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PRACA POGLĄDOWA
REVIEW

Therapeutic potential of flavonoids used in traditional Chinese medicine – a comparative study of galangin, kaempferol, chrysin and fisetin

Potencjał terapeutyczny flawonoidów wykorzystywanych w tradycyjnej medycynie chińskiej – porównanie galanginy, kemferolu, chryzyny i fisetyny

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ABSTRACT

One of the branches of traditional Chinese medicine (TCM) is herbal medicine. In this paper, we focus on the biological activity of substances belonging to flavonoids and specific examples of their impact on various body systems. Flavonoids are a group of chemical compounds included in plant materials, honey, propolis or mushrooms used in TCM. Chrysin, galangin, kaempferol and fisetin are examples of flavonoids showing, among others, antioxidant, anti-inflammatory or antibacterial properties, which are the subject of various scientific studies aimed at examining their potential therapeutic effect.

KEYWORDS

flavonoids, chrysin, galangin, kaempferol, fisetin, traditional Chinese medicine

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STRESZCZENIE

Ziołolecznictwo stanowi jedną z głównych gałęzi tradycyjnej medycyny chińskiej (*traditional Chinese medicine* – TCM). W pracy skupiono się na aktywności biologicznej wybranych flawonoidów, a także konkretnych przykładach wpływu tych substancji na różne układy organizmu. Flawonoidy to grupa związków chemicznych zawartych w surowcach roślinnych, miodzie, propolisie czy grzybach stosowanych w TCM. Chryzyna, galangina, kemferol i fisetyna to przykłady flawonoidów wykazujących m.in. właściwości przeciwutleniające, przeciwzapalne czy przeciwbakteryjne. Właściwości te są przedmiotem wielu badań naukowych, mających na celu zbadanie ich potencjalnego działania terapeutycznego.

SŁOWA KLUCZOWE

flawonoidy, chryzyna, galangina, kemferol, fisetyna, tradycyjna medycyna chińska

Introduction to traditional Chinese medicine and flavonoids

Traditional Chinese medicine (TCM) is a thousand years old healthcare system that heavily depends on herbal medicine and dietetics [1]. In addition, nonmedication practices such as bodywork and general physical activity are important aspects of therapy in TCM. The main principal regarding medicines used in TCM is strong presence of synergistic effects of many active substances within one plant or common, targeted effects of many plants. This methodology has led TCM to develop methods for the preparation of plant infusions, decoctions, herbal mixtures in form of capsules, pills and tablets, as well as, whole plant parts, which contain a significant number of substances with proven medicinal and supporting properties. The unique combination of substances as well as the wide application of traditional Chinese medicines is the reason why more and more scientists are looking for clues and grounds for developing new drugs in them, as well as clues to discover previously unknown indications of substances known to evidence-based medicine (EBM) [1,2,3]. Flavonoids are a frequently occurring group of compounds with a vast, proven therapeutic effects.

Flavonoids can be extracted from plant samples using organic solvents but specific extraction parameters are varied among flavonoid family (Table I).

Table I. Proposed parameters of extraction of chrysin, galangin, kaempferol and fisetin

Flavonoid	Sample	Solvent: (solvent: sample ratio)	Temperature [°C]	Time [h]	Reference
Chrysin	*Alpinia oxyphylla*	70% ethanol (20:1)	60	0.5	[4]
Galangin	Galangal	90% ethanol (25 ml:1 g)	80	3	[5]
Kaempferol	Strobilanthes crispus leaves	Supercritical CO_2, 10% ethanol solution as cosolvent, 20 MPa pressure	50	1	[6]
Fisetin	Strawberries	Methanol/water 80/20 v/v with renewals of solvent every 24 hours. After that a liquid-liquid extraction with chloroform used as solvent system	20	72	[7]

Flavonoids are polyphenolic secondary metabolites which are commonly found in most plants. Compounds can occur as glycoside or aglycone form. Glycoside derivatives of flavonoids are the most common form that can be found in plants. The skeleton of flavonoid contains 15 carbon atoms that are divided into two, six-membered phenyl rings. The rings are linked together by three-carbon unit with an oxygen atom as a fourth, which can then cyclize, forming a third ring (Figure 1) [8,9,10,11].

