Micro Nano Bio Aspects

https://www.mnba-journal.com

Online ISSN: 2980-8081

Novel formulations of hesperidin for antitumor, antimicrobial, and neuroprotective effects: A review

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ARTICLE INFO

Mini-review paper

Article history:
Received: 05 May 2023
Revised: 15 July 2023
Accepted: 15 July 2023
ePublished: 17 July 2023

Keywords:
Flavanone glycoside, Flavanoglycone, Antiangiogenic, Apoptosis, DNA repair, Cell cycle arrest, Hippocampal

ABSTRACT

Hesperidin as a flavanone glycoside has various pharmacological activities. This phytoactive compound can damage the cell wall of bacteria and lead to a leakage of bacterial macromolecules by the generation of reactive oxygen species (ROS). Modulating cell cycle arrest, antiangiogenic, apoptosis, DNA repair, and antimetastatic have been indicated as the significant anticancer mechanisms of this flavanoglycone. Hesperidin in combination with anticancer drugs can be used as an adjuvant therapy. The Neuroprotective activity of hesperidin resulted from the reduction of 5-HT/IL-β/TNF-α and the increase of BDNF/NE levels in the hippocampal. Moreover, neuropathologic degeneration and spinal cord injury-induced motor dysfunction may be ameliorated by the antioxidant and anti-inflammatory mechanism of hesperidin via the Nrf-2/HO-1 pathway. An effective micro- or nano-delivery system of hesperidin is required to reach its therapeutic target owing to the poor solubility and bioavailability of this bioactive agent. In this review, we have presented recent findings about novel micro- and nano-formulations of hesperidin.

DOI: https://doi.org/10.22034/mnba.2023.394932.1030

Introduction

To combat the bacterial infections resulting from multiple drug-resistant (MDR) bacteria, new antibacterial biocompatible compounds with new modes of action are needed [1]. Furthermore, cancer cells exhibit drug resistance to many chemotherapeutic drugs by several mechanisms. In this regard, finding new effective drugs is a critical affair [2]. There are abundant phytocompounds with various therapeutic effects (Figure 1) [3]. A wide range of pharmacological activities, including anticarcinogenic, anti-inflammatory, and antimicrobial have been found for this metabolite. For instance, flavonoids hinder pro-inflammatory IFN-γ production and antigen-specific memory T cell proliferation [4]. Hesperidin ($C_{28}H_{34}O_{15}$) is a flavanone glycoside isolated from citrus fruits such as lemon, lime, mandarins, grapefruits, and orange (Figure 2)[5]. However, clinical formulations of these bioactive agents are limited because of low water solubility and bioavailability [6]. For solving these problems, novel efficient strategies have been reported based on micro and nanoformulations. Similar to other bioactive compounds, hesperidin can be loaded and encapsulated via various nanocarriers such as liposomes, tocosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric (proteins or polysaccharides) nanoparticles (NPs), and metal/metal oxide NPs or nanocomposites [7-11]. These nanoformulations may increase the bioavailability of hesperidin in physiological conditions. In this regard, this review has tried to address these new strategies.

Anticancer effects

Modulating cell cycle arrest, antiangiogenic, apoptosis, DNA repair, and antimetastatic have been found as the prominent anticancer mechanisms of hesperidin [12]. An efficient delivery system of hesperidin is needed to reach its therapeutic target because of the poor solubility and bioavailability of this metabolite [13]. Hesperidin can be loaded on metal or metal oxide NPs such as gold (Au) NPs and Fe_3O_4 NPs. Hesperidin-Au

