	Maceration	HPLC/DAD	[23,24]
			Soxhlet	HPLC	[80]
Gochnatia pulchra Cabrera	Asteraceae	Aerial parts	Maceration	RP-HPLC	[29]
Vernonia fasciculata Nichx.	Asteraceae	Leaves	Not reported	NMR, IR, UV and MS	[40]
Eremanthus elaeagnus Schultz-Bip.	Compositae	Stem parts	Maceration	HPLC	[41]
Daphne genkwa Sieb. et Zucco.	Thymelaeaceae	Flowers	Maceration	Counter-current chromatography (CCC)	[66]
			Maceration	^{1} H- and^{13}C NMR	[56]
			Maceration	HPLC-ESI-MS NMR	[43]
			Not reported	Not reported	[79]
			Shaking	UHPLC-PDA-MS	[119]
Propolis		Not reported	Maceration	HPLC- UV	[44]
Ocimum basilicum L.	Lamiaceae	Leaves	Maceration	HPLC NMR	[45]
Baccharis trimera Less.	Compositae	Aerial parts	Infusion	HPLC NMR	[47]
Nepeta ssp.	Lamiaceae	Leaves	Infusion	HPLC-DAD	[50]
Artemisia afra Jacq. ex Willd.	Asteraceae	Not reported	Not reported	HPLC	[51]
				HPLC-UV-MS	[61]
Artemisia iwayomogi Kitam.	Asteraceae	Aerial parts	Maceration	Not reported	[53]
Rumex induratus Boiss. and Reuter.	Polygonaceae	Leaves and roots	Ultrasonic	HPLC-DAD-MS/MS-ESI	[57]
Alnus glutinosa (L.) Gaertn.	Betulaceae	Seeds	Soxhlet	HPLC^{1}H and^{13}C NMR	[58]
Combretum erythrophyllum (Burch.) Sond.	Combretaceae	Leaves	Infusion	RP-HPLC with DAD	[63]
Sidastrum micranthum (A. St.-Hil.) Fryxell	Malvaceae	Aerial parts	Maceration	HPLC^{1}H and^{13}C NMR	[72]
Aquilaria crassna Pierre ex Lecomte	Thymelaeaceae	Leaves	Maceration	–ESI–MS	[75]
				HPLC	[120]
Coleus forskohlii (Willd.) Briq	Lamiaceae	Roots	Not reported		[82]
Salvia aegyptiaca L.	Lamiaceae	Seeds	Infusion	HPLC analysis	[83]
Leonurus artemisia (Lour.) S.Y.Hu	Lamiaceae	Not reported	Decoction	HPLC/MS system	[84]
Teucrium ramosissimum Desf.	Lamiaceae	Aerial parts	Not reported		[85]
Phegopteris decursive-pinnata Fée	Thelypteridaceae	Leaves	Maceration	^{1} H and^{13}C NMR	[91]
Aquilaria sinensis (Lour.) Gilg.	Thymelaeaceae	Leaves	Ultrasonication	HPLC-UV	[134]
Mentha piperita L.	Lamiaceae	Leaves	Not reported	DESI-MSI	[95]
Callicarpa americana L.	Lamiaceae	Leaves	Maceration	NMR HRESIMS	[96]
Tinospora crispa Miers.	Menispermaceae	Whole plant			[98]
Moquiniastrum floribundum (Cabrera) G. Sancho	Asteraceae	Leaves	Not reported	HPLC-UV	[97]

various inflammatory disorders, including rheumatoid arthritis [144]. Additionally, another study revealed that in LPS-activated RAW264.7 macrophages, genkwanin inhibited the transcriptional and translational levels of inflammatory factors like iNOS, TNF-α, IL-1β, and IL 6 [4]. Mechanism studies showed that genkwanin upregulated mitogen-activated protein kinase phosphatase 1 (MKP-1) expression and decreased the expression of microRNA-101, p38, and JNK-mediated AP-1 signaling pathway.

Furthermore, anti-angiogenic blockers have become a novel option for rheumatoid arthritis management [145]. Genkwanin has been revealed to act as a potent anti-angiogenic agent, which inhibited the secretion of vascular endothelial growth factor (VEGF), endothelial intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), and matrix metalloproteinase-3 (MMP-3) factors by human umbilical vein endothelial cells [111].

On the other hand, Ni et al. [123] assessed the ability of genkwanin to protect mice against LPS-induced acute lung injury (ALI). Histopathological examination revealed that genkwanin (1 mg/kg) therapy reduced various pathology abnormalities induced by LPS, including lung edema, alveolar-capillary barrier failure, hyaline membrane development, and leukocyte infiltration in ALI mice. It suppressed LPS-induced IL-1β, IL-6, and TNF-α production while targeting the NF-κB pathway by decreasing p65 phosphorylation and IκB degradation. Genkwanin also down-regulated LPs-induced p38 MAPK phosphorylation, suggesting it is an innovative source of protective agent against acute lung injury [123].

Qin et al. [124] examined the beneficial activity of genkwanin against sepsis and its related mechanism in the cecal ligation puncture (CLP) mouse model. Genkwanin has been found to alleviate lung edema and inflammation in CLP mice. Immunoblot study shows that it lowers inflammatory lung injury by blocking the signaling pathway mediated by NF-κB. Moreover, the treatment with genkwanin at doses of 5, 10, and 20 mg/kg has been shown to enhance the liver damage induced by Aflatoxin B1, inhibiting the generation of COX-2, TNF-α, IL-1β, IL6 cytokines through NF-κB pathway [125].

