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Selected biological properties of quercetin, curcumin, and kaempferol

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ABSTRACT

Polyphenols are a large group of organic compounds present in plants, where they play various roles pivotal to their proper physiological functioning. Polyphenols are ubiquitous in many dietary sources such as fruits, vegetables, beverages, seeds, and honeys. Diet plays a crucial role in sustaining overall well-being of the organism and preventing diseases, including cancer. Despite broad spectrum of health promoting activity of polyphenols, such as antioxidant, anti-inflammatory and antimicrobial, many of them are also potent anti-cancer compounds. In this review we focused on presentation of three polyphenols such as quercetin, curcumin, and kaempferol. We discussed recent studies concerning their beneficial impact on human health and potential as anticancer agents.

KEYWORDS: polyphenols, anticancer, anti-inflammatory, neuroprotection

Introduction

Polyphenols are a large group of organic compounds which chemical structure is characterized by presence of at least one hydroxyl group affixed to an aromatic ring. They are found in the tissues of many plants, where they play crucial role in defending from environmental stress, such as unfavourable temperature and light (Lattanzio, 2013). Numerous studies investigated various health benefits of dietary intake of polyphenols. They are known to have anti-inflammatory, antioxidant, and antimicrobial properties. Moreover, polyphenols have an immense potential for development of anticancer drugs (Zhou *et al*., 2016). Quercetin, curcumin and kaempferol are well-known phenolic compounds ubiquitous in human diet, especially sources such as fruits and vegetables (Fig. 1).

Bioavailability

Even though polyphenols are immensely common in human diet, their impact on health is intricate due to their relatively low bioavailability, with estimated rate of absorption from 0.3 to 43%. Moreover, human body reacts to phenolic compounds such as polyphenols in the same way it reacts to xenobiotics, thus they are being rapidly excreted (Albuquerque *et al*., 2021). The term

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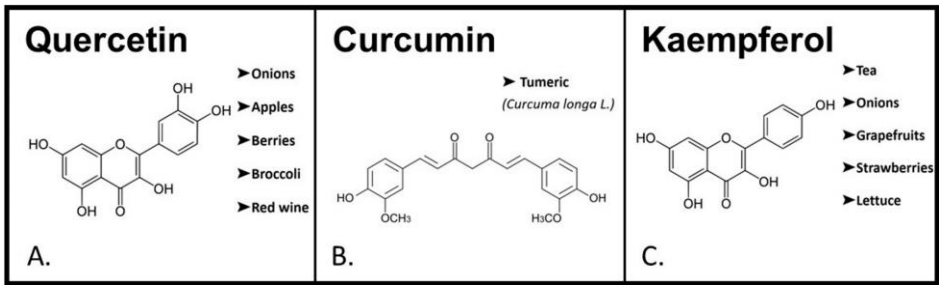

Figure 1. Chemical structures of quercetin (A), curcumin (B), and kaempferol (C) and their main dietary sources.

"bioavailability" derives from pharmacology and refers to the time and amount to which a drug reaches its target of action. Currently the most accurate definition of this term is probably "that fraction of an ingested nutrient or compound that reaches the systemic circulation and the specific sites where it can exert its biological action" meaning simply how much of ingested polyphenol will reach target tissue and perform its beneficial action (D'Archivio *et al*., 2010).

Bioavailability of polyphenols depends on their concentration in food, kind of food matrix, its preparation and interactivity with other compounds such as protein bonding (Visioli *et al*., 2014). Moreover, despite their large bioactivity, they might perform poor effectivity in the human body due to their lower intrinsic activity or poor absorption from the intestine or expeditious elimination. Interestingly, although detailed mechanisms of intestinal absorption and metabolism of are not investigated, it is assumed that most of the polyphenols might be too hydrophilic to infiltrate the gut wall by passive diffusion (Manah *et al*., 2004). Furthermore, absorption of phenolic compounds depends on the release of microbial metabolism and activity of digestive enzymes localized in epithelial cells of small intensine, such as lactase phloridzin hydrolase (LPH) and cytosolic b-glucosidase (CBG), which facilitates absorption of polyphenols through hydrolysation of their glycosides. However, it is assumed that compounds with high level of polymerization are not able to be absorbed properly the in small intensine, as a result of which only small part of them undergo further metabolism and reaches circulatory system (Hui Teng and Lei Chen, 2018).

Quercetin

Quercetin (3,3',4',5,7-pentahydroxy-flavone) (Fig. 1A) draws its name from the Latin word *Quercetum*, which means "Oak Forest" and belong to one of the six subclasses of flavonoids called flavonols. It is a plant pigment present in high concentrations in onions, grapes, berries, and broccoli (Anand David *et al*., 2016). In plants, quercetin plays various tasks in facilitating their proper physiological functioning, through regulating ROS (reactive oxygen species) level. Quercetin also takes part in modulating auxin signalling and, therefore has an impact on the growth of the plant (Singh *et al*., 2021). Selected biological properties of quercetin are presented in Figure 2.