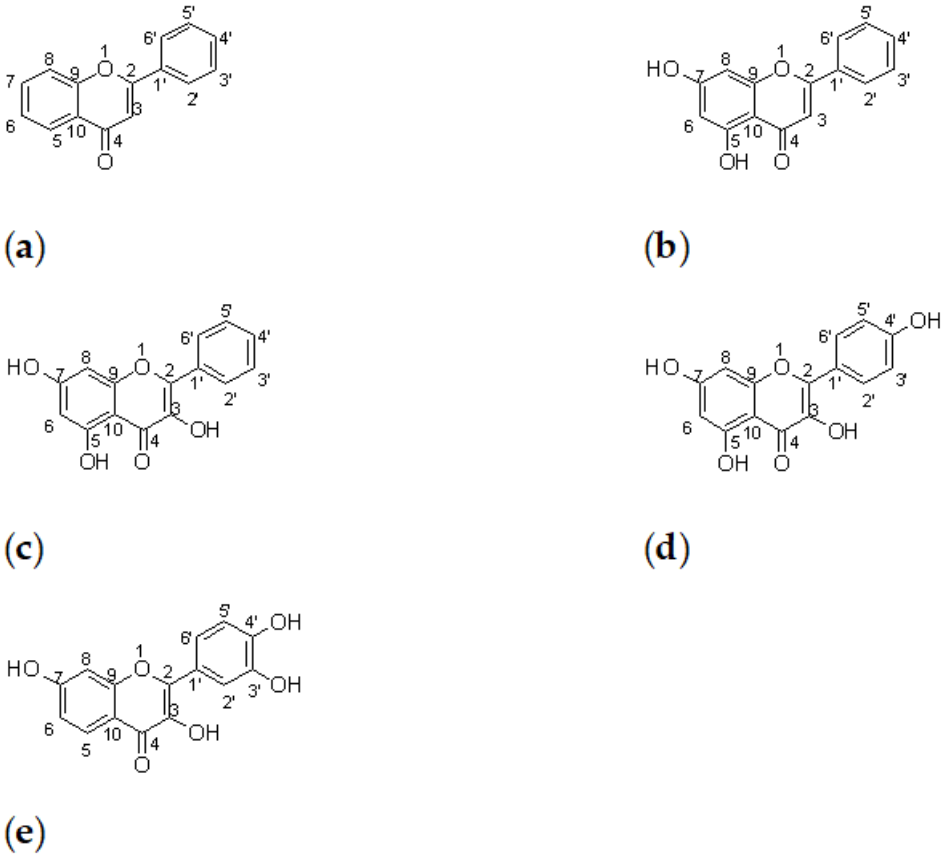

Fig. 1. Chemical structure of flavonoids (a); chrysin (b); galangin (c); kaempferol (d); and fisetin (e).

However, this large group of compounds can be divided into subgroups based on their chemical structure. Flavones like chrysin or apigenin lack hydroxyl group at the C3 position contrary to flavanols where this group is present i.e. in kaempferol and galangin. Flavanones do not have double bond between C2 and C3. Hesperitin and naringenin are examples of flavanones. Isoflavonoids, such as genistein, are characterized by connection of prime ring in C3 rather than usual C2. Last group that shares the common basic skeleton are anthocyanins, like cyanidin or malvidin with a double bond between oxygen atom in O1 position and C2 [12].

Flavonoids exhibit wide spectrum of biological activity, like anti-inflammatory, neuroprotective, hepatoprotective, antibacterial, anti-mutagenic, anticancer, cardiovascular protective, antifungal, antiviral, and anti-allergic properties [8,13,14,15,16]. Potential mechanisms of anti-inflammatory activity of flavonoids are represented on Figure 2.

Due to the different structure of flavonoids, their biological activities are varied. The anti-inflammatory effect is directly related to the double bond between C2 and C3 atoms. Moreover, double bond between C4 and oxygen atom was determined to play a crucial role in anti-inflammatory effect of flavonoids. Number and position of hydroxyl group in molecule also play an important role in modulating inflammatory responses [17,18].

