https://www.nmb-journal.com

Nano Micro Biosystems

Online ISSN: 2980-8057

Anticancer, antimicrobial, cardioprotective, and neuroprotective activities of luteolin: A systematic-narrative mini-review

Danial Kahrizi[1*] and Shadieh Mohammadi[2]

[1]*Department of Plant Production and Genetics, Faculty of Agriculture, Razi University, Kermanshah, Iran*

[2]*Environmental Health Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Kurdistan, Iran*

ARTICLE INFO

Mini-review paper

Article history:
Received: 25 June 2023
Revised: 08 Aug 2023
Accepted: 09 Aug 2023
ePublished: 10 Aug 2023

Keywords:
Phytoactive compound, Breast cancers, Alzheimer's disease, Hypertension, PubMed database

ABSTRACT

Luteolin is a flavone subclass of flavonoids usually available as glycosylated forms in plant species. The low aqueous solubility or bioavailability of this herbal compound is the dominant limitation for its clinical formulation. The benzylation of the hydroxy groups at 7-, 3′- and 4′- positions improves the oral bioavailability of this phytoactive compound. We systematically searched the biomedical database of PubMed to categorize related studies about luteolin with antimicrobial, anticancer, cardio protective, and neuroprotective activities from 1946 to May 2023. Literatures were analyzed based on data extracted from PubMed, an online, researchable database. The minimum and maximum number of publications was indicated respectively for antifungal and anticancer activities of luteolin in 2021-2022. In the case of cancers, breast and lung cancers have demonstrated a higher number of publications compared to prostate and uterine cancers. Moreover, luteolin has been evaluated significantly for Alzheimer's disease and hypertension.

DOI: https://doi.org/10.22034/nmbj.2023.403963.1022

1.Introduction

Understanding the therapeutic effects and the cellular and molecular mechanisms of bioactive compounds can result in the possibility of new drug design [1-4]. Luteolin ((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one); $C_{15}H_{10}O_6$) is a flavone related to flavonoids isolated from a wide spectrum of vegetables and fruits (Figure 1). This bioactive compound displays a variety of biomedical activities [5, 6]. However, luteolin is a hydrophobic metabolite with poor bioavailability and bioactivity as the main hindrance to obtaining effective formulations [7]. Many studies have been carried out for evaluating the antibacterial, antifungal, antiviral, anticancer, cardioprotective, and neuroprotective of this tetrahydroxyflavone compound [8-10]. In this systematic-narrative mini-review, PubMed was used as a free database supporting the search of life sciences and biomedical literatures. In addition, cellular, molecular, and biochemical mechanisms of antibacterial, antifungal, antiviral, anticancer, cardioprotective, and neuroprotective activities of luteolin based on recent scientific literature have been presented.

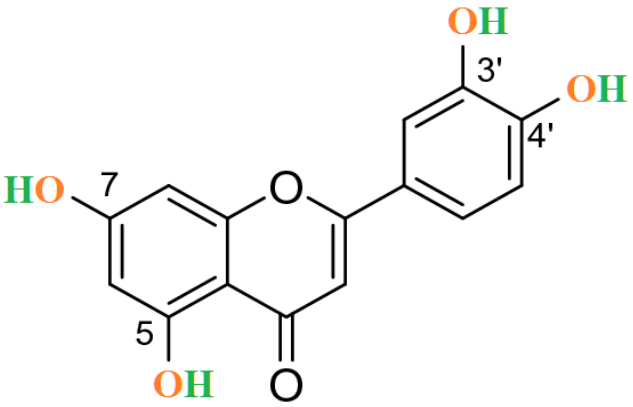

Fig. 1. Chemical structure of luteolin (adapted and modified from [7]).

2. Materials and Methods

2.1. Search strategy

Literature in different years was analyzed systematically based on studies, which were published until May 2023. All data have been

*Corresponding author. E-mail: d.kahrizi@cellmolbiol.org

extracted from PubMed, an online biomedical database. Several keywords related to luteolin with anticancer, antibacterial, antiviral, antifungal, cardioprotective, and neuroprotective were selected for this study. In the first step, the search was carried out by different combinations of the following keywords: "luteolin", "luteolin, virus, AND antiviral", "luteolin, bacteria, AND antibacterial", "luteolin, fungi, AND antifungal" (d), "luteolin, cancer, AND anticancer", "luteolin AND cardioprotective", and "luteolin AND neuroprotective". In the second step, additional information was collected according to keywords of "luteolin AND prostate cancer", " luteolin AND lung cancer", "luteolin AND breast cancer", "luteolin AND uterine cancer", "luteolin AND *Escherichia coli*", "luteolin AND *Staphylococcus aureus"*, "luteolin AND multidrug-resistant bacteria", "luteolin AND *Aspergillus niger*", "luteolin AND coronary heart disease", "luteolin AND hypertension", "luteolin AND Alzheimer", "luteolin AND Parkinson", and "luteolin AND multiple sclerosis".

3. Results and discussion

As illustrated in figures 2a-g, there are an increasing pattern of studies about the therapeutic applications of lutein with the peaks in years 2021 and 2022. The least and more investigations were observed for antifungal (Figure 2d) and anticancer (Figure 2e) activities in 2021-2022.