Occurrence

Quercetin is present in many dietary and medical plants. It is abundant in onions, apples, tea, red wine, and *Ginkgo biloba* (Williamson *et al*., 2005). It might

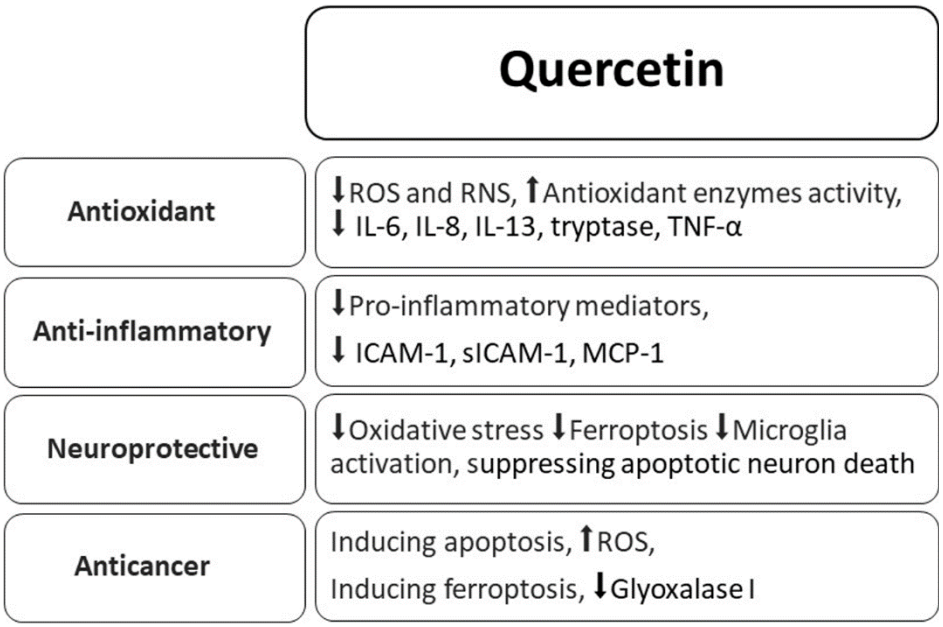

Figure 2. Summary of the most important biological properties of quercetin discussed in the review.

also be found in berries. Häkkinen *et al*. (1999) analysed 16 species of cultivated berries and 9 species of wild berries and found quercetin in all of them, unlike other flavonols examined in the study. The highest concentration of quercetin was found in the wild bog whortleberry *Vaccinium uliginosum* (158 mg/kg, fresh weight). A high concentration of quercetin was also noted in cranberries (83 and 121 mg/kg). Numerous glucoside forms and quercetin aglycone were found in onion bulbs (*Allium cepa* L.), which belong to the richest sources of flavonoids in human diet (Slimestad *et al*., 2007). Interestingly, the kind of food matrix is important, when it comes to concentration and bioavailability of polyphenols, including quercetin. Wiczkowski *et al*. (2008) examined, that in dry shallot skin total content of quercetin was more than 20 times higher than in the flesh. Moreover, authors suggest that quercetin aglycone which is abundant in dry shallot skin is more bioavailable due to its low hydrophilicity than quercetin glucosides present in the flesh. Furthermore, quercetin was also detected in 19 honeys of different floral and non-floral sources (Petrus *et al*., 2011).

Anti-inflammatory Activity

Quercetin is known for its anti-inflammatory properties (Oršolić *et al*., 2004). Inflammation is a complex immune response of the organism triggered by the harmful biological, chemical of physical stimuli. Immune mechanisms include the involvement of immune cells, for example, basophils, mast cells, macrophages, monocytes, and inflammatory mediators. Examples of these mediators are inflammatory cytokines, especially interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), and ROS. Excess of ROS might offset and exacerbate inflammation via degradation of the IκB – inhibitor associated with transcription factor NF-

κB. As a result of that, active NF-κB upregulates expression of genes associated with inflammatory response, increasing production of proinflammatory cytokines (Morgan *et al*., 2011). With that being said, the antioxidative properties of flavonoids such as quercetin are important factors in reducing inflammation. Carullo *et al*. (2017) compared the effects of quercetin and its derivatives derived from different plant extracts. These compounds performed anti-inflammatory actions via e.g., ROS reduction, inhibition of NF-κB and decreasing levels of proinflammatory mediators. Extracts containing quercetin appeased inflammation in gastrointestinal disorders, obesity, gout, and atherosclerosis.

Multiple in vitro and in vivo studies examined mechanism of inflammation reduction as a result of quercetin intake. Quercetin was confirmed to suppress release of pro-inflammatory mediators such as IL-6, IL-8, IL-13, tryptase, and TNF-α in human mast cells. Moreover, quercetin inhibited activation of the calcium-insensitive protein kinase C theta (PKC θ), suggesting its potential in the treatment of allergies (Kempuraj *et al*., 2005). Mast cells products such as tryptase might also be associated with the process of neurodegenerative disease, which indicates quercetin's potential in their treatment since it suppresses mast cells exocytosis (Chirumbolo *et al*., 2010). Additionally, Bureauet *et al*. (2008) investigated that treatment with quercetin suppressed the apoptotic death of PC12 neurons mediated by microglial inflammatory activation. It also inhibited IL-1a and TNF-α gene expression in N9 microglia cells treated with lipopolysaccharide (LPS). Furthermore, Cheng *et al*. (2019) examined that quercetin suppressed protein and gene expression of intercellular adhesion molecule-1 (ICAM-1), soluble ICAM-1 (sICAM-1), monocyte chemoattractant protein-1(MCP-1), IL-6 and IL-8, which level increased as a result of stimulation of ARPE-19 cells with proinflammatory cytokine IL-1β. Several *in vivo* studies showed various health effects of quercetin, such as regulating immune response in obese rats and improving retrieval of motor functions in rats with severe spinal cord injury (Di Petrullo *et al*., 2022; Li *et al*., 2016)

