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Authors' Affiliation:
[1]Department of Plastic and Burns Surgery, Multispecialty Hospital in Nowa Sól, ul. Chałubińskiego 7, 67-000 Nowa Sól, Poland
[2]Collegium Medicum of the University of Zielona Gora, ul. Zyty 28, 65-046 Zielona Góra, Poland

[*]**Corresponding author:**
Żanna Gawrysz, Department of Plastic and Burns Surgery, Multispecialty Hospital in Nowa Sól, ul. Chałubińskiego 7, 67-000 Nowa Sól, Poland;
Email: zhanna.gavrysh@gmail.com; Phone: +48 734 393 139

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ORCID List

Żanna Gawrysz	0009-0001-9929-1332
Zofia Cholewa	0009-0003-0855-1843
Stanisław Derewjanko	0009-0009-2308-2575
Joanna Gaik	0009-0005-5774-4494
Julia Woźniak	0009-0004-6866-4281
Karolina Capar	0009-0008-8492-6957

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Curcumin as a neuroprotective agent: mechanisms and therapeutic potential in neurodegenerative diseases, acute brain injuries, and neuroinflammation. A review of the literature

Żanna Gawrysz[1*], Zofia Cholewa[2], Stanisław Derewjanko[2], Joanna Gaik[2], Julia Woźniak[2], Karolina Capar[2]

ABSTRACT

Curcumin is a bioactive compound that comes from the underground stem of the plant called turmeric or Curcuma longa. Researchers have studied curcumin due to its anti-inflammatory and oxidative properties. In this article, we have attempted to summarize the latest information on the medicinal value and specific characteristics of curcumin. Some of them are preventing and treating neurodegenerative diseases, inflammatory disorders, and acute brain injury. As a natural polyphenol, curcumin can go through the blood-brain barrier, which makes it a potential neuroprotective agent. It prevents the accumulation of pathogenetic polypeptides, promotes neuronal plasticity, and ameliorates the effects of secondary inflammatory and oxidative responses in the brain after injury. All these properties of curcumin make it desirable in the treatment of diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. There are also many prospects for use in the treatment or prevention of brain injury and ischemic stroke.

Keywords: curcumin, neuroprotection, neurodegenerative diseases, anti-inflammatory

1. INTRODUCTION

The rhizome of turmeric (Curcuma longa) contains a yellow polyphenolic pigment curcumin, also known as diferuloylmethane (Gupta et al., 2013). Curcumin is a substance with a wide range of biological properties. For many years, it has attracted scientific and medical interest. Curcumin defends cells from oxidative stress due to its potent antioxidant properties through interactions with reactive oxygen species and modulation of the activity of antioxidant enzymes. The above changes can lead to chronic and neurodegenerative diseases (Aggarwal and

Harikumar, 2009; Hewlings and Kalman, 2017). The cause of neurodegenerative diseases is the loss of neurons. Chronic inflammation, stress, and abnormal protein aggregation in the brain also contribute to this (Barnham et al., 2004; Heneka et al., 2015).

Curcumin has anti-inflammatory, antioxidant, and neuroprotective properties and inhibits protein aggregation. It may be helpful in the treatment and prevention of these illnesses (Yang et al., 2005; Zhang et al., 2006). Curcumin protects neuronal cells from destruction and promotes regeneration. This ability can be valuable in cases of traumatic brain injury (TBI) (Sundaram et al., 2017).

Interestingly, curcumin affects the aging process. It has the effect of modulating cellular pathways genetically related to inflammation and oxidative stress. It can also cross the blood-brain barrier (BBB). This therapeutic property has potential in the treatment of brain diseases (Begum et al., 2008; Anand et al., 2007). The low bioavailability of curcumin limits its effectiveness in the body. This observation led researchers to develop preparations and delivery systems that increase the absorption of curcumin and improve its biological effects. (Hewlings and Kalman, 2017).

2. REVIEW METHODS

We conducted the literature review based on an analysis of publications available in the scientific database PubMed, using carefully selected keywords relevant to the study topic, such as curcumin, neuroprotection, neurodegenerative diseases, and curcumin bioavailability. This review includes clinical studies, meta-analyses, and systematic reviews on the properties of curcumin. Selected articles specifically focus on the possible clinical applications of curcumin as an adjunctive treatment in neurodegenerative and proinflammatory diseases, as well as for the prevention of these disorders. The article screening process adhered to the PRISMA guidelines (Figure 1).