3.1. Anticancer activity

The number of publications of the most common cancers in men and women including prostate, lung, breast, and uterine cancers has been opted in different year ranges (Figures 4a-d). Cancer, a dangerous invasive disease characterized by the abnormal cell growth and proliferation, which is increasing each year [11]. The disadvantages related to the conventional chemotherapy drugs, such as severe side effects, have led to cancer therapeutic investigation for design and discover alternative anticancer agents with suitable biocompatibility toward normal cells [12]. Pharmacokinetic studies show that the more prominent part of luteolin is conjugated after intestinal absorption [13]. Luteolin can interact with the bovine serum albumin (BSA) via electrostatic forces and its oxidovanadium (IV) complex bind the protein by van der Waals and H bonding with antioxidant and anticancer activities [14]. Luteolin regulate apoptosis, autophagy, angiogenesis, cell cycle progression, metastasis, and epithelial–mesenchymal transition in cancer cells. Luteolin can induce apoptosis in cancer cells by regulation of both extrinsic and intrinsic apoptotic pathways (Figure 3) [15]. A combination therapy based on luteolin and quercetin combined with 5-Fluorouracil (5-FU) inhibited the growth of HT-29 human colorectal cancer cells. Gene expression levels of PTEN (phosphatase and tensin homolog deleted on chromosome ten), p38 MAPK (mitogen-activated protein kinases), Bax, and p53 increased compared with the control group by values of 3.29, 3.26, 1.42, and 1.71-fold under 5-FU + luteolin therapy, respectively. In addition of vascular endothelial growth factor (VEGF) was decreased by this combination therapy [16].

Breast and lung cancers with 64 and 48 counts, respectively in the years 1992-2023 and 2004-2023 have shown higher number of publications than prostate (18) and uterine (10) (Figures 4b and c). Luteolin derivatives may be synthesized to enhance therapeutic outcomes. The benzylation of the hydroxy groups at 7-, 3′- and 4′- positions can improve the lipophilicity and bioavailability of luteolin. In a comparative study, ten different mono-acyl (nine 5-O-acyl and one 7-O-acyl) derivatives of luteolin (Figure 1) hindered the proliferation of MDA-MB-231 breast cancer and HCT116 colon cancer cell lines [7].

3.2. Antimicrobial activity

E. coli and *S. aureus* were respectively common Gram-negative and Gram-positive bacteria, which have been used to evaluate the antibacterial activity of luteolin or plant extract containing luteolin. In 2020, there were 10 studies for *E. coli* compared to 12 studies for *S. aureus* (Figures 5a and b). As shown in Figure 5 c, there were 4 studies in 2014 compared to 3 studies in 2023 for luteolin metabolite against multidrug-resistant bacteria. Considering antifungal activity, there were 5 studies for *A. niger* (Figure 5d). In a comparative study, antibacterial and antifungal activities of luteolin-7-O-glucoside compared to methyl angolensate were assessed

against various types of bacteria and fungi. At a concentration of 400 µg/disc, *E. coli*, *S. aureus*, *A. niger*, and *Aspergillus fumigatus* showed inhibition zone diameters (IZDs) of 11, 10.4, 14.6, and 17.5 mm, respectively [17].