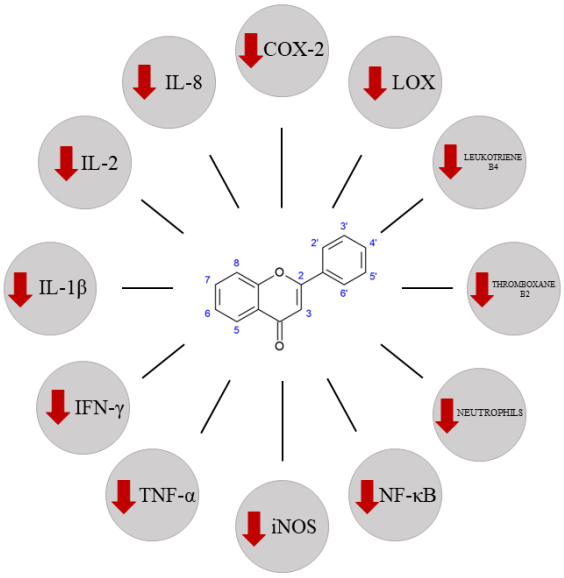

Fig. 2. Anti-inflammatory activity of flavonoids (based on [17,18]). COX-2 – cyclooxygenase-2; LOX – lipoxygenase; NF-κB – nuclear factor κ B; iNOS – inducible nitric oxide synthase; TNF-α – tumor necrosis factor α; IFN-γ – interferon γ; IL – interleukin.

One of the most important activities of flavonoids is their antioxidant properties. The large number of unsaturated bonds in their structure are able to reduce the reactive oxygen species (ROS). Second important aspect is the number and position of hydroxyl group in phenyl ring. Another mechanism may be direct inhibition of ROS formation by chelating reaction with trace elements, inhibition of ROS generating enzymes such as microsomal monooxygenase. It is also worth mentioning that chelating potential of flavonoids is related to the number and position of the hydroxyl group within the molecule. Presence of hydroxyl group in position 3 contributes to high chelating capacity and oxidative reduction. Hydroxyl group connected to the prime ring has less impact on the chelating ability with the postulated temperature-dependent mechanism of action. The last postulated mechanism is activation of antioxidant defenses by flavonoids molecules [8,18,19].

The aim of this study is to present the potential medical applications and therapeutical effects of flavonoids often used in TCM – chrysin, galangin, kaempferol and fisetin. We focused on neuroprotective, hepatoprotective and antibacterial properties of selected flavonoids.

Chrysin

Chrysin (5,7-Dihydroxyflavone; Figure 1b) belongs to the polyphenolic phytochemicals. It is present in many plants such as *Passiflora caerulea*, *Passiflora incarnata*, *Oroxylum indicum*, *Cytisus multiflorus*, *Crataegus oxyacantha*, *Pelargonium crispum*, *Scutellaria immaculata* or *Alpinia oxyphylla*, moreover it can be also found in honey, propolis and some species of fungi like *Lactarius deliciosus* [20,21,22,23]. Studies, both in vitro and in vivo, have shown that chrysin has a protective effect on the cardiovascular system as well as hepatoprotective, anticancer and neuroprotective actions [24,25,26].

Additionally, some studies postulate antiviral activity of chrysin against hepatitis B virus (HBV) or enterovirus 71 (EV71) [21,27,28].

Neuroprotective activity

Neuroprotective effect of chrysin is related to its antioxidative effect on dopaminergic neurons, which increase synthesis of neurotrophic factors e.g. brain--derived neurotrophic factor (BDNF). Antiapoptotic and anti-inflammatory effects as well as neural regeneration were observed [26,29,30,31]. The research results show that chrysin could be used in the treatment of movement associated diseases or cognitive disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis, or brain damage associated with head injuries or ischemic strokes. The anticonvulsant properties of chrysin have been demonstrated, which makes it possible to consider its use in the treatment of epilepsy [32,33,34,35,36]. The study conducted on a rat model reports that the neuroprotective effect of chrysin may be used in the neurodegenerative processes caused by lead (Pb) poisoning. Long-term treatment with chrysin (experiment lasted 8 weeks) alleviated problems with memory and learning ability, probably by improving the functioning of the neural mechanism underlying these processes, i.e., long-term potentiation (LTP), which is impaired due to Pb poisoning by inhibiting LTP induction, additionally, chrysin suppresses inflammatory processes and lowers the concentration of Pb, which can prevent the loss of neurons [37].

Cardioprotective activity

The literature describes the effect of chrysin on the circulatory system, which may reduce the likelihood of developing or alleviate the course of diseases such as atherosclerosis, hypertension, myocardial damage as a result of a heart attack, or thrombosis [38,39,40]. In addition, it has a protective effect against inflammatory processes within the endothelium of blood vessels, which can play an important role in preventing the development of such diseases as atherosclerosis and thromboangitis obliterans [41]. For this reason, chrysin could be used in the prevention of hypertension, and thus also preventing the development of diseases associated with it. The hypotensive effect of chrysin is related to its influence on many processes related to, like the regulation of blood vessel tone. Studies on the influence of chrysin on the relaxation of coronary arteries show that this compound affects many mechanisms related to the vasorelaxation. It inhibits indirectly calcium-activated chloride channels (CaCCs) in smooth muscle cells of the coronary arteries (ASMC), preventing coronary artery spasms, and also lowers blood pressure in L-NAME--induced hypertension by modulating oxidative stress in the aorta, heart and blood. This activity could be used in the treatment of diseases with an etiology associated with vasomotor dysfunctions, such as hypertension or stroke. In addition, chrysin in mitoxantrone cardiotoxicity studies in a mouse model reduced cardiomyocyte apoptosis and loss of intermediate filaments, which may indicate its anti-apoptotic properties and their importance in cardioprotective action [24,42,43].