Molecular docking simulation indicated that genkwanin had high interaction energy with human COX-1/2 enzyme as compared to non-steroidal anti-inflammatory medications, such as ibuprofen and mefenamic acid. In an effort to elucidate the possible anti-inflammatory effect of genkwanin and its related mechanisms in the treatment of rheumatoid arthritis, Bao et al. [99] carried out an investigation using adjuvant-induced arthritis (AIA) in mice model. The findings showed that genkwanin (10 mg/kg/day) considerably reduced paw inflammation, arthritis index in AIA mice, and bone damage in joint tissues (Fig. 4). It has also inhibited the production of NO, TNF-α, and IL-6 cytokines. Immunohistochemistry analysis revealed that in AIA rats, genkwanin inhibited the Janus kinase (JAK)/STAT and NF-B signaling pathways [99].

New findings revealed that genkwanin could prevent LPS-induced inflammatory bone destruction. Thus, in bone marrow macrophage cells, genkwanin treatment inhibited the expression of TNF-α and IL-6 in a dose-dependent manner. Furthermore, it reduced RANKL-promoted osteoclast formation by inhibiting the p38 and ERK/MAPK signaling pathway, which could be used in postmenopausal osteoporosis management [126].

4.3. Neuroprotective activity

Some investigations have reported that genkwanin exerts promising neuroprotective activities. Indeed, Li et al. [27] indicated that this typical bioactive flavonoid displays a neuroprotective action against 1-methyl-4-phenylpyridinium (MPP)+ triggered inflammatory

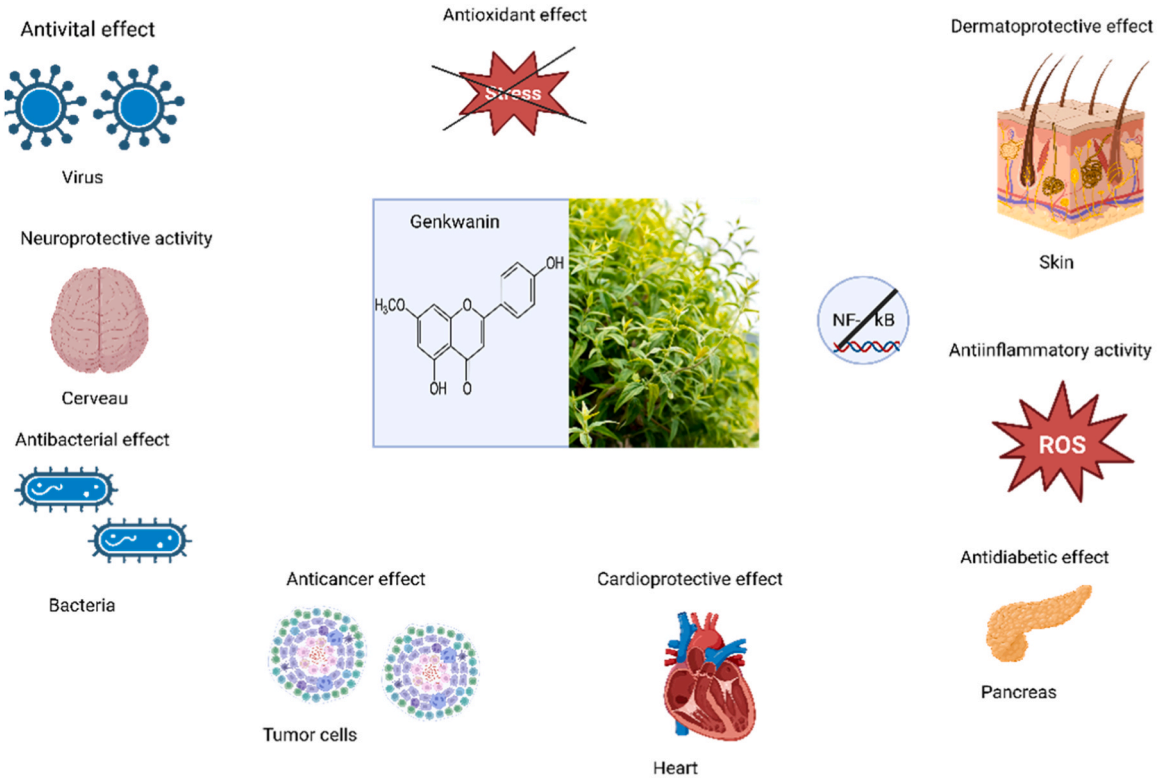

Fig. 3. Biological and pharmacological properties of genkwanin. This molecule represents one of the most highly regarded flavonoids among phenolic compounds, with a range of promising pharmacological properties. It has powerful anti-inflammatory, antidiabetic, antiradical, anticancer, immunomodulatory, cardioprotective, neuroprotective, dermato-protective, antibacterial, and antiviral effects.

responses, oxidative damage, and apoptosis in SH-SY-5Y cells. The treatment with genkwanin inhibited MPP+ -induced release of pro-inflammatory agents, such as prostaglandin E2 and COX-2, which up-regulate TNF-α, IL-1β, and IL-6 inflammatory cytokines in SH-SY5Y cells. Toll-like receptors (TLRs) are cell surface components known as pattern recognition factors that play a crucial function in controlling natural immune reactions [146]. TLR4 is one of the TLR proteins responsible for triggering inflammation related to Parkinson's disease [147]. It has been shown (Fig. 5) that genkwanin mitigated the over-expression of TLR4, myeloid differentiation primary response 88 (MyD88), and NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome-related proteins induced by MPP+ , providing a scientific basis on the potential application of this molecule in the management of Parkinson's disease [27]. On the other hand, using molecular docking simulation, Khandagale et al. [127] revealed that genkwanin showed a high degree of interactions with active site amino acid residues of acetylcholinesterase, as well as butyrylcholinesterase enzymes, suggesting their potential application as anti-Alzheimer's disease agents after experimental validation.