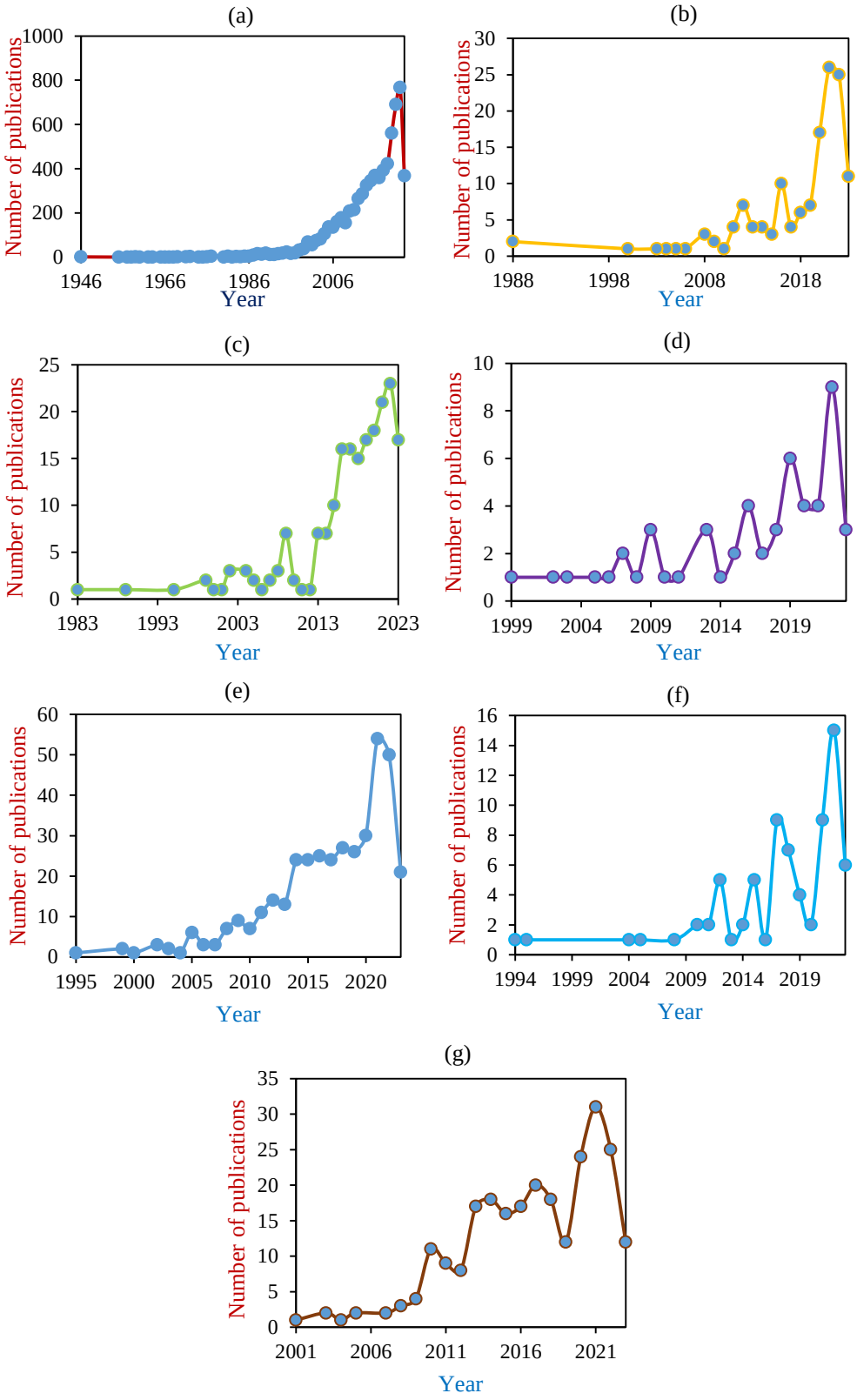

Fig. 2. Number of publications per year for keywords of "luteolin" (a), "luteolin, virus, and antiviral" (b), " luteolin, bacteria, and antibacterial" (c), "luteolin, fungi, and antifungal" (d), "luteolin, cancer, and anticancer" (e), "luteolin and cardioprotective" (f), and "luteolin and neuroprotective" (g) (Source: PubMed).

3.3. Cardioprotective activity

Cardiovascular diseases can lead to high levels of mortality and morbidity worldwide. Luteolin or plant extracts with luteolin have been tested for coronary heart disease and hypertension. 59 and 25 publications were identified by the PubMed database for “luteolin AND hypertension” and “luteolin AND coronary heart disease” keywords, respectively (Figures 6a and b). Luteolin has cardioprotective activity by several extrinsic and intrinsic effectors. Activation of anti-apoptosis key protein kinase B or Akt (PKB/Akt; Akt kinases lead to cell survival both indirectly and directly by promoting growth factor), blocking of oxidative stress through heme oxygenase-1 (HO-1), improvement of cardiomyocyte function by regulating MAPKs family, regulation of nitric oxide and nitric oxide synthases isozymes, improvement of systolic and diastolic function of cardiomyocytes via the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a (SERCA2a), increase autophagy by MST1 (mammalian STE20-like kinase 1) inhibition, protection of cardiac remodeling by restoring angiotensin II-induced pro-fibrotic cytokine TGF-β1 (transforming growth factor beta 1) expression, inhibiting proliferation and migration of vascular smooth muscle cell, and suppressing inflammatory response [1].

3.4. Neuroprotective activity

Neuroinflammation results to cognitive defects, neurodegeneration, and neurodegenerative diseases by activation of neurons, neuroimmune cells, and glial cells in the brain to release various neuroinflammatory mediators [18]. Pretreatment by luteolin at a concentration of 10 μM significantly protected cortical cell lines against amyloid β (Aβ) (25–35)-induced neurotoxicity [19]. Luteolin restored the level of malondialdehyde and the activity of glutathione peroxidase, and decreased the intracellular reactive oxygen species level and augmented the translocation of Nrf2 to the nucleus *in vitro* and *in vivo* [20]. Luteolin inhibits neuroinflammatory and systemic responses in Coronavirus disease 2019 (COVID-19) and shows neuroprotective effects via different mechanisms, including suppressing as mast cells and inflammatory mediators. Furthermore, luteolin can hinder oxidative stress, activation of microglia and astrocytes, neuroinflammatory response, neuroinflammation, and the severity of neuroinflammatory diseases such as Parkinson's disease, Alzheimer's disease, and multiple sclerosis (MS) [21]. Luteolin can reverse the activation of glial cells-mediated neuroinflammation and stress kinases in the human Aβ1–42 peptide-treated mice brains (Figure 7) [22]. Luteolin led to the reversed cortical adverse reactions induced by means of lead acetate and also inhibited the neuroinflammation, cortical cell death, and the oxidative damage [23].