Osteoprotective activity

Previous studies indicate that the use of a diet enriched in chrysin can positively affect bone formation and improve bone reconstruction processes through antioxidant, anti-inflammatory and phytoestrogenic effects. In patients with rheumatoid arthritis (RA), chrysin reduces the concentration of oxidative stress

mediators, alleviating inflammation, and has an antioxidant effect on chondrocytes, protecting against cartilage degradation. In addition, it has an osteoprotective effect, regulating bone remodeling processes by reducing bone resorption, increasing the activity of osteoblasts and reducing the activity of osteoclasts. As a result of the described actions, chrysin may reduce the likelihood of developing chronic diseases within the bone tissue, such as osteoporosis [44,45].

Galangin

Galangin (3,5,7-Trihydroxyflavone; Figure 1c) is a flavanol that can be found in many members of the *Zingiberaceae* family. *Alpinia officinarum*, identified as a natural raw material characterized by one of the highest galangin contents (observed in relation to plant materials), has been used in case of emesis, abdominal pain and diarrhea treatment. *Helichrysum aureonitens* as well as propolis have been also recognized as a potent source of this compound [46,47,48]. Galangin was also identified as an active compound in Ershiwuwei Lvxue Pill, traditional Tibetan medicine that was officially recorded in the Drug Standard of the Ministry of Public Health of the Peoples Republic of China for the treatment of RA [49]. As other flavonoids, galangin exhibits antioxidant and anti--inflammation activities, but other potential medical applications have also been explored.

Anticancer activity

Anticancer activity is one of the most often mentioned effects of galangin. It has been tested against numerous types of human cancers' cell lines. Hepatocellular carcinoma (HCC) due to its high morbidity and mortality is the subject of extensive research, with aim to find safe and effective pharmacotherapy. Latest research suggests that galangin may be considered as a potential antitumor agent against HCC. Postulated mechanisms of action are inducing cell apoptosis by elevating expression of TP-53 and p53 related genes. Moreover, treatment with galangin inhibits cell migration and invasion of HCC cells, which can be potentially used in cancer therapy as a result of its multidirectional mechanism of action. Furthermore, in mouse model galangin significantly reduces tumor growth by down-regulating H19 expression which strongly corelates with increased cell apoptosis and decreased invasion [50]. Another promising therapeutic effect was observed by Atwa et al. [51] during their research regarding galangin effect on HCC in mice model. It was postulated that galangin may also be considered as a synergistic agent in HCC chemotherapy. Galangin, together with luteolin, strongly ameliorates doxorubicin therapy in chemically induced HCC rat model, in contrast to only doxorubicin therapy which led to minimal improvement in liver function. This effect may be used to development a new type of chemotherapy with reduced side effects and the highest safety. Anticancer effect against HCC was also investigated by Fang et al. [52]. Cell cycle arrest at the G0/G1 phase, ROS and endoplasmic reticulum (ER) stress induced apoptosis, induction of autophagy are modes of action that have not been mentioned in previous research.

Galangin effect on other cancers was also tested. Glioblastoma multiforme (GBM), a malignancy of central nervous system which recurrence cannot be avoided even after successful pharmacotherapy, radiotherapy or surgical intervention. That is a reason why new drugs are needed to either effectively eradicate cancer cell or successfully inhibit their growth, without severe side effects for the patients. Proposed mechanism of galanin's antitumor action is the inhibition of the epithelial-to-mesenchymal transition (EMT), a process that has been proven to promote the cell growth, migration and facilitation which are directly linked to malignant tumor. Galangin achieves this by directly binding to oncogene – Skp2 promoting its degradation via the ubiquitin pathway and consequently inhibiting EMT and cell growth both in vivo and in vitro [53].