Anti-cancer Activity

'Cancer' is a generic term that embraces a wide spectrum of diseases affecting different parts of the body. It is an effect of a multi-step and multi mechanism process called oncogenesis (Nakamura *et al*., 2005). Heavy issue of this disease is the rapid formation of abnormal cells which grow beyond their usual size and invade vicinal areas, eventually causing the process called metastasis (invasion of other organs and generating secondary tumours), which is a final stage of the cancer leading to death. As already mentioned above, multiple studies demonstrated potential of quercetin in regulating inflammation. Prolonged or chronic inflammation might lead to carcinogenesis.

First to make connection between inflammation and cancer after noting presence of lymphocytes in neoplastic tissue was Rudolf Virchow in 1863 (Balkwill and Mantovani, 2001). Certain chronic infections, such as autoimmune disease and microbial infections are associated

with certain types of cancer (for instance, inflammatory bowel disease with colon cancer and infection with *Helicobacter pylori* with gastric cancer) (Mantovani *et al*., 2008). Moreover, infection with *Schistosomiasis* is associated with bladder malignancy and infection with *Papillomavirus* is linked to cervical cancer (Balkwill and Mantovani, 2001).

Chronic inflammation results in excessive generation of ROS. Macrophages produce reactive oxygen and nitrogen species in order to eradicate harmful stimuli such as pathogens. This immoderate production of inflammatory mediators taking place during chronic infection might lead to mutations and DNA damage. Tumour and tumour-associated cells might produce major pro-inflammatory cytokines and chemokines which might lead to malignant progression. Many of them are induced by hypoxia, which significantly differentiates tumours from normal tissue (Singh *et al*., 2019).

Diet plays pivotal role in prevention and treatment of cancer (Narimatsu and Yaguchi, 2022). Quercetin is the most common flavonoid in the human diet and one of the most sufficient antioxidants (Formica and Regelson, 1995; Prior, 2003). Thus, it is a potent compound in anti-cancer therapy due to its health beneficial properties. Quercetin inhibits glyoxalase I which plays crucial role in production and regeneration of key factors of tumour growth, such as D-lactase and glutathione (Formica and Regelson, 1995). Quercetin also inhibits ferroptosis which is a special kind of programmed cell death, connected with excessive production of ROS and accumulation of iron, characteristic for many diseases including diabetes, renal and liver injuries, and neurodegenerative diseases such as Parkinson's disease and epilepsy. In all of these injuries, quercetin alleviated ferroptosis by preventing ROS production and other mechanisms like preventing iron accumulation, increasing level of glutathione (GSH), and glutathione peroxidase 4 (GPX4) (Cruz-Gregorio and Aranda-Rivera, 2023). GSH is a key molecule used by many enzymes to neutralize ROS (Ferreira *et al*., 2023). GPX4 is an important antioxidant enzyme which plays crucial role in alleviating ferroptosis via reduction of phospholipid hydroperoxides (Xue *et al*., 2023).

Quercetin also inhibits ferroptosis present during lung inflammation and asthma through decreasing levels of pro-inflammatory mediators. On the other hand, quercetin promotes ferroptosis in cancer cells by increasing the iron level leading to excessive production of ROS. Moreover, quercetin decreases level of GPX4 and induces ferritinophagy, which facilitates iron 'recycling' and induces apoptosis (Cruz-Gregorio and Aranda-Rivera 2023). Interestingly, in comparison with normal cells, cancer cells are more iron-dependent and vulnerable to ferroptosis. Wang and colleagues examined that quercetin induces cancer cell death via ferroptosis induced by ROS and lysosome activation mediated by transcription factor EB (TFEB) (Wang *et al*., 2021). Among cancers, lung cancer is the main cause cancer-related deaths worldwide (Ferlay *et al*., 2015). Non-small cell lung cancer (NSCLC) is a histological subtype of lung cancer involving adenocarcinoma, squamous cell carcinoma and large-cell carcinoma histosubtypes, referring to about 85% of new cases of lung cancer (Gridelli *et al*., 2015). Recent studies reveal that quercetin and its derivatives perform therapeutic effects on NSCLC (Alsharairi, 2023). In the research conducted by Zhou *et al*. (2023) quercetin reduced proliferation in A549 and H1299 NSCLC cells while not having such effect on normal lung epithelial BEAS-2B cells. Moreover, authors concluded that quercetin via SIRT5/PI3K/AKT pathway induces apoptosis and DNA damage in NSCLC cells but not in normal cells. In another recent study, quercetin inhibited glucose-6-phosphate dehydrogenase (G6PD) which level is increased in many cancers and is associated with drug resistance. Via inhibiting G9PD quercetin had an impact on degradation of

EGFRT790M, a common mutation in NSCLC (Ge *et al*., 2023).