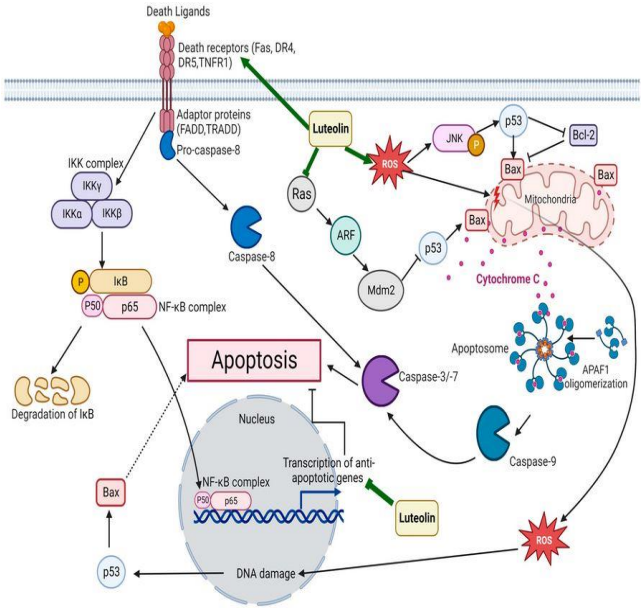

Fig. 3. Schematic showing the possible mechanisms for regulation of intrinsic and extrinsic apoptotic pathways in cancer cells by luteolin. Inhibition and activation of the molecules by luteolin have been shown via arrows (⊥) and (↑), respectively (Extracted from [15]).

There were more publications for Alzheimer’s (58) and Parkinson’s (25) diseases compared to MS (8) (Figure 8a-c). Neurodegenerative disorders and neurodegeneration, cognitive defects result from neuroinflammation. Effective therapeutic strategies are needed to treat these neurodegenerative diseases or brain damage. Anti-inflammatory of flavone luteolin can reduce inflammation of neuroinflammatory diseases such as Parkinson's disease, MS, and Alzheimer's disease by several cellular pathways based on suppressing immune cell activation and inflammatory mediators released from mast cells [21].

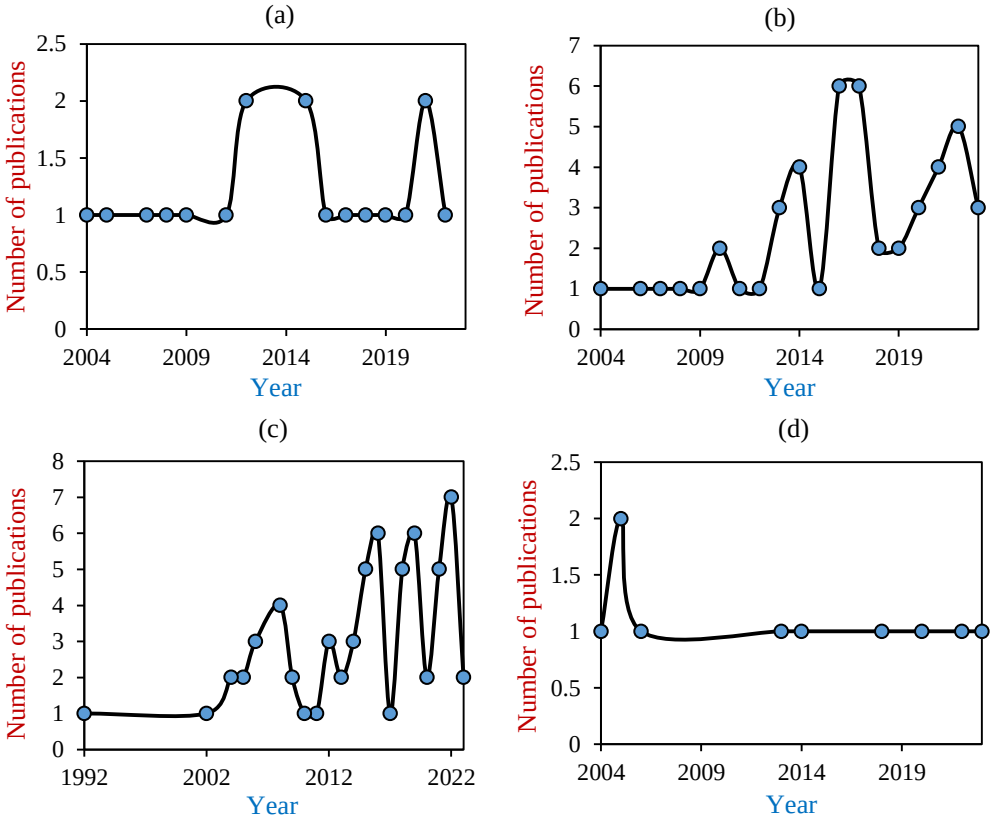

Fig. 4. Number of publications per year for prostate cancer (a), lung cancer (b), breast cancer (c), and uterine cancer (d) (source: PubMed database).