Rampogu et al. [54] in their review about chemotherapeutic potential of galangin summarized its effect on various cancer types. It was concluded that galangin may inhibit breast cancer, ovarian cancer, cervical cancer, laryngeal carcinoma, colon cancer, renal carcinoma, lung cancer and oesophageal carcinoma through various mechanisms. Modulation of apoptotic pathways such as caspases and p53, inhibition of glyoxalase-1 and elevation of oxidative and carboxyl stress, modulation of PI3K/AKT/NF-κB, BCL-2, cFLIP, Mcl-1, and mTOR pathways.

This summary provides background information for further research regarding anticancer activity of galangin. Complex and multitarget mechanisms of action provide unique possibilities for creating new type of pharmacotherapy that is based on galangin, which may be effective, lacking severe side effects, compatible with today used therapies and safe.

Antidiabetic activity

Diabetes mellitus (DM) is one of the most frequently diagnosed chronic disease with severe consequences such as diabetic nephropathy. Untreated it may lead to chronic kidney disease and contribute to major excess mortality among diabetic patients. Galangin has been postulated to exert positive effects on diabetic nephropathy, as well as other effects of DM in mouse and rat models through various mechanisms. Improvement in kidney function and prevention of kidney damage were observed in diabetic rats treated with galangin for 8 weeks in comparison to untreated

diabetic rats, as confirmed by histopathology. Postulated mechanisms are presented on Figure 3 [55,56].

Effects presented on Figure 3 does not affect the health of non-diabetic rats' model [55,56]. In vitro models have also shown that galangin has a potential to inhibit renin-angiotensin system activation and PI3K/AKT/mTOR signal pathway which is directly related to increased ROS production, decreased cell viability and proapoptotic activity [56].

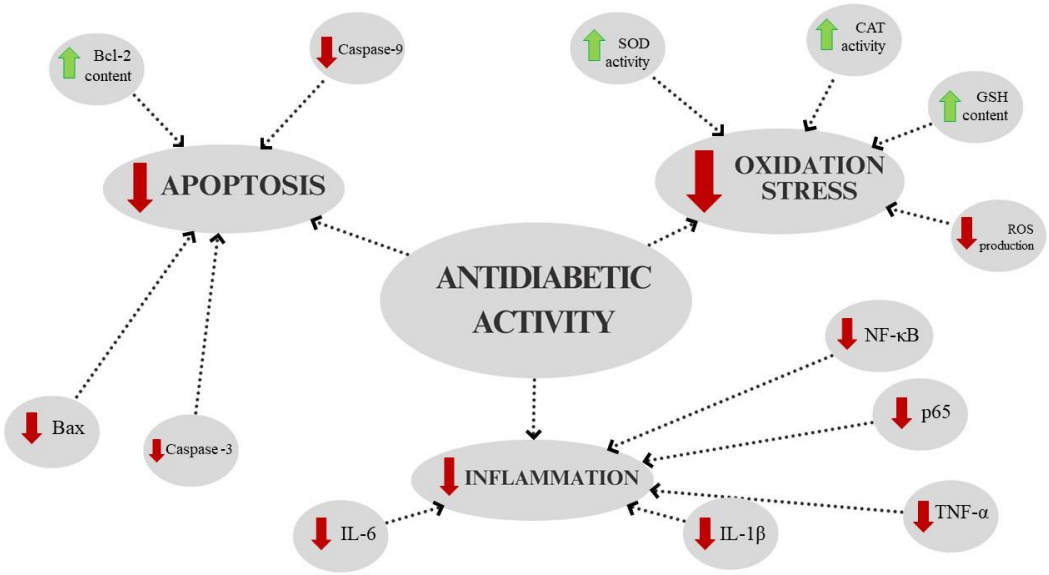

Fig. 3. Mechanisms of nephroprotective activity of galangin in mouse and rat model. SOD – superoxide dismutase; CAT – catalase; GSH – reduced glutathione; ROS – reactive oxygen species; NF-κB – nuclear factor κ B; TNF-α – tumor necrosis factor α; IL – interleukin.