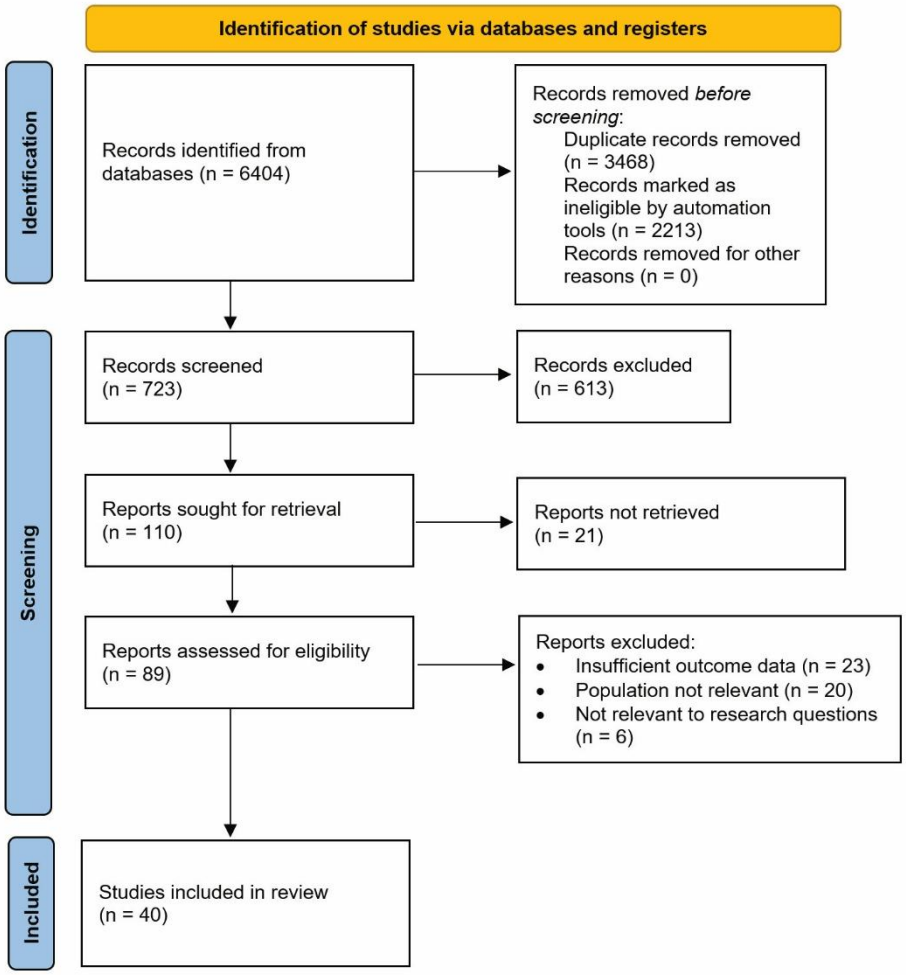

Figure 1. PRISMA flow diagram.

3. RESULTS & DISCUSSION

This article aims to examine the possible therapeutic uses of curcumin in neurological disorders, brain injuries, and acute conditions. The molecular mechanisms involved in its action, as well as the barriers that need to be overcome to increase the efficacy and bioavailability of the compound, require special attention. Curcumin passes the BBB. This possibility has a potential application for diseases of the central nervous system, such as neurodegenerative diseases. Its action results from the removal of reactive oxygen species, suppression of inflammatory pathways, and preservation of neurons against oxidative damage. Curcumin is characterized by low bioavailability and poor solubility in water, which hinders its practical clinical application. In recent years, ways have been developed to increase the bioavailability of curcumin.

Known for its powerful anti-inflammatory and antioxidant qualities, curcumin also has significant neuroprotective effects. This fact led the researchers to analyze the effects of curcumin, which would support the prophylaxis and treatment of inflammation and neurodegenerative diseases.

Curcumin – molecular structure and its biological activity

There are three reactive functional groups in the molecular structure of curcumin. It has two phenolic groups and one ketone group. Figure 2 shows the chemical structure of curcumin.