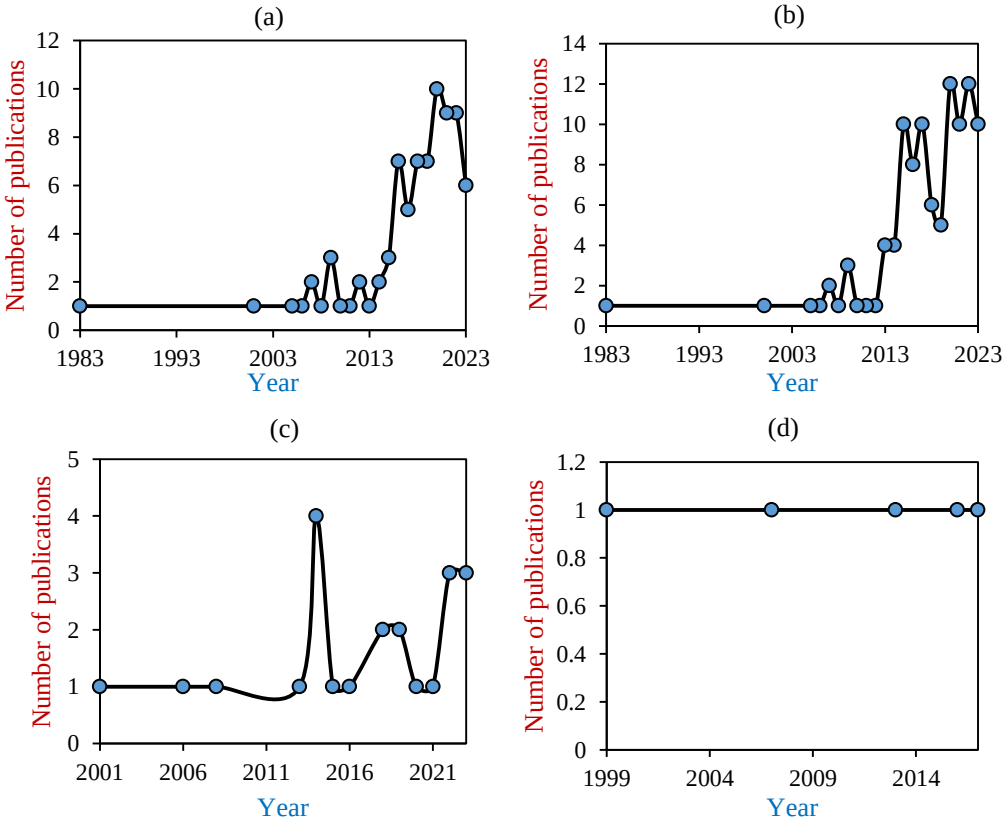

Fig. 5. Number of publications per year for *E. coli* (a), *S. aureus* (b), multidrug-resistant bacteria (c), and *A. niger* (d) (source: PubMed database).

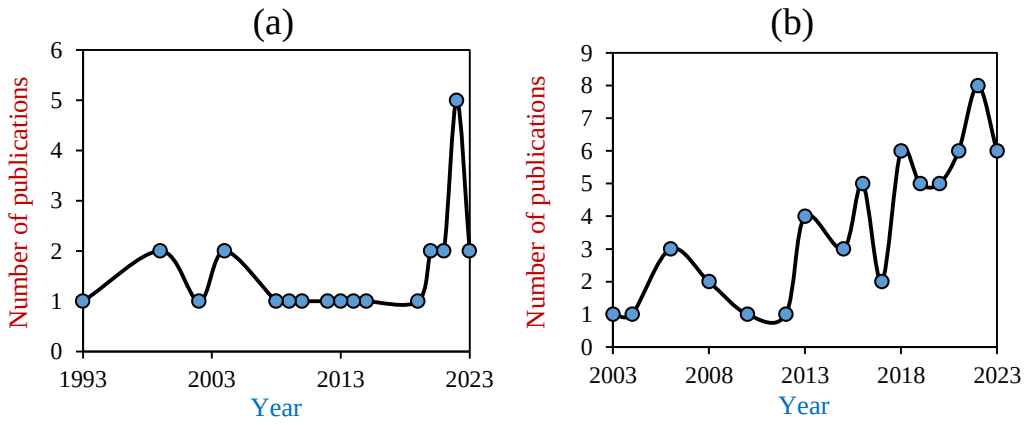

Fig. 6. Number of publications per year for coronary heart disease (a) and hypertension (b) (source: PubMed database).