Other potential use of galangin in diabetes mellitus is the direct regulation of glucosee homeostasis. Mechanisms for controlling glucose metabolism are linked to dipeptidyl peptidase-4 (DPP-4) inhibition, improvement of insulin activity by activating insulin receptor gene, attenuation of insulin resistance via the Akt/mTOR signaling pathway. Additionally, it can improve glucose tolerance by stimulating insulin secretion and increasing insulin sensitivity. This effect elevates glucose uptake in peripheral tissues, muscles, and adipose tissue [55,57,58]. Aloud et al. [59] proposed different mechanisms in their papers. In rat model galangin improved glucose homeostasis by modulating the activity of enzymes such as glucokinase, G6PD and G6P. A study conducted by Aloud et al. suggested how galangin potentially operates as an anti-diabetic agent. This investigation was carried out on a rat model with disrupted glucose homeostasis induced by streptozotocin. The findings indicated that galangin might counteract the elevated function of enzymes involved in gluconeogenesis and glycolysis. Despite these findings, the precise workings of this mechanism were not entirely elucidated, emphasizing the need for further research to comprehensively grasp the anti-hyperglycemic effects of galangin.

Kaempferol

Kaempferol (3,4',5,7-Tetrahydroxyflavone; Figure 1d) is a flavonoid that can be commonly found in many medicinal plants, like *Carthamus tinctorius*, *Glycyrrhiza glabra*, *Anemarrhena* spp., *Punica granatum*, *Equisetum* spp., *Sophora japonica*, *Ginkgo biloba*, *Euphorbia pekinensis.* Moreover, it occurs in beans, broccoli, cabbage, gooseberries, grapes, kale, strawberries, tomatoes, citrus fruits, brussels sprouts, apples and grapefruit [60,61,62,63,64]. Kaempferol is an active component in many plants that are being used in TCM mixtures (Table II).

Table II. Examples of traditional Chinese medicine drugs containing kaempferol as an active substance

Name (acronym)	Intendent use	Reference
Taohong Siwu Decoction (TSHWD)	Various blood stasis, blood deficiency syndromes	[60]
Suanzaoren decoction (SZRD)	Providing nourishment to the bloodstream, soothing the thoughts, alleviating heat, and eliminating irritation	[61]
Huangqi Sijunzi Decoction (HQSJZD)	Replenish blood, enhance bodily resistance, and address deficiencies, it possesses effects that promote overall wellbeing	[65]
Wumeiwan (WMW)	Treatment of inflammation in respiratory tract	[66]
Gegen Qinlian decoction (GGQLD)	As an antipyretic and antidiarrheal medicine, eliminate dampness and heat	[67]
Huanglian Jiedu Decoction (HLJDD)	Treatment of type 2 diabetes mellitus	[68]
LiuWei DiHuang Pill (LWDH Pill)	Treatment of type 2 diabetes mellitus	[69]
Fuzheng–Jiedu Decoction (FJD)	Improving resistance against “deficiency, dampness, stasis, and toxin”	[70]
Huoxin pill (HXP)	Treatment of cardiovascular diseases	[71]
Simiao pill (SM)	Treat gout through eliminating dampness retention and strengthening the liver and kidney	[72,73]
Ling Gui Zhu Gan formula (LGZG)	Treatment of spleen deficiency and dampness syndrome	[74]

Neuroprotective activity

The neuroprotective properties of kaempferol are mainly related to its antioxidant and anti-inflammatory effects. Kaempferol may inhibit inflammation in neural system due to reduction of microglial activation. Mechanism of action was found to be related to downregulation of p38, MAPK, JNK, and ERK which are inflammatory response mediators. Moreover, kaempferol inhibits the NF-κB and TLR4, which further reduce the proinflammatory mediators’ secretion [75,76,77,78]. Antioxidant activity in the central neural system may result from inhibition of ROS formation, scavenging of free radicals, endogenous antioxidants (superoxide dismutase and glutathione) modulation, inhibition of β-amyloid protein aggregation and BDNF modulation [76,79,80,81]. The regulation of apoptosis is also postulated as a kaempferol’s neuroprotective effect. Zhang et al. [82] proposed regulation of BDNF-TrkB--PI3K/AKT signaling pathway for antiapoptotic effect. Down regulation of p-NF-κB and p-GSK-3β together with up regulation of p-Akt and Nrf-2 was also proposed as a potential mechanism of KE protection against cerebral oxidative stress, inflammation and apoptosis [77,78,81].

Another neuroprotective mechanism of kaempferol was proposed by Inden et al. [83]. Misfolding and aggregation of α-synuclein protein are directly linked to PD, PD with dementia, dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). For now, there are no disease-modifying therapies regarding an α-synuclein aggregation [84]. Kaempferol due to ameliorating of lysosomal function and autophagy activation may exhibit a protective effect against α-synuclein protein, and in result ameliorates pharmacological therapy.