Curcumin

Curcumin (1,7-Bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione) (Fig. 1B) also known as diferuloyl methane, is a compound extracted from the rhizomes of turmeric (*Curcuma longa* L.). Curcumin is one of the curcuminoids, which are a subclass of non-flavonoid polyphenols. Curcumin has multiple applications worldwide and is being used in food, beverages, cosmetics, as a colorant, and as antiseptic (Hewlings and Kalman, 2017). It has been used in medicine for centuries due to its various health promoting properties (Fig. 3) (Priyadarsini, 2014). For example, in traditional Indian medicine turmeric is being used for healing diabetic wounds, rheumatism, and hepatic disorders (Eigner and Scholz, 1999). In recent years curcumin has been the subject of many studies and it has been examined to have antioxidative, anti-inflammatory, anti-cancer, anti-aging, antimutagenic, antimicrobial, cardioprotective, hepato-protective, anti-diabetic, and anti-aging properties (Hewlings and Kalman, 2017; Kotha and Luthria, 2019; Monroy *et al*., 2013).

Antioxidant Activity

Curcumin is a strong, lipid soluble antioxidant that, contrary to most natural antioxidants, has both phenolic and a b-diketone group on the same molecule (Priyadarsini, 1997). Important property of curcumin is the ability to scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS), thus preventing lipid membrane peroxidation which has deleterious results for the whole organism (Visioli *et al*., 2014; Wright, 2002). Curcumin also increases the activity of catalase, glutathione peroxidase (GPx), superoxide dismutase (SOD) and heme oxygenase-1 (OH-1), important antioxidant enzymes (Pulido-Moran *et al*., 2016). Moreover, curcumin can inhibit the of expression ROS-generating enzymes such as cyclooxygenase-2 (COX-2) and 5-lipooxygenase (5-LOX), as well as vascular endothelial growth factor (VEGF), phosphorylated signal transducers and activators of transcription 3 (STAT3) and matrix metalloproteinase-9 (MMP-9), factors directly associated with tumorigenesis (Lin *et al*., 2007). Due to its lipophilic character, curcumin is often compared to vitamin E and considered as a chain-breaking antioxidant (Hewlings and Kalman, 2017; Priyadarsini *et al*., 2003).

Anti-Inflammatory Activity

As already mentioned in this review, oxidative stress is associated with exacerbation of inflammation, which leads to development of numerous chronic illnesses. Curcumin performed therapeutic effect on many of them, including such as neurodegenerative disease, allergy, metabolic syndrome, cancer, asthma, diabetes, obesity, depression, epilepsy, cerebral injury arthritis, and acquired immune deficiency syndrome (AIDS). Supplementation of curcumin was proved to significantly decrease serum levels of TNF-a, IL-6, MCP-1 and transforming growth factor beta (TGF-β) in subjects with metabolic syndrome (Panahi *et al*., 2016). Moreover, curcumin inhibited NF-κB-related upregulation of cardiac pro-inflammatory genes, which is involved in inflammation causing cardiomyocytic injury in cardiopulmonary bypass (CPB) and cardiac and global ischemia and reperfusion (I/R). Furthermore, curcumin is able to regulate glucose levels in blood and increase plasma insulin levels in diabetes via decreasing oxidative stress and lipid peroxidation (Aggarwal and

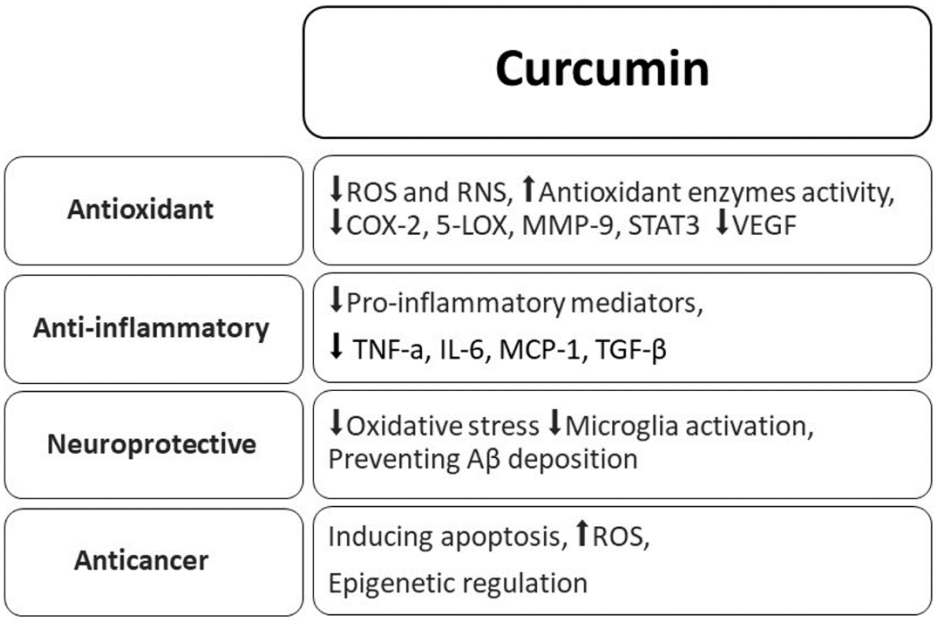

Figure 3. Summary of the most important biological properties of curcumin discussed in the review.