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NPs (spherical shape by a diameter in the range of 15-30 nm) inhibited proliferation, growth of human breast cancer cell line (MDA-MB-231) (Figure 3), and the secretion of tumor necrosis factor (TNF), interleukin 6 (IL-6), and interleukin 1 beta (IL-1β). These nanoparticles showed biocompatibility at a concentration of 240 µg/mL with lower hemolytic toxicity compared to hesperidin and AuNPs alone (Figure 4) [14]. In a similar study, hesperidin isolated from orange peel was loaded on chitosan-functionalized Fe_3O_4 NPs. In addition to significant antioxidant activity, these nanoformulations showed more toxicity against MCF-7 breast cancer cells compared to chitosan-functionalized Fe_3O_4 NPs [15]. Combination therapy of hesperidin and apigenin with doxorubicin drug intensified anticancer activity against MCF-7 breast cancer cells. The MCF-7 cells viability values after treatment by apigenin-doxorubicin and hesperidin-doxorubicin were 15.35 % and 19.93 % compared to apigenin and doxorubicin alone with 49.02 % and 98.70 %, respectively (Figure 5). As the prominent anticancer mechanism, these formulations caused significant DNA oxidative damage [16]. To decrease the cardiotoxicity of imatinib mesylate in mice with solid Ehrlich carcinoma, PLGA (poly lactic-co-glycolic acid) NPs were used to load hesperidin and imatinib mesylate in combination therapy. In comparison to monotherapy by imatinib mesylate, there were remarkable decreases in tumor volume, tumor MDR-1 genes, and hematological and cardiac markers in mice under combination therapy by polymeric NPs [17].

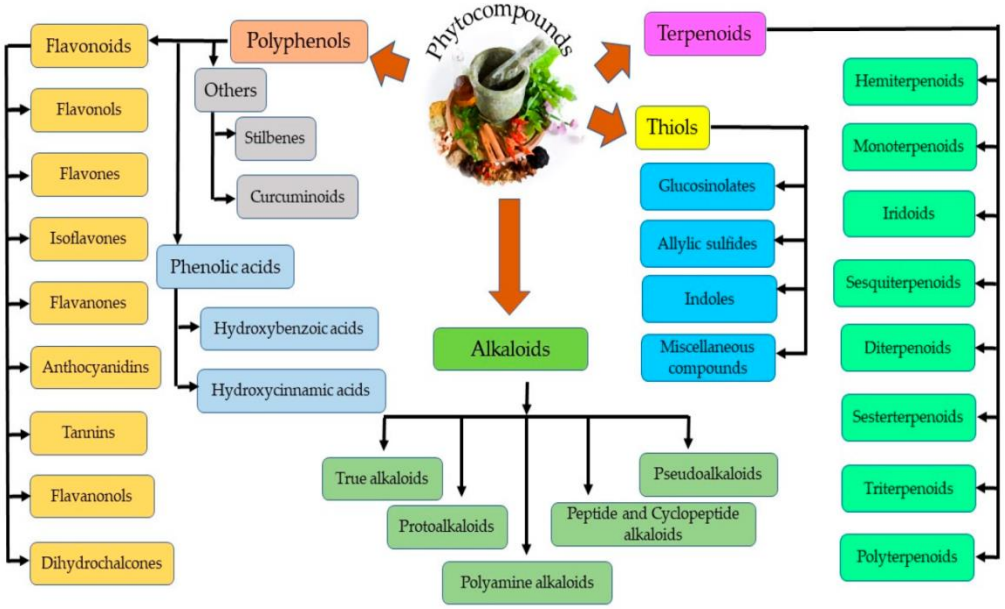

Fig. 1. Various bioactive compounds are isolated from plant sources [3].

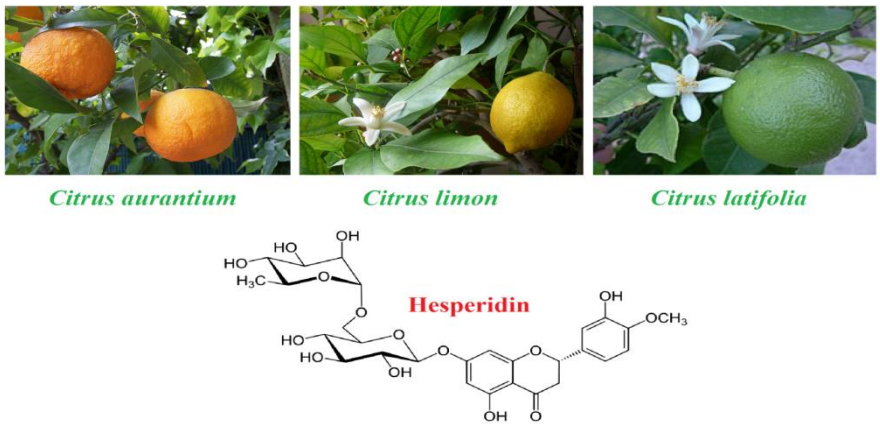

Fig. 2. Chemical structure of hesperidin (a flavanone glycoside) and the main plant sources.