Antibacterial activity

Antibacterial activities of kaempferol against *A. baumannii*, *Bacillus* spp., *K. pneumoniae*, *Mycobacterial* spp., *Staphylococcus* spp., *Enterococci*, *Vibrio cholera* were investigated by Periferakis et al. [85]. The main mechanisms of action are proposed to be the cell membrane disruption, activation of apoptosis, fragmentation of DNA in bacteria cells [85,86].

Drug resistance plays a pivotal role in treatment of bacterial infection. Presence of multidrug resistant bacteria species that are able to infect humans, animals and plants is one of the biggest problems of future medicine. It is crucial to find new types of drugs, that can improve present antibacterial therapy and provide a base for future research. Zhou et al. [87] analyzed and described potential synergistic effect of kaempferol and colistin, medicine used as a last chance during therapy of multidrug-resistant Gram-negative bacteria (MDR-GNB). The synergistic effect of kaempferol was also observed with penicillin against methicilin--resisitant *Staphylococcus aureus* (MRSA) by He et al. [88]. Synergistic therapy increased penicillin sensitivity of MRSA as well as antibiofilm activity. Proposed mechanisms of action are inhibition of penicillinase expression and involvement in biofilm development on initial and mature stage, respectively. These studies can be a basis for the search of new types of drugs that will be effective against current drug-resistant bacteria [88].

Hepatoprotective activity

Hepatic illness such as viral hepatitis, liver cirrhosis, hepatocellular carcinoma, hepatic cancer, and also metabolic illnesses together with unhealthy lifestyle

like excessive alcohol consumption, obesity and untreated diabetes can lead to severe liver inflammation and liver injury, that require medical intervention and pharmacological treatment. Unfortunately, these drugs exhibit many side effects and sometimes are not safe to use. This prompts researchers to look for safer drugs that can be effectively used as a hepatoprotective agent [89]. Kaempferol is a promising chemical that can be safely used as a hepatoprotective agent [89,90,91, 92,93]. Anti-inflammatory effect in hepatic cells is a result of inhibition of PI3LK/pAkt, Nrf2 pathways, pro-inflammatory cytokines (IL-6, TNF-α, IL-β1) generation. Inhibition of hepatic enzyme activity (ALT, AST) during active toxication and maintaining their level during liver injury as well as modifying activity of antioxidant enzymes (SOD, CAT, GSH) are responsible for maintaining homeostasis in stressful conditions. Antiapoptotic activity of kaempferol is related to inhibition of NF-κB/p65, downregulation of COX-2, iNOS protein production, suppression of upstream kinases (ERK, JNK, p38, MAPKs) and activation and upregulation of SIRT1. These effects may increase cell survivability and proliferation and reduce inflammation and oxidative stress and result in hepatoprotective effect [94,95,96].

Fisetin

Fisetin (3,3',4',7-Tetrahydroxyflavone; Figure 1e) is a flavonoid that is present in many commonly used fruits and vegetables. Significant amount of it have been found in strawberries, grapes, onions and cucumbers [97]. This flavonoid was also identified as an active compound in many TCMs such as Gan Shuang granulates, Xintong granulates, *Acacia catechu – Scutellariae Radix* formula, Gualou and Niubang Decoction. These medicines are used in various health problems e.g. treatment of chronic liver diseases, pulmonary infection therapy, coronary artery disease treatment and more [98,99,100,101].
Fisetin has so far been poorly studied, however multiple therapeutic effects were postulated. In literature, anticancer [102,103], anti-inflammatory [104,105], hypoglycemic [106] activities have been described. In our review, we focused on senotherapeutic and neuroprotective activity of fisetin.