4.4. Anticancer activity

Several studies have demonstrated that genkwanin possesses promising anticancer activity against a variety of tumor cell lines, notably hepatocarcinoma, melanoma, leukemia, colon, breast, and lung cancer, suggesting its probable application in cancer pharmacotherapy (Table 4). Indeed, genkwanin demonstrated considerable anti-proliferative activity against human MCF-7 breast cancer (IC_{50} = 13.6 ± 0.3 μg/mL), HepG-2 human hepatocellular carcinoma (IC_{50} = 22.5 ± 0.3 μg/mL), and HCT-116 colon cancer cell lines (IC_{50} = 15.4 ± 0.5 μg/mL) compared to the anticancer drug cisplatin [28]. Moreover, using human HT-29 and SW-480 colon cancer cell lines, Wang et al. [35] revealed that genkwanin suppressed proliferation and cell growth and attenuated the synthesis and secretion of pro-inflammatory cytokine IL-8. The in vivo experiments indicated that genkwanin treatment reduced tumor size and progression, triggering inflammatory responses through down-regulating the expression of IL-1α, IL-1β, granulocyte -colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6 and IL-8 cytokines in APCMin/+ mice compared to untreated groups [35]. Genkwanin has been shown to exhibit significant anti-proliferative activity on B16F10 in a concentration-dependent manner. It promotes the arrest of the cell cycle at the G0/G1 stage and induces cell apoptosis [138]. Interestingly, Zhang et al. [36] investigated the ability of flavonoids, including genkwanin, to inhibit human breast cancer cell proliferation MDA-MB-231. As a result, genkwanin significantly inhibited cell growth and proliferation (Fig. 6). By investigating the underlying mechanisms, the outcomes demonstrated that genkwanin caused cell cycle arrest at the G2/M phase by lowering the expression levels of the proteins cyclin-dependent kinase 2 (Cdc2) and cyclin B1. It promoted cell apoptosis through down-regulation of poly [ADP-ribose] polymerase 1 (PARP1), B-cell lymphoma-2 (Bcl-2), and B-cell lymphoma-extra large (Bcl-xL) proteins and enhanced levels of caspase-3 that has been cleaved by p53 in MDA-MB-231 cells [94]. Moreover, genkwanin induced cell autophagy-mediated degradation of p62. Genkwanin inhibited the expression of phosphoinositide 3-kinase (PI3K)γ-p110, phospho-PI3K, phospho-protein kinase B (AKT), phospho-p70S6K, phospho-mammalian target of rapamycin (mTOR), and phospho-ULK signaling pathways. The molecular docking simulation also indicated that this molecule interacts in the ATP binding pocket of PI3Kγ [94].

Targeting the PI3K/Akt signaling pathway, genkwanin decreased lung cancer cell migration, invasion, and proliferation, suggesting a new and effective option for the treatment of cancer proliferation and metastasis [114]. Furthermore, Leu and his colleagues [104] examined the anticancer activity of hydroxygenkwanin extracted from *Daphne genkwa* and illustrated the underlying mechanism of action using the

Table 3
Anti-inflammatory effects of genkwanin.

Experiment	Results and Mechanisms	Ref.
In vitro - LPS-activated RAW264.7 macrophages	- ↓ pro-inflammatory mediators (iNOS, TNF-a, IL-1b, IL- 6) - ↓ p38- and JNK-mediated AP-1 signaling pathway - ↑ MAPK phosphatase 1 (MKP-1) expression - - ↓ miR-101 production, a negative regulator of MKP-1 expression	[28]
In vitro - human intestinal epithelial cells In vivo - C57BL/6 male mice	- ↓ ROS production, oxidative stress - ↓ proinflammatory cytokines (TNF-α, IL-1β, IL-6) - ↑ mitochondrial function - - ↑ SIRT1 expression	[35]
In vitro - LPS-induced RAW 264.7 macrophages and ConA-induced T lymphocytes	- ↓ NO, iNOS, TNF-α, IL-6, IFN-γ, IL-2 expressions - ↓ phosphorylation levels of IKK, IκB, and NF-κB - ↓ expressions COX-2 and IL-6 mRNA - - ↓ NF-κB pathway	[64]
In vitro - LPS-induced RAW 264.7 macrophages	- ↓ VCAM and MMP-3 - - ↓ VEGF and ICAM	[138]
LPS-induced acute lung injury in mouse model	- -↓ lung edema, alveolar-capillary barrier dysfunction - ↓ NF-κB pathway activation - - ↓ p38 MAPK phosphorylation	[73]
In vivo - male Sprague Dawley mice	- ↓ TNF-α, IL-6, IL-1β levels - ↓ lung edema and inflammation - - ↓ NF-κB pathway	[104]
In vivo - aflatoxin-induced hepatotoxicity in male albino rats	- ↓ TNF-α, IL-6, IL-1β levels - ↓ COX-2 activity - - ↑ antioxidative and anti-inflammatory potential	[118]
In vivo - adjuvant-induced arthritis (AIA) rats	- ↓ TNF-α, IL-6, NO levels - ↑ IL-10 concentration - - ↓ JAK/STAT and NF-κB pathways	[94]
In vitro - bone marrow macrophages (BMMs) from C57 mice *In vivo* - C57BL/6 mice	- ↓ TNF-α, IL-6 levels - ↓ osteoclast differentiation via p38/c-Fos/NFATc1 signaling pathway inhibition - - ↓ RANKL-induced osteoclastogenesis	[126]