Harikumar, 2009). Additionally, curcumin alleviates skin disorders via moderating inflammation. For example, in psoriasis curcumin decreased levels of TNF-α, IL-2, IL-12, IL-22, IL-23, and IFN-gamma. Due to its antimicrobial properties, curcumin also performed therapeutic effects in bacterial skin infections by inhibiting growth and disruption of bacterial cell membrane and was efficient even against multi drug resistant bacteria (Vollono *et al*., 2019).

Curcumin also has potential as a drug in neurodegenerative disease treatment and neuroprotection. It is able to reduce inflammation in central nervous system (CNS) by inhibiting expression of pro-inflammatory cytokines (IL-1α, IL-6 and TNF-α) by microglial cells, innate macrophages of CNS, which activation plays crucial role in pathogenesis of neurodegenerative disorders such as Alzheimer's disease (AD) (Hansen *et al*., 2018; Monroy *et al*., 2013). Moreover, curcumin may stimulate microglia to phagocytize β-amyloid (Aβ) aggregates, which formation is involved in the pathogenesis of Alzheimer's disease and Huntington's disease. Interestingly, curcumin itself is able to inhibit formation of β-amyloid fibrils due to its high affinity to this protein (Monroy *et al*., 2013). Furthermore, curcumin inhibits neuronal death and mitochondrial dysfunctions induced by various factors such as stimulating and neurotoxic compounds, lifestyle- and excitotoxicity- induced neurodegeneration, and pathologies associated with protein aggregation, thus it has an excellent potential to protects CNS against neurodegenerative disease (Bagher *et al*., 2020).

Anticancer Activity

On the other hand, depending on the concentration and presence of metal ions, curcumin might selectively perform pro-oxidative activities in malignant cells, which may indicate her potential as an

anti-cancer drug (Pulido-Moran *et al*., 2016). In recent years, numerous studies investigated anti-cancer properties of curcumin in many cancers such as breast and lung cancer, haematological cancers, cancers of digestive system and in other kinds of cancer, such as prostate cancer and head and neck cancers (Giordano and Tommonaro, 2019). In the study conducted by Kim *et al*. (2016), curcumin reduced proliferation and induced apoptosis in human cervical cancer cells via generating endoplasmic reticulum (ER) stress resulting in unfolded protein response (UPR), which increased level is a marker of cell death. Interestingly, curcumin did not show any of these actions on normal cells. Moreover, curcumin induced apoptosis small cell lung cancer (SCLC) cells. In comparison with NSCLC already mentioned in this review, SCLC occurs less frequently but is more aggressive and has much higher fatal rate. Yang and colleagues examined that curcumin caused ROS overproduction, decrease of mitochondrial membrane potential, and activation of apoptosome, thus led to apoptosis of NCI-H446 cancer cells (Yang *et al*., 2012). Curcumin is a potential therapeutic agent in colorectal cancer (CRC), which is second the most fatal cancer worldwide (Ionescu *et al*., 2023). Studies suggest the role of curcumin in epigenetic changes in cancer cells. Epigenetic changes, such as DNA methylation and histone modifications which cause remodelling of the chromatin and result in phenotype changes, are involved in the pathogenesis of many diseases, including cancer (Rajendran *et al*., 2022). Treatment with curcumin caused alterations in gene expression and DNA methylation in HCT116, RKO and HT29 colorectal cancer cells (Link *et al*., 2013). In recent study it was examined that curcumin increased ROS levels in HCT116 cancer cells and therefore activated KEAP1/NRF2/miR-34a/b/c pathway leading to suppression of the tumour (Liu *et al*., 2023).

Kaempferol

Kaempferol, (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) (Fig. 1C), owning its name after Engelbert Kaempfer who was a German doctor, naturalist, and historian thanks to which Europe could acquaint with traditional methods of Asian medicine (Periferakis *et al*., 2020), is an organic chemical compound belonging to the group of flavonoids which are a class of polyphenols (Chen *et al*., 2022). It is a tetrahydroxyflavone in which the four hydroxy groups are located at positions 3, 5, 7, and 4' (Imran *et al*., 2019). Kaempferol is immensely substantial in most edible plants such as tea, fruits and vegetables including species: onion (*Allium cepa*) (Rodríguez Galdón *et al*., 2008), tea (*Camellia sinensis*) (Lee *et al*., 2008), grapefruit (*Citrus paradisi*) (Gupta *et al*., 2018), strawberry (*Fragaria vesca*) (Sun *et al*. 2014), and lettuce (*Lactuca* sativa) (Złotek *et al*., 2014) as well as in medicinal plants for instance *Kaempferia galanga* (L.) (Huang *et al*., 2008), *Acacia nilotica* (L.) (Al-Nour *et al*., 2019), *Aloe vera* (L.) (Keyhanian *et al*., 2007), *Crocus* sativus (L.) (Mokhtari-Zaer *et al*., 2015), *Ginkgo biloba* (L.) (Zhang *et al*., 2008), *Hypericum perforatum* (L.) (Silva *et al*., 2008), and *Rosmarinus officinalis* (L.) (Bai *et al*., 2010).