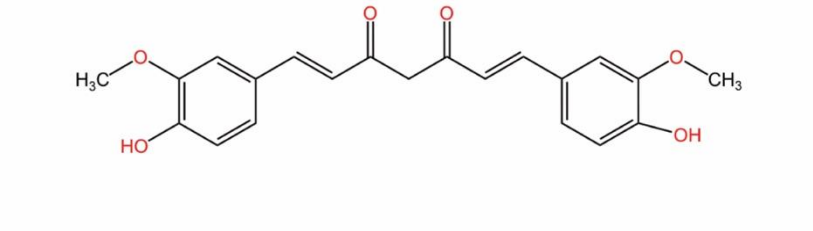

Figure 2: Chemical structure of curcumin.

The biological activity of curcumin is mediated by several key chemical reactions (Prasad et al., 2014). The hydrogen donation leads to the oxidation of curcumin. Also, it undergoes hydrolysis, degradation, and enzymatic transformations. Curcumin neutralizes free radicals and protects cells from oxidative stress. Water-soluble antioxidants, such as ascorbic acid, help the phenoxy radicals formed from curcumin confirm their antioxidant capacity and enhance protection against oxidative stress (Priyadarsini, 2014). Figure 3 shows the regeneration of curcumin radicals by ascorbic acid.

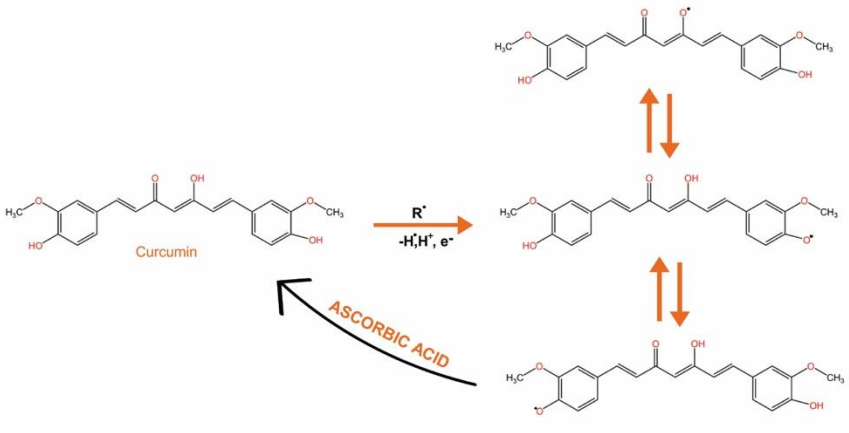

Figure 3: Regeneration of curcumin radicals by ascorbic acid.

Curcumin and anti-inflammatory effects

Curcumin exerts powerful anti-inflammatory and neuroprotective properties. One of its primary mechanisms of action is the inhibition of nuclear factor kappa light chain enhancer (NF-κB) of activated B cells, followed by a subsequent reduction in cytokine expression (IL-6, IL-8) and cyclooxygenase-2 (COX-2) activity. Inhibition of this signaling pathway decreases the activity of calcium ATPase in neurons, resulting in reduced oxidative stress and a lower likelihood of central nervous system (CNS) cell damage (Concetta et al., 2019; Hassan et al., 2019). Furthermore, treatment with curcumin has shown a positive effect on cognitive restoration. Improved motor function recovery has been associated with its protective effects on the BBB, including suppression of extracellular matrix metalloproteinases (MMPs) and other proteins involved in BBB disruption and tissue remodeling. Specific reports have indicated that curcumin may also regulate the PI3K/Akt signaling pathway, regulate the expression of nuclear factor erythroid 2-related factor 2 (Nrf2), and induce the transcription of antioxidant genes such as heme oxygenase-1 (HO-1). This activation leads to further protection against apoptosis and reactive oxygen species (ROS) in the ischemic brain area (Wu et al., 2013). In addition, curcumin shows anti-edematous properties and may promote vascular regeneration following stroke-induced cerebral atrophy. Additionally, curcumin may have a beneficial effect on neurogenesis and synaptic plasticity, implying its potential benefits to encourage the formation of new neural networks during the post-injury recovery phase (Bhattacharjee et al., 2016).

Curcumin and anti-aging effects

Curcumin is a powerful anti-aging substance. It has a lot of different pharmacological activities. These mechanisms likely work in multiple ways. Those ways include affecting gene expression and reducing oxidative stress and inflammation. Curcumin treatment activates a major anti-aging pathway by targeting Nrf2. Nrf2 binds to antioxidant response elements (AREs). It's to upregulate the genes encoding cytoprotective enzymes. Such enzymes include HO-1, thioredoxin (TRX), heat shock protein (HSP) 70, and superoxide dismutase (SOD) (Concetta et al., 2019; Lee et al., 2004).