non-small cell lung cancer (NSCLC) and xenograft mice model. With IC_{50} values of 22.0 ± 0.9 μM, 18.3 ± 3.1 μM, and 18.3 ± 0.3 μM, the findings demonstrated that hydroxygenkwanin has significant anticancer action against A549, PC9, and H1975 cells, respectively. Flow cytometry analysis showed that hydroxygenkwanin disturbed cell cycle progress only in H1975 cell lines [104]. Moreover, the authors indicated that the anticancer potential of hydroxygenkwanin was mediated via its ability to induce cell apoptosis through the cleavage of PARP and caspase 9 in NSCLC. Hydroxygenkwanin at a dose of 1.0 mg/kg body weight has also shown a significant antitumor effect on xenograft mice, which reduced tumor growth and progression [104]. When exposed to genkwanin for 48 h at a concentration of 70 μM, B16F10 melanoma cells showed strong anti-proliferative activity, with apoptotic cell percentage increasing from 52% [138]. Additionally, genkwanin inhibited tyrosinase activity and reduced melanin synthesis in a dose- and time-dependent manner.

4.5. Antibacterial effect

The antibacterial activity of genkwanin has been reported in several studies (Table 5). Genkwanin isolated from *Gochnatia pulchra* inhibited the growth of *S. pyogenes* and *E. faecalis*, with minimum inhibitory concentration (MIC) values of 100 and 25 μg/mL, respectively [29]. In another study, the MIC of genkwanin derived from *Crythrophyllum* was discovered to be 0.05 mg/mL against *E. faecalis* [30].

Based on the microplate culture assay, at concentrations below 200 μM, the effect of flavonoids on *E. coli* O157:H7 growth appeared to be bacteriostatic instead of bactericidal. Moreover, according to the LAL test, genkwanin exhibited a greater suppression action on the production of LPS by the cells than other flavones tested. It decreased LPS levels by 61.18 ± 1.1% (control). Hence, it had an effect on the pathogenicity of *E. coli* O157:H7 [70]. In addition, the antimicrobial activity of *Daphne gnidium* stem methanol extract was evaluated against six isolated Gram (±) bacteria. Genkwanin has proven to be effective against *S. aureus* and *B. lentus*. It was more toxic than the crude extract [48].

Maia et al. demonstrated that of the six flavones derived from *Praxelis clematidea* and tested against a *Staphylococcus aureus* SA-1199B strain with NorA efflux pump effect, only the most methoxylated demonstrated the strongest efflux pump inhibition [74]. Nevertheless, compared to the other compounds, genkwanin showed less antibacterial

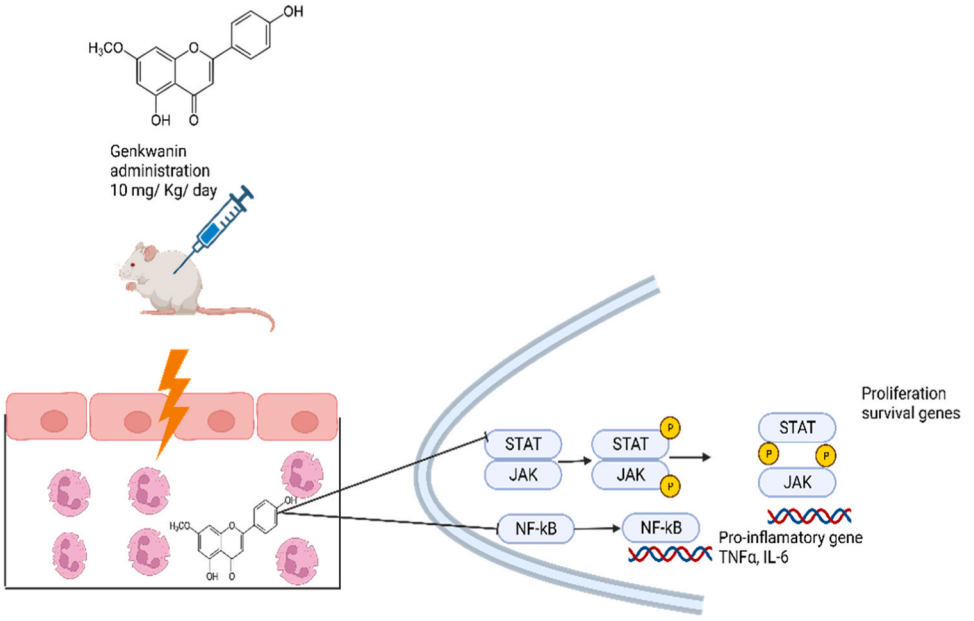

Fig. 4. Representation of the anti-inflammatory mechanisms of genkwanin in the treatment of rheumatoid arthritis. *Genkwanin has the potential to substantially decrease paw inflammation* via *the JAK/STAT and NF-κB signaling pathways using a murine model of adjuvant-induced arthritis. Genkwanin markedly diminished both arthritis index and paw swelling in rats with adjuvant-induced arthritis and also diminished inflammation and bone damage in articular tissues. TNF-α and IL-6 serum levels were significantly downregulated by genkwanin administration (10 mg/Kg/day). Abbreviations: JAK: Janus kinase; STAT: signal transducer and activator of transcription protein; TNF-α: tumor necrosis factor-α; IL-6: Interleukin-6.*