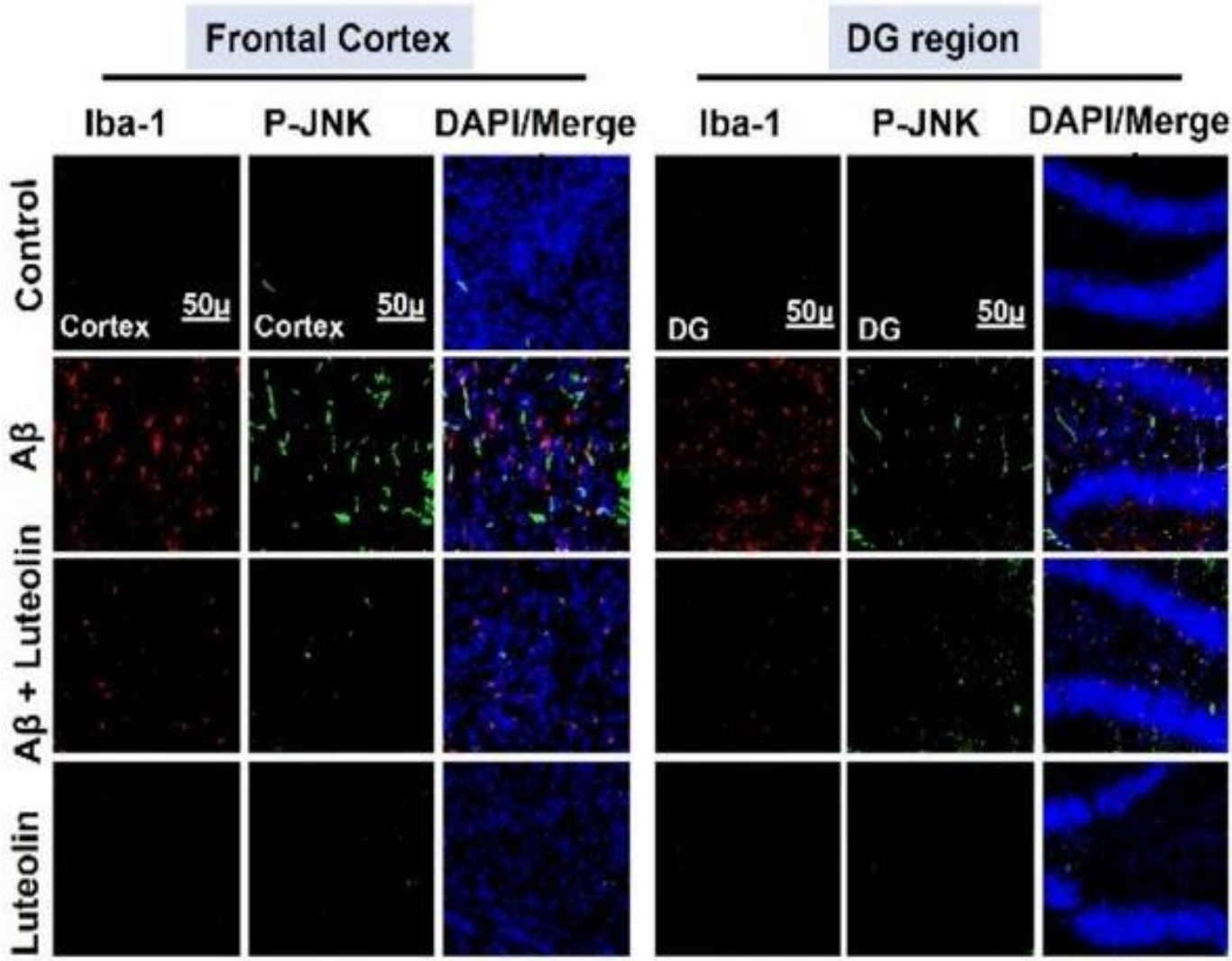

Fig. 7. The neuroprotective effect of luteolin on Aβ1–42-induced neuroinflammation, (Glial fibrillary acid protein (GFAP), ionized calcium-binding adaptor molecule 1 (Iba-1), DG (Dentate Gyrus) region of the hippocampus (Extracted from [22]).

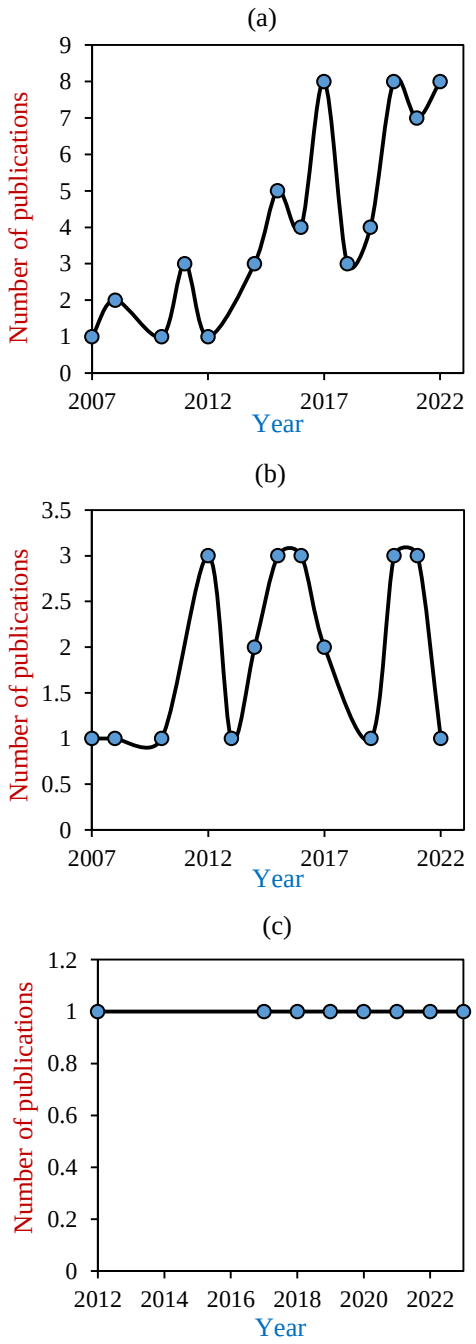

Fig. 8. The number of publications per year for Alzheimer's (a) and Parkinson's (b), and MS (c) diseases (source: PubMed database).