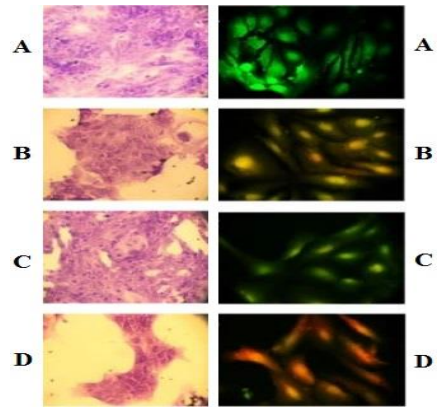

Fig. 3. Growth of breast cancer MDA-MB-231 cell lines was inhibited by hesperidin-AuNPs. (A) control cells (B) cells treated by hesperidin (C), cells treated by AuNPs (D), and cells treated by hesperidin-AuNPs (adopted and modified from [14]).

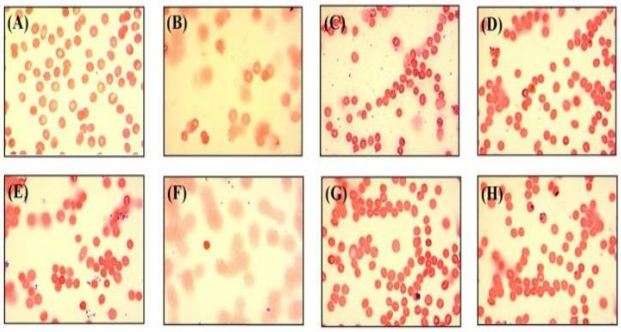

Fig. 4. Hemolytic effects of the negative (A) and positive (B) controls, AuNPs (C and D), hesperidin (E and F), and hesperidin-AuNPs (G and H) at concentrations of 20 and 240 µg/mL (adopted and modified from [14]).

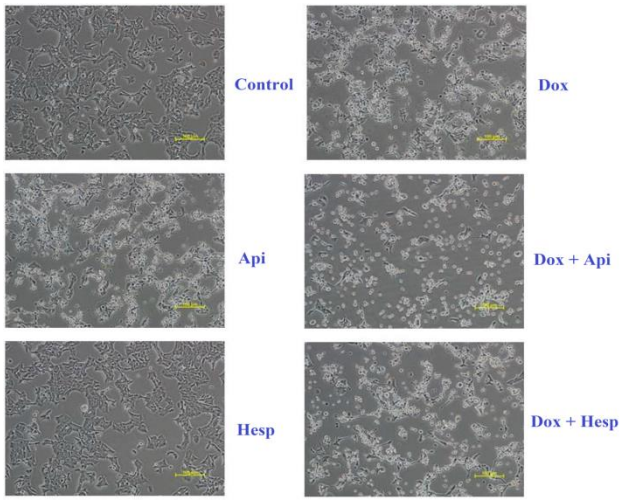

Fig. 5. Morphological changes of MCF-7 cancer cells. The cells were treated for 48 h with 1 µM of 50 µM of apigenin (Api)/50 µM of hesperidin, doxorubicin (Dox) and or combined (Dox + Api, Dox + Hesp). (Scale bar = 100 µm and magnification × 200,) (Adopted and modified from [16]).