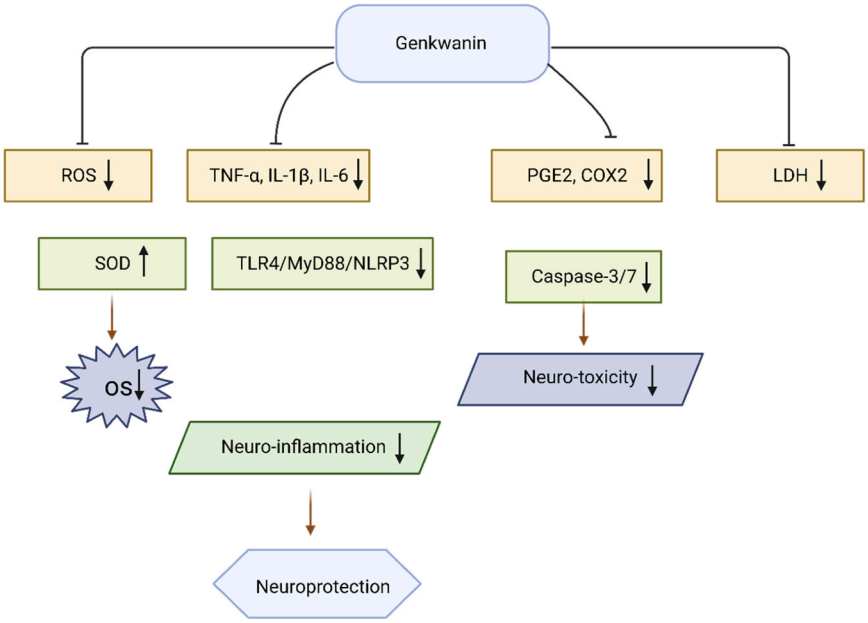

Fig. 5. Schematic illustration of the neuroprotective activity of genkwanin. *This compound alleviates neuroinflammation and neurotoxicity by inhibiting the TLR4/MyD88/NLRP3 inflammasome pathway, resulting in neuroprotection against neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. The molecule reduced levels of lactate dehydrogenase (LDH) release, caspase-3/7 activity, prostaglandin E2 (PGE2) secretion, tumor necrosis factor (TNF)-α, interleukin (IL.)−1β and IL-6. It also decreased protein levels of cycloxygenase-2 (COX-2), Toll-like receptor 4 (TLR4), myeloid differentiation factor 88 (MyD88), and NOD-like receptor (NLR) protein 3 (NLRP3).*

activity. Martini et al. confirmed that seven flavones, including genkwanin, isolated from *Combretum erythrophyllum* leaf extracts, were reported to have antibacterial activity [55]. Yu et al. [148] used an assay to determine the mode of action of genkwanin presented in *Aquilegia oxysepala* against antimicrobial resistance. HPLC/DAD/ESI-MS0 was used to obtain the metabolic characteristics of *S. aureus* processed with nine antibiotics and *A. oxysepala*. It was found that genkwanin suppressed the growth of *S. aureus*, possibly targeting nucleic acid [148]. Genkwanin also disclosed strong antibacterial activity against *Micrococcus luteus*, *Vibrio cholera*, *Enterococcus faecalis*, and *Shigella sonei* [149].

4.6. Antidiabetic effect

Diabetes mellitus is a chronic metabolic disease closely linked to the epidemic of obesity. It occurs when the body cannot adequately utilize the insulin produced by the pancreas or when there is insufficient insulin production [129]. As an antidiabetic factor, genkwanin has the ability to prevent the breakdown of dietary carbohydrates (Table 6). The enzyme α-amylase is crucial to this process. In this context, Muhammad et al. confirmed these results using simulation of molecular dynamics, molecular docking, ADMET, and MMPBSA testing [31]. They showed that genkwanin has a good binding score of − 8.9 kcal/mol and interacted with a catalytic triad of α-amylase and Glu 233. According to Gaspersz et al., genkwanin has shown the best results in alpha-amylase enzyme inhibition with a binding affinity of − 8.3 kcal/mol [38]. Moreover, Qiu et al. [39] and Tang et al. [150] suggested that the cellular biotransformation of *Ginkgo biloba* extract (GBE) in H.G. was markedly dissimilar to that in N.G., suggesting that the screened components, including genkwanin, could be relevant in GBE with an effect to prevent diabetic nephropathy.

Furthermore, genkwanin could activate glucokinase, an enzyme that acts as a glucose sensor, increasing insulin release when blood glucose levels grow and playing an essential function in carbohydrate metabolism management. The stable ligand energy of genkwanin was 206.69 kcal/mol, and it had a binding free energy of 7.5 kcal/mol with the glucokinase enzyme. It interacted hydrophobically with ILE159, VAL455, ALA456, LYS459, VAL62, PRO66, and VAL452. Glucokinase activators might be useful in treating type 2 diabetes [151].

A new investigation revealed that *Phaleria nisidai* leaf extract containing genkwanin glycosides improved insulin sensitivity, stimulated glucose uptake into adipocytes, and ameliorated glucose homeostasis comparably to metformin. *Phaleria nisidai* extract promoted insulin-independent glucose absorption and enhanced the regulation of glucose homeostasis, thus being a promising glucoregulatory phytochemical [152].