Traditionally, plants rich in kaempferol were used to treat the symptoms of hypertension, abdominal pains, headache, rheumatism, toothache, dyspepsia, coughs, and inflammatory tumour. Currently, many studies have shown kaempferol's much broader spectrum of health-promoting effects (Fig. 4). In particular, antioxidant, anti-inflammatory, antimicrobial, anticancer,

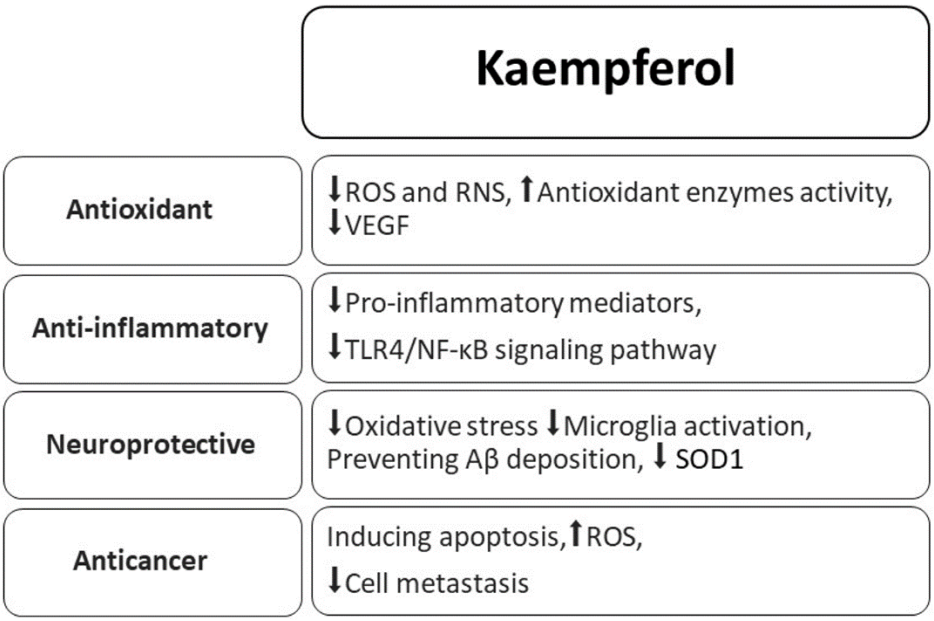

Figure 4. Summary of the most important biological properties of kaempferol discussed in the review.

cardioprotective, neuroprotective, anti-diabetic, anti-osteoporotic, estrogenic/ antiestrogenic, antiviral, anxiolytic, analgesic, and antiallergic activities (Calderón-Montaño *et al*., 2011).

As a result, because of its pervasiveness and comprehensiveness in pharmacological properties this compound is once again gaining importance in modern medicine. Furthermore, nowadays there is essential hope in kaempferol's cytotoxic activity against multiple types of human cancer cells while showing high selectivity for tumour cells and little or non-effect on normal cells (Matsuda *et al*., 2002; Zhang *et al*., 2008). The abovementioned qualities make kaempferol an ideal nominee for an agent associated with cancer prevention or cancer co-therapy as chemotherapeutic (Lim *et al*., 2007; Ninomiya *et al*., 2013; Sak, 2014; Szliszka *et al*., 2011).

Antiviral Activity

Kaempferol has shown antiviral action against both DNA and RNA viruses. Moreover, it is also confirmed that compound has effects on enveloped viruses, such as hepatitis B (Yang, 2014). In an *in vitro* study carried out by Parvez *et al*. this compound exhibited its anti-hepatitis B activity by inhibiting HBsAg and HBeAg (HBe which is a marker for cccDNA replication) synthesis (Parvez *et al*., 2022). Furthermore, the research shows kaempferol's ability to form stable complexes with HBV- polymerase binding-pocket amino acids, therefore it could be potentially used as a therapeutic agent against HBV virus (Parvez *et al*., 2022).

Another virus in which kaempferol may be used in the treatment is African Swine Fever Virus. African Swine Fever (ASF) caused by mentioned virus in a repeatedly fatal disease which targets monocytes and macrophages (Njau *et al*.,

2021). It is entering the cells principally through endocytosis, mediated by receptors, and via micropinocytosis. Kaempferol is said to inhibit the endocytosis, by such means the virions are prevented from releasing to the cell. It is resulting in the suppression of viral infection even over 90% (Arabyan *et al*., 2021).

A fortiori, studies have evaluated the efficacy of kaempferol in action against SARS-CoV-2 (Anand *et al*., 2021; Khazdair *et al*., 2019). It exhibited promising molecular docking parameters on the N3 side in the Covid-19 main protease, which shows its promising use in the treatment (Owis *et al*., 2020).