Senotherapeutic effect

Cellular senescence is an irreversible replicative arrest of a cell that is characterized by increased survivability and often up regulated metabolism. This state is an effect of both intra and extracellular signals that are related to cellular and tissue damage and more importantly, to cancer development. In this state DNA damage, oncogene activation, telomeres dysfunction, protein misfolding and aggregation together with failed protein removal and other undesirable processes take place with high intensity. Senescence main function is a tumor suppressing but, it was also proved to play a causal role in aging and age-related diseases. That is why counteracting this phenomenon is crucial for improving health and extending life [107,108,109].
The last mentioned finding may be confirmed by the results of Yousefzadeh et al. [108] in vivo and in vitro examinations revealing fisetin to reduce the fraction of senescent T and NK, playing an important role in maintaining tissue homeostasis as well as for the alleviation the symptoms of age-related disorders. Anti-inflammatory and antioxidant properties of fisetin have also been postulated as a potential mechanism of its action. Verdoorn et al. [110] postulated that proinflammatory, proapoptotic agents such as TNF-α, IL-1α, IL-6 expression is up regulated in senescent cells. This may affect neighbor cells and spread senescence which can lead to chronic inflammation, frailty, mortality and comorbidities. Senolytic activity of fisetin inhibits this effect and as a result reduces systematic inflammation and increases resilience and health span. Fisetin was also proved to inhibit bone cellular aging in mouse model. Proposed mechanism is modulating signaling pathways: SIRT1, BCL-2/BCL-XL, AKT. This leads to clearance of senescent cells and in conclusion, reduction of ROS generation and inhibiting senescence associated secretory phenotype inflammation [111]. In rat model of senescence induced by D-galactose and in naturally aged rat erythrocytes fisetin significantly increases antioxidant levels by down regulating age induced ROS generation, lipid and protein peroxidation and activation of plasma membrane redox system [112]. Russo et al. [113] in their research postulated that fisetin may also target MEK/ERK/IL-8 pathway which is linked to cell resistance to apoptosis and inflammatory status and AMPK/ULK1 pathway what modify cell susceptibility to autophagy and senescence.

Neuroprotective activity

Neurodegenerative disease leads directly to loss of brain function as a result of permanent loss of neurons. AD, PD and many others diseases are characterized by exposition of neurons to oxidative stress in their pathogenesis. Fisetin as a flavonoid can act as an antioxidant agent and may be used as a protective compound. This effect directly influences many cellular mechanisms. Fisetin inhibits lipid peroxidation, downregulates MAPK – p38 – NF-κB signaling pathway, reduces oxidative stress by ROS scavenging, ameliorate antioxidant enzymes' activity, modulates reduced glutathione concentration and modifies PI3K/Akt/Nrf-2 pathway. All this effects ultimately contribute to reduction of damaged neurons [114]. Fisetin senotherapeutic effect can also be the reason of its neuroprotective activity. Accumulation of senescent cells during life-time may be directly

connected to age-related, neurodegenerative diseases. Senescent cells may influence the neuronal tissue by their metabolic shifts, induced ROS generation and pro-inflammatory senescence-associated secretory phenotype factors. Elimination of senescent cells positively modulates inflammation, which is a frequent symptom in neurodegenerative diseases. Nevertheless, further clinical trials are needed to determine the safety and efficacy of pharmacotherapy using senolitic drugs [115]. Maher [116] in its summary proposed, in addition to the previously mentioned, modulatory effect of protein aggregation and protein stability which both can play a significant role in treatment of AD, PD and others. Another positive effect on PD has been postulated by Rosado-Ramos et al. [97]. Their proposed effect of fisetin in PD treatment, is directly linked to the main PD pathogenesis mechanism, which is excessive expression and deposition of α-synuclein protein in the brain. In their research, it was proven that fisetin reduces toxicity of α-synuclein by modulating the process of intracellular aggregation and localization, although the precise molecular mechanisms of neuroprotective response still need to be fully described [97].

Conclusions

Flavonoids constitute a substantial category of naturally-occurring substances present in plants, and they have been investigated for their potential therapeutic advantages. These substances exhibit a diverse array of biological activity and health-related attributes, rendering them compelling in numerous therapeutic scenarios. Flavonoids have been examined for their therapeutic potential in various ways, including their capacity to act as antioxidants, mitigate inflammation, provide cardiovascular assistance, enhance vascular function, promote brain health, bolster the immune system, and potentially exhibit anti--cancer properties. Consequently, their attributes have been and continue to be harnessed in therapeutic applications, as illustrated by their utilization in TCM.
However, it is important to continue research on the mechanisms of action of these compounds to better understand their complex interactions with the human body. Moreover, they play a key role in the search for new drugs, especially in the context of the treatment of chronic diseases and cancer. It is worth pursuing further research aimed at exploiting the therapeutic potential of these flavonoids and developing new treatment strategies based on their biological properties. An important aspect that should be thoroughly investigated are the interactions between flavonoids used in TCM and drugs used in EBM. This will increase the safety of pharmacotherapy and significantly improve the effectiveness of treatment. Another issue, the description of which will significantly improve the safety of using mixtures of TCM origin, are their side effects, which are currently still a blank spot in the world of medicine and pharmacotherapy.
A lot of research needs to be carried out, but thanks to the knowledge contained in TCM, we can learn a lot about phytotherapy and the actions of flavonoids, which may one day form the basis of new drugs and therapies.

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Author's contribution

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