4.7. Antiviral effect

The antiviral effect of genkwanin was reported in several studies [102,106,117,153]. Indeed, genkwanin-6-C-beta glucopyranoside was recognized by Mohammed et al. [153] as a substance that could act as a newly developed antiviral agent for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) [153]. It showed the highest binding affinity for nsp10, a closer binding affinity (-37.4 ± 1.3 Kcal/mol), and presented high bioactivity with no toxicity. It is an effective substance that prevented the nsp10-nsp16 interaction, and its low IC_{50} (0.029–0.035 M) suggested that it could exhibit great effectiveness as a target protein inhibitor. All of these characteristics show that genkwanin-6-C-beta-glucopyranoside is a naturally occurring substance that may attack the SARS-CoV-2 nsp10-nsp16 complex interaction interface. In addition to ASFV Ba71V, genkwanin also showed significant antiviral activity against a highly virulent ASFV isolate that is currently spreading in China and Europe [102]. It inhibited viral DNA and protein synthesis, targeted viral entry and exit stages of infection, and prevented the reproduction of the extremely pathogenic ASFV isolate. Thus, it may be a candidate for antiviral drug development. Another in vitro study showed that genkwanin could be effective against COVID-19. Through interactions that control the catalytic dyad (Cys-145, His-41) of SARS-CoV-2 3CLpro, it might target 3CLpro and interfere with the SARS-CoV-2 3CLpro protease activity [117]. Moreover, the use of structure-based approaches allowed the preselection of genkwanin, which featured stronger inhibitory properties against the coronaviruses compared to Remdesivir [106].

4.8. Dermato-protective effect

The dermato-protective activity of genkwanin was evaluated using several methods. According to kinetic analysis docking studies, genkwanin was a noncompetitive inhibitor of tyrosinase and could not bind with the active site of the enzyme. Compared to the positive control, this compound showed a modest tyrosinase inhibitory effect [107]. In a

Table 4
Anticancer effects of genkwanin.

Cell Lines	Key Results	Ref.
MCF-7, HepG-2 and HCT-116 cancer cell lines	Showed significant cytotoxic effects MCF-7 cells: $IC_{50} = 13.6 \pm 0.3$ μg/mL HepG-2 cells: $IC_{50} = 22.5 \pm 0.3$ μg/mL HCT-116 cells: $IC_{50} = 15.4 \pm 0.5$ μg/mL	[28]
HT-29 and SW-480 cell lines APCMin/+ mice	Suppressed cell growth and proliferation Attenuated IL-8 release Exhibited in vivo antitumor activity through modulating inflammatory responses	[35]
Human MCF7 and MDA-MB-231 breast cancer cells	Inhibited cell proliferation Arrested cell cycle at G2/M phase Stimulated apoptosis autophagy by up-regulating p53 and downregulating Bcl-2 and Bcl-xL proteins Showed to bind in PI3K's ATP-binding pocket by molecular docking modeling	[94]
MDA-MB-468 breast cancer cells	Showed a strong anti-proliferative effect related to CYP1 family-mediated metabolism	[64]
K562 Human chronic myelogenous leukemia cell line	$IC_{50} = 225$ μg/mL	[73]
A549 NSCLC cell line	$IC_{50} = 91.64 \pm 11.0$ μg/mL Exhibited potent anticancer activity Induced cell apoptosis through cleavage of PARP and caspase 9	[104]
MCF7 and MDA-MB-231 cell lines	Showed important cytotoxic effects against both cells Exhibited consistent drug release characteristics Showed similar therapeutic effectiveness as paclitaxel in vivo	[118]
Human A549 and H69AR lung cancer cell lines	Inhibited lung cancer progression by suppressing proliferation Restrained cell migration and invasion via PI3K/Akt pathway	[114]
MDCK-II cellosaurus cell line	Exhibited a strong inhibitory effect (> 50%) on BCRP in BCRP-MDCKII cells by reducing the BCRP-mediated efflux of doxorubicin and temozolomide, which in turn increased the cytotoxicity of those drugs	[101]
B16F10 melanoma cells	Inhibited cell proliferation Arrested the cell cycle at G0/G1 phases Induced apoptosis	[138]

recent study, RBL-2H3 cells from *Stellera chamaejasme* demonstrated in vitro antiallergic action [103]. Genkwanin was the most effective inhibitor of -hexosaminidase release among the 11 isolated compounds in immunoglobulin E (IgE)/DNP-BSA-induced RBL-2H3 cells.

When applied to a 2, 4-dinitrochlorobenzene (DNCB)-sensitized mouse model of atopic dermatitis (A.D.), stechamone (genkwanin 5-O-xylosyl (12) glucoside) was found to have anti-atopic effects [154]. Stechamone reduced the production of β-hexosaminidase and IL-4 in RBL-2H3 cells. Additionally, the study showed that administering therapy with 0.5% stechamone for 14 days substantially decreased the symptoms of atopic dermatitis by safeguarding skin barrier functions, preventing DNCB-induced spikes in serum IgE and IL-4 levels, and preventing DNCB-induced changes in histopathology. In mice treated with DNCB, transdermal stechamone administration (0.5%) diminished the number of mast cell densities in the dermis, enhanced skin hydration by 26.7%, and lowered TWEL by 23.1%. Jung et al. used an in vitro model system to examine the preventive effects of different methoxy flavonoids, including genkwanin, on markers of skin photoaging [86]. According to their results, genkwanin presented no effect on cell (keratinocyte) viability up to 20 M, no influence on MMP-1 protein level, and no appreciable inhibitory effect on MMP-1 mRNA expression induced by UV-B.

5. Pharmacokinetic investigations

The absorption and bioavailability of the flavonoids deserve special attention. Only small quantities are absorbed in the upper gastrointestinal tract, while the largest amount is metabolized by the gut microbiota in the lower gastrointestinal tract. Flavones, same as other flavonoids, are rapidly absorbed and excreted in the urine, resulting in low bioavailability [155,156]. The main metabolic pathways of genkwanin are demethylation, hydroxylation, and o-glucuronidation [157].