Interestingly, in many cases kaempferol has a treatment effectiveness comparable to the specific drugs, which appears to be important considering the side effects of a drug therapy. Thus, supplanting or supplementation a drug with kaempferol, seems to be a good alternative (Periferakis *et al*., 2023).

Inhibition of low-density lipoprotein (LDL) oxidation

Flavonoids in general are considered as potent inhibitors od LDL oxidation, which is a complex process during which both the protein and the lipids undergo oxidative alterations causing in formation of complex products. Inhibitory effect is shown by cell protection against damage induced by reactive oxygen species (ROS) and copper ion-induced oxidation, exhibition of radical-scavenging activity and scavenging free radicals, exhibition of affinity to ATP-binding proteins (associated with their structural analogy with ATP) (Fuhrman *et al*., 2002; Tomás-Barberán *et al*., 2012). This activity is prominently important taking into consideration how many diseases are connected with oxidative stress and the oxidation of low-density lipoprotein, e.g. atherosclerosis linked by various studies to those processes since last century (Quinn *et al*., 1987; Steinberg *et al*., 1989; Steinbrecher *et al*., 1984)

Neuroprotective activity

Kaempferol has presented a neuroprotective action via the modulation of some proinflammatory signalling pathways including the nuclear factor kappa B (NF-kB), p38 mitogen-activated protein kinases (p38MAPK), serine/ threonine kinase (AKT), and β-catenin cascade (Silva dos Santos *et al*. 2021)., This compound has shown its value in potential neuropathic pain (NP) treatment via regulating the activation of TLR4/NF-κB signalling pathway, which hyperactivity has been proven to cause chronic inflammation (Chang *et al*., 2022). Moreover, research to date have suggested that kaempferol and its derivatives possess neuroprotective properties and may have potential therapeutic benefits in neurodegenerative diseases (NDDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). Kaempferol has a positive effect on the nervous system and structures directly related to it. Specifically, said compound influence prevention of the deposition of amyloid fibrils (e.g. amyloid β-protein (Aβ), tau, α-synuclein),inhibition of microglia activation, reduction of the release of inflammatory factors, scavenging free radicals, restoration of the mitochondrial membrane (which prevent oxidative stress), protection of the blood-brain barrier, and inhibition of specific enzyme activities (e.g. cholinesterase which is an enzyme responsible for catalysation of the hydrolysis of the neurotransmitter acetylcholine (ACh) into choline and acetic acid (Colović *et al*., 2013).

ALS is a fatal, progressive NDD that selectively affects motor neurons (Yang *et*

al., 2021). Characteristic changes occur in these neurons under the influence of the disease, i.e., aggregation and accumulation of ubiquitinated protein inclusions (Bendotti *et al*., 2012). Studies have proven that there is a correlation between the activity of the SOD1 enzyme and the pathogenesis of ALS and the progression of the disease. For example, transgenic mice expressing human ALS-related variants SOD1G93A, SOD1G37R, and SOD1G85R exhibited a distinct ALS-like phenotype, such as SOD1 aggregation, mitochondrial dysfunction, death of motor neurons, and overall motor disability (Chen *et al*., 2021; Bk *et al*., 2019; Pambo-Pambo *et al*., 2009). In contrast, loss of SOD1 function significantly improved motor system dysfunction. Kaempferol protects against neurotoxicity caused by mutant SOD1 in an ALS model, furthermore, inhibits mutant SOD1-induced cell death, and also reduces intracellular aggregation of SOD1 mutants and significantly inhibits SOD1-induced mitochondrial superoxide mutants, suggesting that kaempferol is a candidate for naturopathic treatment of ALS (Jin *et al*., 2023).

Anticancer activity

It is said that diet rich in vegetables and fruits (particularly those rich in flavonoids such as kaempferol) significantly reduces the risk of multiple diseases, such as cancer. Interestingly, there is a monitored low cases of cancer disease in the population of vegetarians (Petrick *et al*., 2015; WHO, 2014). Deducing, that diet is closely related to the incidence and prevention of different cancer types. Moreover, convincing epidemiological evidence suggests that ingestion of foods saturated in the kaempferol could lead to reduction of development of certain cancers, which has been proven by numerous in vitro studies. Besides this aspect, there are much research showing the inhibitory ability of this flavonoid on the growth of different cancers, among others glioma/glioblastoma (Sharma *et al*., 2007), breast adenocarcinoma (Diantini *et al*., 2012), leukaemia (Ren *et al*., 2010), lung cancer (Leung *et al*., 2007), colorectal carcinoma (Li *et al*., 2009).