4. Conclusions

According to data obtained from PubMed, the least and most studies were found respectively for antifungal and anticancer activities of luteolin in 2021-2022. Breast and lung cancers have shown a higher number of publications compared to prostate and uterine cancers. In addition, luteolin has been evaluated for hypertension and Alzheimer's disease, prominently. Luteolin can inhibit oxidative stress, activation of microglia and astrocytes, neuroinflammation, neuroinflammatory response, and the severity of neuroinflammatory diseases such as Parkinson's disease, Alzheimer's disease, and MS. In mono-acyl derivatives of luteolin, the benzylation of the hydroxy groups at 7-, 3′- and 4′- positions can enhance the oral bioavailability of this compound. Suppressing immune cell activation and inflammatory mediators released from mast cells have been recognized as the main neuroprotective mechanisms of luteolin. Luteolin modulate apoptosis, autophagy, angiogenesis, cell cycle progression, metastasis, and epithelial–mesenchymal transition in cancer cells. In addition, luteolin induce apoptosis in cancer cells via regulation of extrinsic and intrinsic apoptotic pathways. Understanding of the therapeutic effects and the relative cellular and molecular mechanisms of luteolin may lead to the possibility of new drug designs and effective formulations. In this way, we need a combination of knowledge of basic research and further clinical application of luteolin against cancers, cardiovascular diseases, microbial infections, and neurodegenerative diseases.

Study Highlights

- Breast and lung cancers have shown a higher number of publications compared to prostate and uterine cancers.
- Luteolin can inhibit oxidative stress, activation of microglia and astrocytes.
- In mono-acyl derivatives of luteolin, the benzylation of the hydroxy groups at 7-, 3′- and 4′- positions can enhance the oral bioavailability of this compound.
- Luteolin modulate apoptosis, autophagy, angiogenesis, cell cycle progression, metastasis, and epithelial–mesenchymal transition in cancer cells.
- Luteolin induce apoptosis in cancer cells via regulation of extrinsic and intrinsic apoptotic pathways.

Abbreviations

5-FU: 5-Fluorouracil
Aβ: Amyloid β
BSA: Bovine serum albumin
DG: Dentate Gyrus
GFAP: Glial fibrillary acid protein
Iba-1: Ionized calcium-binding adaptor molecule 1
IZDs: Inhibition zone diameters
MAPKs: Mitogen-activated protein kinases
MS: Multiple sclerosis
MST1: Mammalian STE20-like kinase 1
PKB/Akt: Protein kinase B or Akt
PTEN: Phosphatase and tensin homolog deleted on chromosome ten
SERCA2a: Sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a
TGF-β1: Transforming growth factor beta 1
VEGF: Vascular endothelial growth factor

Funding

This work was not supported by any institutes.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Author contributions

Both authors: conceptualization, writing the first draft, and revising the manuscript.

Acknowledgements

Declared none.

References

1.Luo Y, Shang P, Li D. Luteolin: A Flavonoid that Has Multiple Cardio-Protective Effects and Its Molecular Mechanisms. Frontiers in Pharmacology. 2017;8. doi:https://doi.org/10.3389/fphar.2017.00692
2.Mirzaei A, Mohammadi MR. Anticholinergic, antimicrobial, and anticancer perspectives of atropine: a mini-review. Micro Nano Bio Aspects. 2023;2(1):39-44. doi:https://doi.org/10.22034/mnba.2023.389924.1027
3.Javid H, Ahmadi S, Mohamadian E. Therapeutic applications of apigenin and its derivatives: micro and nano aspects. Micro Nano Bio Aspects. 2023;2(1):30-8. doi:https://doi.org/10.22034/mnba.2023.388488.1025
4.Aljelehawy QHA, Mohammadi S, Mohamadian E, Raji Mal Allah O, Mirzaei A, Ghahremanlou M. Antimicrobial, anticancer, antidiabetic, antineurodegenerative, and antirheumatic activities of thymol: clarification of mechanisms. Micro Nano Bio Aspects. 2023;2(1):1-7. doi:https://doi.org/10.22034/mnba.2023.381107.1019
5.Kempuraj D, Thangavel R, Kempuraj DD, Ahmed ME, Selvakumar GP, Raikwar SP, et al. Neuroprotective effects of flavone luteolin in neuroinflammation and neurotrauma. Biofactors. 2021;47(2):190-7. doi:https://doi.org/10.1002/biof.1687
6.Ganai SA, Sheikh FA, Baba ZA, Mir MA, Mantoo MA, Yatoo MA. Anticancer activity of the plant flavonoid luteolin against preclinical models of various cancers and insights on different signalling mechanisms modulated. Phytotherapy Research. 2021;35(7):3509-32. doi:https://doi.org/10.1002/ptr.7044
7.Lo S, Leung E, Fedrizzi B, Barker D. Syntheses of mono-acylated luteolin derivatives, evaluation of their antiproliferative and radical scavenging activities and implications on their oral bioavailability. Scientific Reports. 2021;11(1):12595. doi:https://doi.org/10.1038/s41598-021-92135-w
8.Mitra S, Tareq AM, Das R, Emran TB, Nainu F, Chakraborty AJ, et al. Polyphenols: A first evidence in the synergism and bioactivities. Food Reviews International. 2022:1-23. doi:https://doi.org/10.1080/87559129.2022.2026376
9.Caporali S, De Stefano A, Calabrese C, Giovannelli A, Pieri M, Savini I, et al. Anti-Inflammatory and Active Biological Properties of the Plant-Derived Bioactive Compounds Luteolin and Luteolin 7-Glucoside. Nutrients. 2022;14(6):1155. doi:https://doi.org/10.3390/nu14061155
10.Gendrisch F, Esser PR, Schempp CM, Wölfle U. Luteolin as a modulator of skin aging and inflammation. BioFactors. 2021;47(2):170-80. doi:https://doi.org/10.1002/biof.1699
11.Hingorani SR. Epithelial and stromal co-evolution and complicity in pancreatic cancer. Nature Reviews Cancer. 2023;23(2):57-77. doi:https://doi.org/10.1038/s41568-022-00530-w
12.Ahmadi S, Emamirad S. Recent progresses and challenges in formulations of vincristine and its derivatives for hindering cancer cells. Nano Micro Biosystems. 2023;2(1):36-41. doi:https://doi.org/10.22034/nmbj.2023.389869.1017
13.Chen T, Li, Lu X-Y, Jiang H-D, Zeng S.