Consequently, in vivo, studies currently focus on improving their bioavailability via particle formulations or food processing [158]. The pharmacokinetic study of genkwanin was investigated by Wei et al. [87]. Using UPLC-ESI-MS/MS results exposed that t 1/2 of genkwanin in rats was 3.07 ± 0.90 h and AUCs was 218 ± 40 ng h/mL. On the other hand, using HPLC-MS/MS assay to study the pharmacokinetics of this compound after being administered to mice orally and intravenously, genkwanin was shown to be insufficiently absorbed, with an absolute bioavailability of only 1.1% [78].

The maximum concentration in plasma (Cmax) was 36.9 ± 9.4 ng/mL, and the area under the curve (AUC0–12 h) was 218 ± 40 ng h/mL for the oral administration, while for intravenous administration, Cmax and AUC0–12 h were 1755 ± 197 ng/mL and 2349 ± 573 ng h/mL, respectively. Using the same method, Tao et al. studied the bioavailability of genkwanin in mice following oral ingestion of a crude and vinegar-treated extract of *Daphne genkwa* and showed that vinegar-processing enhanced the bioavailability of this compound with AUC0 −t 692.77 ± 145.43 ng h/mL and Cmax 659.09 ± 64.14 ng/mL [93]. Jiang et al. investigated the absorptive transport behavior of genkwanin by single-pass intestinal perfusion of rats [81]. They found that this molecule was absorbed throughout the whole human intestine, with the duodenum serving as the primary absorption site and having an effective permeability coefficient of 1.97×10^{-4} cm/s and an absorption rate constant of 0.62×10^{-2} s^{-1}. Moreover, the permeability obtained by the co-administration of probenecid showed that the transport of genkwanin in the gut wall involves both passive diffusion and MDR-mediated efflux pathways.

Recently, genkwanin nanosuspensions prepared using D-alpha tocopherol acid polyethylene glycol succinate as a stabilizer revealed stronger in vitro cytotoxicity against MCF-7, MDA-MB-453, HeLa, HepG2, BT474, and A549 cells compared to free genkwanin. Moreover, the genkwanin nanosuspensions showed antitumor potential in MCF-7 tumor-bearing nude mice with very low toxicity [89]. The study of Ao et al. confirmed these outcomes [108].

Similarly, genkwanin using lipid nanoparticles as a drug delivery carrier exhibited higher solubility, intestinal permeability, oral bioavailability, and excellent anti-colitis-associated colorectal cancer activity [93].

6. Concluding remarks and perspectives

Based on the findings highlighted in this review, it is believed that genkwanin, as a natural compound, is endowed with a wide range of biological activities and pharmacological properties such as antioxidant, anti-inflammatory, neuroprotective, anticancer, antibacterial, and antidiabetic activities. Due to its powerful antioxidant properties, genkwanin is a potential candidate for protecting cells against oxidative stress-related damage. Additionally, this flavone has proven to be a potential anti-inflammatory agent due to its effective action against pro-inflammatory mediators, including the cytokines TNF-α, IL-1β, IFNγ and IL-6, inhibition of ROS production, or down-regulation of microRNA-101, the AP-1 signaling pathway mediated by p38 and JNK. Also, genkwanin, to our knowledge, is the first chemical obtained from a plant source to demonstrate that its anti-inflammatory effects are primarily due to a reduction in miR-101 production. Given that it has been demonstrated to inhibit tumor development and proliferation and to promote the apoptosis of cancerous cells, genkwanin's anticancer effect