Via Nrf2, curcumin also indirectly influences the NF-κB pathway, which controls the synthesis of proinflammatory cytokines. Contrary to the typical proinflammatory function of NF-κB, during aging, curcumin supports its bias toward a homeostatic function, decreasing microglial expression of cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α). This effect may play a role in the mitigation of neuroinflammatory processes, which are widely observed in the aging brain (Concetta et al., 2019; Lim et al., 2001).

Curcumin also regulates miR-34a production, whose overexpression contributes to aging and glial cell degeneration. By inhibiting the overexpression of miR-34a, curcumin may indirectly elevate levels of triggering receptor expressed on myeloid cells 2 (TREM2), thereby enhancing microglial capacity to clear damaged structures and proteins in the brain (Bhattacharjee et al., 2016).

Curcumin and epigenetic regulation in neurodegeneration

The neuroprotective effect of curcumin in the course of neurodegenerative diseases also involves epigenetic modulation. Epigenetics concerns the phenomenon of altered gene expression. This includes methylation of cytosine bases in DNA, acetylation of histones, or even the actions of miRNAs, none of which involve changes in the DNA sequence. The effects of curcumin stem from its action on factors modifying epigenetics and, as a result, can decrease inflammatory processes, oxidative stress, and neuronal apoptosis (Hassan et al., 2019; Concetta et al., 2019). Curcumin modulates the addition of acetyl groups to histones H3 and H4, reduces proinflammatory gene expression, and enhances neuronal cell survival. Researchers have shown that curcumin affects DNA methylation by altering the activity of methyltransferase enzymes, which may help stabilize the expression of protective and repair genes in neurons. Curcumin has been found to regulate specific miRNAs in both in vitro and in vivo models, acting as a repressor (Bhattacharjee et al., 2016; Hassan et al., 2019).

Curcumin modulates epigenetic regulation of gene expression regulators such as NF-κB and Nrf2, thereby influencing inflammation control and antioxidant activities. Curcumin may improve Nrf2 activation in the nervous system and increase the expression of antioxidant enzyme genes, while simultaneously inhibiting NF-κB and reducing inflammation in nervous tissue via an epigenetic modulatory effect (Yu et al., 2016; Hassan et al., 2019).

Curcumin and the protection of the blood-brain barrier

Neurogenesis, occurring most effectively in the hippocampus and olfactory bulb, involves the production of new nerve cells out of stem or progenitor cells. Researchers consider curcumin, a biologically active polyphenol, a potential regulatory candidate for these

responses. Curcumin has neuroprotective and neurorestorative effects in diseases of neural degeneration and brain injuries. It can modulate signaling pathways, including brain-derived neurotrophic factor (BDNF). It enhances the proliferation and differentiation of hippocampal neural stem cells. BDNF is a neurotrophic factor that is essential in neuronal survival and synaptogenesis, whose expression is often decreased in neurodegenerative diseases, including Alzheimer's disease. In cells, curcumin-mediated increase in BDNF has been linked with improved cognitive performance in animals (Xu et al., 2007). Also, curcumin affects synaptic plasticity and is implicated in the expression of proteins such as synapsin I and postsynaptic density protein 95 (PSD-95), which play a role in synapse formation and strengthening. Increased levels of these proteins promote synaptic stability in the mature brain and adaptive synaptic remodeling, which is essential for optimal information processing and learning (Zhang et al., 2006).

Curcumin and bioavailability

Curcumin attributes its hydrophobicity to the nonpolar structure of its molecule. Poor curcumin solubility in water leads to its limited absorption into the bloodstream and target tissues. It is rapidly metabolized in the liver, leading to fast excretion. Moreover, the photosensitivity of curcumin and its short-term chemical stability are other barriers to its production and storage, which further complicate its therapeutic use (Concetta et al., 2019). In addition, research has shown that curcumin combined with piperine, an alkaloid present in black pepper, markedly improves curcumin absorption. Results from one randomized study suggest that administration of two grams of curcumin results in serum concentrations that are almost undetectable. In a crossover clinical trial, study participants received two regimens: curcumin at a dose of two grams alone, and curcumin combined with twenty milligrams of piperine. The data showed an increase in curcumin absorption by almost two thousand percent under the combined regimen compared to curcumin alone. Studies show that the effects of curcumin can be observed as soon as one hour after ingestion (Bhat et al., 2019). Piperine inhibits glucuronidation enzymes present in the intestines and liver, thus interfering with the breakdown of curcumin. This slows down the metabolism of curcumin and prolongs its circulation time in the plasma (Shoba et al., 1998; Yu et al., 2016).