Anti-neuroinflammatory and neuroprotective effects

The inflammation process is the major contributor to the progression of neurodegenerative diseases. Prominent neuroprotective in different models of central nervous system (CNS) disorders, antioxidant, and anti-inflammatory activities have been found for hesperidin [18]. Hesperidin reduces 5-HT/IL-β/TNF-α and increases BDNF/NE levels in the hippocampal. In addition, the anti-depression effects of this metabolite can result from activating the Nrf2/ Glo-1/ARE pathway [18]. Mechanical injury and secondary degeneration by infiltration of inflammatory cells result in spinal cord injury and motor dysfunction. Neuro-pathologic degeneration and spinal cord injury-induced motor dysfunction in rat model were ameliorated by hesperidin. The main healing mechanism for this flavanoglycone was the antioxidant and anti-inflammatory mechanism via the Nrf-2/HO-1 pathway. Furthermore, catalase, superoxide dismutase, heme oxygenase-1, and nuclear factor erythroid 2-related factor-2 were augmented via hesperidin [19]. Different cells such as activated microglia astrocytes contributed to the neuroinflammation process. The reaction of auto-reactive T cells with myelin proteins causes multiple sclerosis (MS) as the common central nervous system (CNS) inflammatory disease. Hesperidin can decrease neuroinflammation and improve the immunological outcome of MS. Treatment of the female mouse model with hesperidin for 21 days increased the forkhead box P3 (Foxp3) expression, but decreased Retinoid-related orphan receptor gamma t (ROR-γt) factor expression [20]. Neurotoxicity, ototoxicity, hepatotoxicity, and nephrotoxicity are the main side effects of cisplatin, a common antineoplastic drug [21]. Histopathological damage and electromyographical alterations in the sciatic nerve can be caused by cisplatin. Lipid peroxidations and reduction in the antioxidant defense system capacity were decreased by a combination therapy composed of hesperidin and cisplatin at the doses of 50 and 7 mg/kg/day, respectively [22].

Antimicrobial effects

To fight the bacterial infections posed by MDR bacteria, new antibacterial compounds with biocompatibility and new functions are required [23].

In a comparative investigation, three secondary metabolites including the antibacterial activity of hesperetin, hesperidin, and hesperidin glucoside were evaluated against *Staphylococcus aureus* (KCTC 3881), *Bacillus cereus* (ATCC 21772), *Escherichia coli* (KCTC 2571), and *Pseudomonas aeruginosa* (KCTC 2513). Minimum bactericidal concentrations (MBCs) against *S. aureus* were 500, >2000, and 1000 µg/mL for hesperetin, hesperidin, and hesperidin glucoside, respectively. Therefore, this study demonstrated a lower antibacterial strength of hesperidin compared to hesperetin and hesperidin glucoside [5]. Primary and secondary metabolites isolated from plants, bacteria, fungi, and lichens may be applied as reducing and stabilizer compounds [24, 25]. In this way, pectin and hesperidin biofabricated silver (Ag) nanoparticles (NPs) by a simple microwave-assisted method. These NPs at a minimum inhibitory concentration (MIC) of 66.7 µg/mL disturbed the cell wall of *E. coli* and caused leakage of bacterial macromolecules by the production of reactive oxygen species (ROS) [26].

One study investigated the antimicrobial effects of hesperidin microemulsion against several strains of bacteria, including *E. coli*, *P. aeruginosa*, *S. aureus*, *S. typhimurium*, *Klebsiella pneumonie*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *B. cereus*. The results showed that hesperidin microemulsion exhibited significant antimicrobial activity against the tested bacterial strains, with MICs ranging from 128 to 8 µg/mL. The researchers concluded that the innovative formation of hesperidin microemulsion could be a potential natural antimicrobial agent for the prevention and treatment of bacterial infections [27].

In a recent study based on phytonanotherapy, Balakrishnan et al. [28] demonstrated that hesperidin-loaded PLGA NPs had a good ability to minimize biofilms' formation and a suitable to weak ability to degrade pre-formed biofilms of *E. coli*, *K. pneumoniae*, *Enterobacter aerogenes*, and *P. aeruginosa*.

Another study investigated the antiviral activity of hesperidin against herpes simplex virus type 1 (HSV-1) due to the reduction of intracellular cyclic AMP (cAMP) levels. The results showed that hesperidin significantly reduced the replication of HSV-1 in vitro. The researchers suggested that hesperidin could be a potential therapeutic agent for the treatment of HSV-1 infections [29]. Khan et al. [30] revealed that hesperidin can serve as a cost-effective potent inhibitor of NS3 protease, and could be used as an antiviral drug against Hepatitis C virus. Moreover, hesperidin was able to inactivate Kaposi's sarcoma-associated herpesvirus (KSHV) postinfection by reducing viral protein expression and inhibiting viral growth [31]. Recent studies, reported the potential anti-coronaviral activity of hesperidin, which interact with the receptor binding site of the angiotensin-converting enzyme-2 (ACE2), papain-like protease (PLpro), and 3C-like protease (3CLpro) of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) [32-34]. For example, Wu et al. found that hesperidin can interrupt the binding of the ACE2 with the ACE2-receptor binding domain [34].