Furthermore, kaempferol display a direct effect on the apoptosis extrinsic pathway, due to the presence of death receptors on the cell surface able to recognize substances responsible for death induction. Mentioned death receptors include tumour necrosis factor alpha (TNF-α), FAS and TRAIL (Thorburn, 2004). The TRAIL receptor is particularly taken into account because of its specification, such as induction of apoptosis in human colon cancer cells and a deficiency in the expression on cell surface which explains resistance of cancer cells to apoptosis (Jin *et al*., 2004). Kaempferol is likely to up-regulate said TRAIL receptors by reducing cancer cells' resistance to apoptosis and sensitization of those cells onto TRAIL-dependent apoptosis (Yoshida *et al*., 2008). Several in vitro and in vivo research showcase kaempferol's impact in induction of apoptosis in cancer cell in various tissues, for instance lung (Conforti *et al*., 2009; Leung *et al*., 2007), breast (Kang *et al*., 2009; Kim *et al*., 2008), colon (Li *et al*., 2009), prostate (Brusselmans *et al*., 2005), liver (Mylonis *et al*., 2010), pancreas (Zhang *et al*., 2008), blood/lymph (Benyahia *et al*., 2004), skin (Li *et al*. 2007), brain (Jeong *et al*., 2009b), uterus (Li *et al*., 2007), and ovary (Luo *et al*., 2010).

Research shows that kaempferol is demonstrating antiangiogenic activities (generation of new blood vessels) (Kim and Choi, 2013). The main mediator of this process is vascular endothelial growth factor (VEGF) (Ferrara, 2004). Kaempferol can significantly reduce

VEGF expression in ovarian cancer cells, which leads to reduction of tumour proliferation. Moreover, kaempferol is able to inhibit HIF-1 transcription factor at a low micromolar range (Luo *et al*., 2009; Mylonis *et al*., 2010), which could be a potential therapeutic target, as the overexpression of HIF-1 causes the induction of tumour aggressiveness.

Metastasis is a process during which cancer cells spread from their original site to other areas of the body. For this process to occur, cancer cells must degrade extracellular matrix (ECM), which allows them to reach the blood vessels and then proliferate throughout the organism. For this purpose, cancer cells use various enzymes, such as the matrix metalloproteinases (MMPs), which give rather poor clinical prognoses in cancer patients (Guan, 2015). For that reason, there are studies testing the usage of various substances in therapy against this process. Kaempferol has exhibited inhibitory effect on cell metastasis through ERK-p38, JNK, and AP-1 signalling pathways in human osteosarcoma cells (Chen *et al*., 2013). This compound has the ability to reduce protein phosphorylations at ERK, p38, and JNK, thus decreasing the DNA binding activity of AP-1, and causing reduction in expression of MMP-2, MMP-9, and uPA (urokinase-type plasminogen activator), therefore overall reduction of metastatic potential (Li *et al*., 2014; Lin *et al*., 2013).

Conclusions

Polyphenols are important compounds in the human diet characterized by their various properties beneficial for health (Fig. 5). Kaempferol, quercetin, and curcumin are strong antioxidants performing health-promoting activities, including anti-oxidative, anti-inflammatory, antimicrobial, antiviral, and neuroprotective properties. These compounds have recently been intensively examined in terms of their anti-cancer activity. Numerous in vivo and in vitro studies investigated their ability to inhibit proliferation and promote cell death via inducing apoptosis in cancer

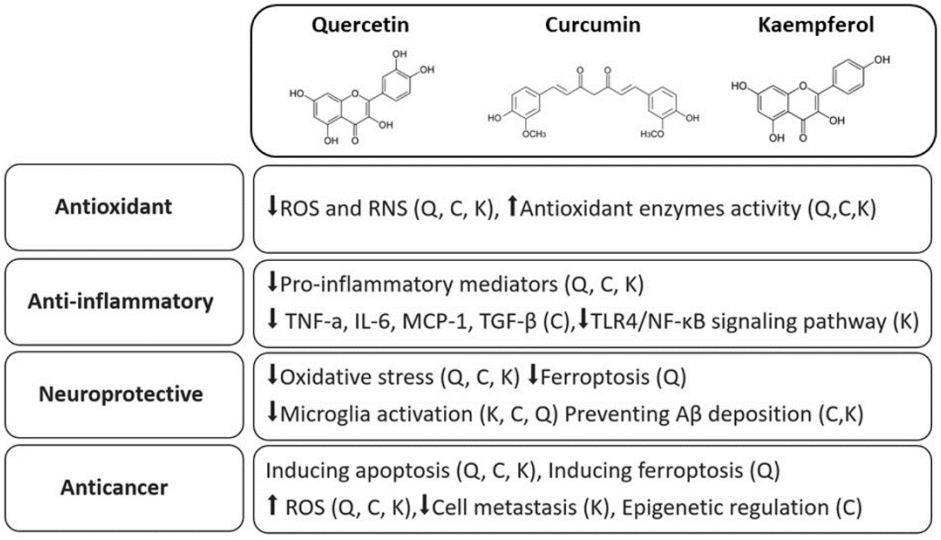

Figure 5. Summary of the most important biological properties of quercetin (Q), curcumin (C), and kaempfrrol (K) discussed in the review.

cells. However, due to the low bioavailability of polyphenols, their health beneficial effect as dietary compounds remains indeterminate. Thus, absorption and interactions with other compounds potentially increasing bioavailability of polyphenols need to be further studied to thoroughly utilize their therapeutic potential. Moreover, anticancer potential of quercetin, curcumin, and kaempferol and their ability to abolish resistance in cancer cells appear to be important areas for further research.

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