Other mechanisms to increase the bioavailability of curcumin are also being developed. These include liposomal, nano-phospholipid complex, and polymeric carriers, which improve solubility, stability, and penetration through biological barriers. Figure 4 shows methods of enhancing curcumin bioavailability.

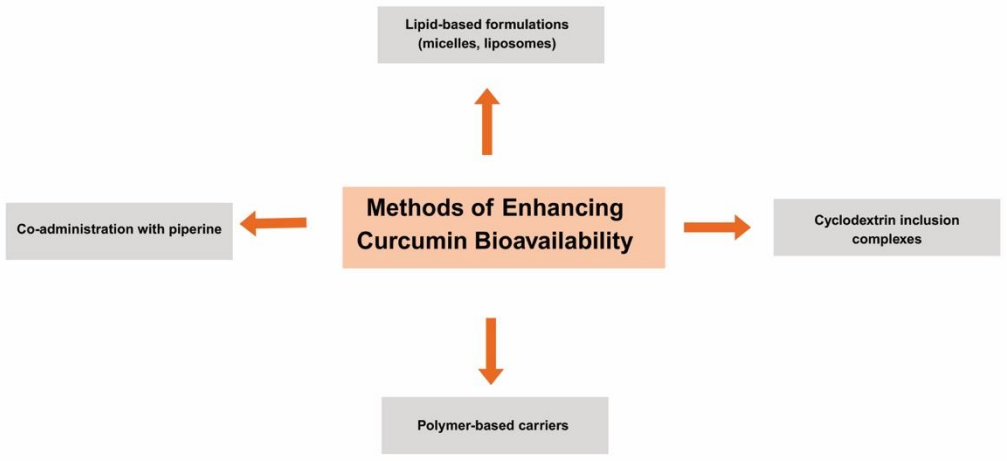

Figure 4: Methods of enhancing curcumin bioavailability.

Curcumin in TBI and Ischemic Stroke

Researchers have studied curcumin as a neuroprotective agent. This is primarily due to the wide range of anti-inflammatory, antioxidant, and immunomodulatory effects of the PI3k/Akt pathway, which help reduce secondary neuronal damage. Scientists examined curcumin in non-human primate models of TBI and found that it reduces lipid peroxidation, microglial activation, and suppresses proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Zeng et al., 2017; Wu et al., 2006). Furthermore, they noticed that curcumin supports motor and cognitive recovery following an insult. It has mechanisms that suppress the activation of extracellular matrix metalloproteinases (MMPs), which are associated with the breakdown of the BBB and tissue remodeling. In addition, curcumin not only has anti-edematous effects but also promotes revascularization of the injured brain tissue after stroke.

There is also evidence suggesting that curcumin exhibits beneficial effects on neurogenesis and synaptic plasticity, which helps promote the repair of neuronal networks during post-injury recovery (Bhattacharjee et al., 2016).

Curcumin and Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder. It's characterized by disorientation in space, memory loss, and a progressive decline in intellectual capabilities, synapse and neuron loss, and oxidative injury. Activation of inflammatory cells and the accumulation of both extracellular amyloid plaques – composed predominantly of beta-amyloid – and intraneuronal neurofibrillary tangles – consisting of hyperphosphorylated aggregates of the protein tau – are typical findings in the postmortem brains of patients with AD (Prasad et al., 2014). Research evidence suggests that because curcumin can cross the BBB, it plays a neuroprotective role against β-amyloid accumulation (Sikora et al., 2010). Studies indicate that curcumin may reduce β-amyloid accumulation in the brain and prevent tau aggregation in experimental transgenic models of AD. In addition, it reduces neuroinflammation, free radical–induced damage, and cognitive deficits following the infiltration of β-amyloid into the brain. Preclinical data have also suggested that curcumin decreases β-amyloid plaque load and soluble β-amyloid peptide levels in brain tissue. Curcumin suppresses the processing of amyloid precursor protein and the production of β-amyloid.