In addition to its antibacterial and antiviral effects, hesperidin has also been shown to have antifungal activity. One study investigated the effects of hesperetin, the aglycone of citrus flavonoid hesperidin, on *Candida albicans*, a common fungal pathogen. The results showed that hesperetin inhibited the growth of *C. albicans* at MIC, 0.165 mg/mL. The researchers suggested that hesperetin could be a potential alternative to conventional antifungal agents for the treatment of fungal infections [35]. In an *In vitro* study revealed that hesperidin reduced the radial growth of *Penicillium digitatum by* 38% [36]. In another study, hesperidin achieved an important percentage of growth reduction for *Aspergillus parasiticus* and *Aspergillus flavus* by 38% and 25%, respectively, at 0.8 mM [37].

Conclusions

Hesperidin can disrupt the cell wall of bacteria and cause a leakage of biological macromolecules such as proteins and DNA by the generation of ROS. Cell cycle arrest, antiangiogenic, apoptosis, DNA repair, and antimetastatic of cancer cells are modulated by this phytoactive compound. As an adjuvant therapy, hesperidin in combination with conventional anticancer drugs can be used to reduce the severe side effects of chemotherapy. Besides, the loading of hesperidin on AuNPs exhibited a significant reduction in of the secretion of TNF, IL-6, and IL-1β in the human breast cancer cell lines. Neuropathological degeneration and spinal cord injury-induced motor dysfunction may be ameliorated by antioxidant and anti-inflammatory mechanism of hesperidin via the

Nrf-2/HO-1 pathway and increasing catalase, superoxide dismutase, heme oxygenase-1, and nuclear factor erythroid 2-related factor-2. For improving solubility and bioavailability of this metabolite, an effective micro- or nano-delivery system is required to target unhealthy cells. For antiviral activity, hesperidin has been shown to exhibit strong antimicrobial effects against various microorganisms, including bacteria, viruses, and fungi. Its mechanisms of action involve the disruption of microbial cell membranes and the inhibition of microbial enzymes. These findings suggest that hesperidin could be a potential natural antimicrobial agent for the prevention and treatment of microbial infections.

Study Highlights

- Hesperidin can disrupt the cell wall of bacteria and cause a leakage of biological macromolecules such as proteins and DNA by the generation of ROS.
- Cell cycle arrest, antiangiogenic, apoptosis, DNA repair, and antimetastatic of cancer cells are modulated by hesperidin.
- As an adjuvant therapy, hesperidin in combination with conventional anticancer drugs can be used to reduce the severe side effects of chemotherapy.
- The loading of hesperidin on AuNPs exhibited a significant reduction in of the secretion of TNF, IL-6, and IL-1β in the human breast cancer cell lines.
- Neuropathological degeneration and spinal cord injury-induced motor dysfunction may be hindered by antioxidant and anti-inflammatory mechanism of hesperidin.

Abbreviations

3CLpro: 3C-like protease
ACE2: Angiotensin converting enzyme-2
Foxp3: Forkhead box P3
IL-1β: Interleukin 1 beta
IL-6: Interleukin 6
MDR: Multiple drug-resistant
MS: Multiple sclerosis
NPs: Nanoparticles
PLGA: Poly lactic-co-glycolic acid
PLpro: Papain-like protease
ROR-γt: Retinoid-related orphan receptor gamma t
ROS: Reactive oxygen species
TNF: Tumor necrosis factor

Funding

This work was not supported by any institutes.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

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

Author Contributions

All authors: conceptualization, preparing the first draft, and editing.

Acknowledgments

Declared none.

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HOW TO CITE THIS ARTICLE:
Bahador A, Vaezi M. Novel formulations of hesperidin for antitumor, antimicrobial, and neuroprotective effects: A review. Micro Nano Bio Aspects. 2023; 2(2): 13-19.
doi: https://doi.org/10.22034/mnba.2023.394932.1030