Absorption and Excretion of Luteolin and Apigenin in Rats after Oral Administration of Chrysanthemum morifolium Extract. Journal of Agricultural and Food Chemistry. 2007;55(2):273-7. doi:https://doi.org/10.1021/jf062088r
14.Naso LG, Lezama L, Valcarcel M, Salado C, Villacé P, Kortazar D, et al. Bovine serum albumin binding, antioxidant and anticancer properties of an oxidovanadium(IV) complex with luteolin. Journal of Inorganic Biochemistry. 2016;157:80-93. doi:https://doi.org/10.1016/j.jinorgbio.2016.01.021
15.Çetinkaya M, Baran Y. Therapeutic Potential of Luteolin on Cancer. Vaccines (Basel). 2023;11(3). doi:https://doi.org/10.3390/vaccines11030554
16.Erdoğan MK, Ağca CA, Aşkın H. Quercetin and Luteolin Improve the Anticancer Effects of 5-Fluorouracil in Human Colorectal Adenocarcinoma In Vitro Model: A Mechanistic Insight. Nutrition and Cancer. 2022;74(2):660-76. doi:https://doi.org/10.1080/01635581.2021.1900301
17.Chiruvella KK, Mohammed A, Dampuri G, Ghanta RG, Raghavan SC. Phytochemical and Antimicrobial Studies of Methyl Angolensate and Luteolin-7-O-glucoside Isolated from Callus Cultures of Soymida febrifuga. International journal of biomedical science. 2007;3(4):269-78. doi:PMC3614660
18.Rauf A, Badoni H, Abu-Izneid T, Olatunde A, Rahman MM, Painuli S, et al. Neuroinflammatory Markers: Key Indicators in the Pathology of Neurodegenerative Diseases. Molecules. 2022;27(10):3194. doi:https://doi.org/10.3390/molecules27103194
19.Cheng H-Y, Hsieh M-T, Tsai F-S, Wu C-R, Chiu C-S, Lee M-M, et al. Neuroprotective effect of luteolin on amyloid β protein (25–35)-induced toxicity in cultured rat cortical neurons. Phytotherapy Research. 2010;24(S1):S102-S8. doi:https://doi.org/10.1002/ptr.2940
20.Xu J, Wang H, Ding K, Zhang L, Wang C, Li T, et al. Luteolin provides neuroprotection in models of traumatic brain injury via the Nrf2–ARE pathway. Free Radical Biology and Medicine. 2014;71:186-95. doi:https://doi.org/10.1016/j.freeradbiomed.2014.03.009
21.Kempuraj D, Thangavel R, Kempuraj DD, Ahmed ME, Selvakumar GP, Raikwar SP, et al. Neuroprotective effects of flavone luteolin in neuroinflammation and neurotrauma. BioFactors. 2021;47(2):190-7. doi:https://doi.org/10.1002/biof.1687
22.Ahmad S, Jo MH, Ikram M, Khan A, Kim MO. Deciphering the Potential Neuroprotective Effects of Luteolin against Aβ1–42-Induced Alzheimer's Disease. International Journal of Molecular Sciences. 2021;22(17):9583. doi:https://doi.org/10.3390/ijms22179583
23.Baty R, Hassan K, Alsharif K, El-Hennamy R, Elmahallawy E, Hafez M, et al. Neuroprotective role of luteolin against lead acetate-induced cortical damage in rats. Human & Experimental Toxicology. 2020;39(9):1200-12. doi:https://doi.org/10.1177/0960327120913094

HOW TO CITE THIS ARTICLE:
Kahrizi D, Mohammadi S. Anticancer, antimicrobial, cardioprotective, and neuroprotective activities of luteolin: A systematic-narrative mini-review. Nano Micro Biosystems. 2023;2(2):1-9.doi: https://doi.org/10.22034/nmbj.2023.403963.1022