Furthermore, curcumin lowers the levels of soluble tau protein. Also, it increases the levels of heat shock proteins, which are implicated in the clearance of tau protein (Medeiros et al., 2011; Esatbeyoglu et al., 2012). Research shows that curcumin supplementation can improve mental performance in patients with mild cognitive dysfunction and early-stage AD (Dong et al., 2012; Small et al., 2018).

Curcumin and Parkinson's Disease

Parkinson's disease is the second most common neurodegenerative disorder, following AD (Poewe et al., 2017). Parkinson's is characterized by the presence of Lewy bodies. There is a fibrous inclusion within neurons, which is mainly made of α-synuclein (Gaweł and Potulska-Chromik, 2015). Studies have revealed that curcumin can upregulate the expression of heme HO-1 through modulation of Akt/Nrf2 phosphorylation in rotenone-induced Parkinson's disease models in rats (Cui et al., 2016). Curcumin penetrates the blood-brain barrier and decreases protein misfolding and deposition in the extracellular space (Xie et al., 2011). Researchers link this effect to the modulation of HSP 90, HSP 60, and HSP 40 expression (Huppert et al., 2010). Curcumin prevents damage to the mitochondrial membrane, prevents loss of membrane potential, and reduces the production of free radicals (Mythri and Bharath, 2012). Its primary advantage is the capacity to decrease a-synuclein aggregation and induce autophagy, leading to the removal of pathological proteins from neurons (Yang et al., 2005).

Curcumin and Multiple Sclerosis

In the autoimmune disease multiple sclerosis, leukocytes invade the CNS from the peripheral circulation, leading to both microglial activation and demyelination of neurons (Bennett and Stüve, 2009). A prominent pathway of multiple sclerosis involves the activation of IL-17 and IL-22 receptors. In the pathogenesis of multiple sclerosis, the penetration of Th17 lymphocytes into the brain also plays a role. It is accompanied by reduced expression of occludin and ZO-1, proteins characteristic of intercellular connections. Curcumin also facilitates an increase in ZO-1 protein level. It leads to increased phosphorylation of myosin light chain 1 (MLC1), which has the effect of reducing lymphocyte transmigration into the central nervous system (Kornek and Lassmann, 2003). Some studies were performed on animal models. The results suggest that the addition of 1,5 micrometers (μm) curcumin induces differentiation of oligodendrocyte precursor cells into mature target cells (Bernardo et al., 2021).

4. CONCLUSION

Curcumin, a well-known natural polyphenol, possesses a broad spectrum of bioactivities and has excellent potential as a neuroprotective agent. Many experimental and clinical studies show that these effects are believed to involve anti-inflammatory, antioxidative, and anti-aggregative actions, as well as the ability to modulate the cellular response to oxidative stress. These properties are used in conditions including, but not limited to, Alzheimer's and Parkinson's disease, and multiple sclerosis. Researchers attribute the potential health benefits of curcumin to its ability to regulate the expression of proteins responsible for maintaining neuronal integrity and function and to cross the BBB. Curcumin has demonstrated neuroprotective effects in acute CNS injuries, such as TBI and ischemic stroke, by decreasing secondary neuronal damage and increasing functional recovery. Despite these advances, however, the

low bioavailability of curcumin caused by its low water solubility, rapid metabolism, and poor absorption prevents its use as an actual therapeutic agent. Nevertheless, approaches to enhance bioavailability, co-administration with piperine, nano formulations, or liposomal carriers, seem promising.

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Author's Contribution
Conceptualization: Żanna Gawrysz, Zofia Cholewa
Methodology: Żanna Gawrysz, Zofia Cholewa
Check: Żanna Gawrysz, Stanisław Derewjanko
Formal analysis: Zofia Cholewa, Żanna Gawrysz
Investigation: Żanna Gawrysz, Zofia Cholewa, Stanisław Derewjanko, Julia Woźniak
Resources: Żanna Gawrysz, Zofia Cholewa, Joanna Gaik, Karolina Capar, Julia Woźniak
Data curation: Żanna Gawrysz, Julia Woźniak, Stanisław Derewjanko
Visualization: Stanisław Derewjanko, Zofia Cholewa, Joanna Gaik, Karolina Capar
Supervision: Żanna Gawrysz
Project administration: Żanna Gawrysz, Stanisław Derewjanko, Zofia Cholewa
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Conflict of interest
The authors declare that there is no conflict of interest.

Data and materials availability
All data associated with this work are present in the paper.

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