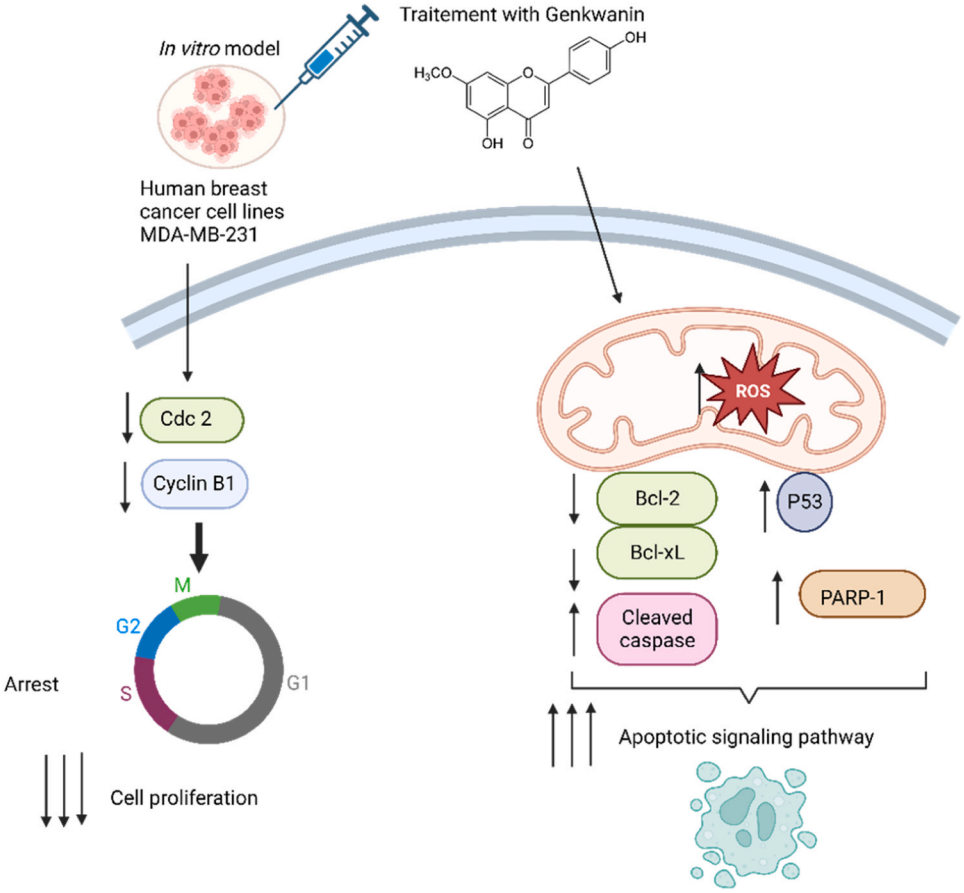

Fig. 6. Schematic illustration of the molecular pathways involved in the inhibition of cell proliferation and induction of apoptosis by genkwanin against human breast cancer cell lines. *Genkwanin promotes cell cycle arrest at the G2/M phase in MDA-MB-231 cells by controlling expression levels of Cdc2 and cyclin B1. It also induces cell apoptosis by down-regulating PARP1, Bcl-2, and Bcl-xL proteins and increasing levels of caspase-3, which has been cleaved by p53.Abbreviations: Cdc2: cyclin-dependent kinase 2; PARP1: poly [ADP-ribose] polymerase 1; Bcl-2: B-cell lymphoma-2; Bcl-xL: B-cell lymphoma-extra-large.*

Table 5
Antibacterial effect of genkwanin.

Methods	Tested strains	Key Results	Ref.
Broth microdilution method	*S. pyogenes* *E. faecalis*	MIC = 100 μg /mL MIC = 25 μg /mL	[29]
Broth microdilution method	*E. faecalis*	MIC = 0.05 mg /mL	[30]
The microplate culture method LAL test	*E. coli O157:H7*	Viable cells (CFU/mL) = (2.4 ± 0.5)× 108 LPS value (×104 EU/mL) = 0.88 ± 0.02	[70]
Agar dilution method	*S. aureus* *B. lentus*	MIC = 100 μg /mL MIC = 100 μg /mL	[48]
NorA efflux pump activity Methoxylated genkwanin	*S. aureus SA-1199B*	Norfloxacin: MIC= 64 (2 ×) Ethidium bromide: MIC= 16 (2 ×) Pefloxacin: MIC= 16	[74]
Protein-fragment Complementation (PCA) Assay	*S. aureus*	Genkwanin (concentration 500, 250 μg/mL) has a target on nucleic acid	[148]
Serial dilution microplate assay	*E. faecalis* *P. aeruginosa* *Vibrio cholerae* *Shigella sonei* *Escherichia coli* *Micrococcus luteus* *Bacillus subtilis*; *Aspergillus niger*; *S. aureus*; *Klebsiella pneumonia*; *Salmonella typhimurium*	MIC = 50 μg /mL MIC = 100 μg /mL MIC = 50 μg /mL MIC = 25 μg /mL MIC = 100 μg /mL MIC = 50 μg /mL MIC > 100 μg /mL	[149]

Table 6
Antidiabetic effects of genkwanin.

Model	Key Results	Ref.
Silico Molecular Docking study	Binding score of −8.9 kcal/mol Hydrogen bond: GLU 233	[31]
Silico study: Molecular Docking approach.	Binding affinity of-8.3 kcal/mol Interaction alpha amylase-Genkwanin: Hydrogen bond: GLU 233 Carbon hydrogen: TRP59, TYR 62, ASP 300, HIS 305	[38]
ESI–MS/MS ionization/ detection	Matrix effect of Genkwanin = 103.4 ± 0.9% The 24-hour Tmax of genkwanin in the GBE-HG group remains unchanged	[39]
Molecular Docking	Binding score of −7.5 kcal/mol Energy of the stable ligand of 206.69 kcal/mol	[151]

is particularly remarkable. As a result, it is a strong option for cancer management, whether administered alone or in combination with other drugs. The potential application of this bioactive substance in treating neurodegenerative illnesses like Parkinson's and Alzheimer's may be advantageous due to its neuroprotective characteristics. Additionally important are the cardioprotective properties of genkwanin, which may lower the risk of cardiovascular disease, one of the main causes of morbidity and mortality worldwide. Consequently, genkwanin can improve well-being, extend life and contribute to anti-aging actions by reducing levels of ROS and inflammatory cytokines, blocking the NF-κB signaling pathway and carcinogenesis, and modulating enzymes involved in neurological function.

Genkwanin's potential as a treatment for inflammatory diseases or its potential underlying mechanisms are both little understood. Besides, genkwanin, a low-toxicity and generally accessible class of flavonoids,

has a wide range of positive effects on human health, as well as specific antitumor actions. However, their low oral bioavailability and solubility have severely limited subsequent in vivo research. The outlook from this analysis underlines the necessity of further studies on genkwanin to fully understand its mechanisms of action and potential therapeutic uses. Efforts should also be undertaken to increase its bioavailability and effectiveness. The genkwanin nanoparticles approach may be applied to antitumor flavonoids to generate new and effective antitumor drugs. On the other hand, clinical trials are also needed to investigate both the effectiveness and safety of genkwanin in humans. Future research will advance our knowledge of genkwanin's beneficial properties and help us to develop strategies for the prevention and management of inflammatory disorders and oxidative stress.

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Declaration of Competing Interest

None.

Data Availability

No data was used for the research described in the article.

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