Micro Nano Bio Aspects

https://www.mnba-journal.com

Online ISSN: 2980-8081

Micro and nano formulas of phyto-drugs naringenin and naringin with antineoplastic activity: Cellular and molecular aspects

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ARTICLE INFO

Mini-review paper

Article history:
Received: 09 June 2023
Revised: 16 July 2023
Accepted: 21 July 2023
ePublished: 25 July 2023

Keywords:
Preclinical application, Clinical application, Drug delivery systems, Molecular volume, Molecular flexibility, Naringin, Naringenin

ABSTRACT

Drug resistance and metastasis process are two well-known hindrances to the eradication of cancer cells. Naringin and naringenin flavonoids have anticancer activities against various types of tumors. The inhibition of several cell signal transduction pathways has been found for combination therapy composed of naringin and naringenin. Naringin has a larger molecular volume with a higher flexibility compound than naringenin. Low water solubility and unsuitable bioavailability are the main disadvantages of these phytocompounds. Tremendous efforts are needed for the transition of the bioactive compounds of hydrophobic naringenin and naringin from preclinical to clinical application. Increasing the half-life of naringenin and naringin in blood circulation is the critical factor for obtaining maximum therapeutic outcomes in physiological conditions. Polymeric and lipid nanocarriers have illustrated unique properties compared to conventional drug delivery systems. This review compared the efficacy of these novel carriers for the loading and encapsulation of naringin and naringenin metabolites.

DOI: https://doi.org/10.22034/mnba.2023.401317.1035

Introduction

Exogenous factors such as tobacco, radiation, alcohol, and infectious agents, and endogenous factors involving inherited mutations, oxidative stress, inflammation, insulin-like growth factor systems, and steroid hormones can cause cancer disease. Common cancer therapies including surgery, chemotherapy, radiation therapy, hormone therapy, and targeted therapies cannot eradicate cancers, specifically the deadliest cancers such as pancreatic cancer (the overall five-year survival rate is in a range of 2-9%) [1, 2]. Long and short-term side effects, multidrug resistance, and metastasis of cancer cells are the main barriers to treating patients. Flavonoids as the common polyphenols in the human diet can be found in fruits, vegetables, and many herbal products. Various flavonoids have shown anticancer, antioxidant, and antimicrobial activities [3, 4]. Naringenin (4′,5,7-Trihydroxyflavonone) is one the most common dietary flavonoids belonging to the flavanones subclass found in some fruits such as bergamot orange (*Citrus bergamia*) (Figure 1a). Glycoside interaction between the disaccharide neohesperidose and naringenin (aglycone) forms naringin [5]. This flavanone-7-O-glycosid can be isolated from citrus fruits, particularly grapefruit (*Citrus paradisi*) (Figure 1b) [6]. Naringenin and naringin have shown a broad spectrum of therapeutic activities such as antineoplastic and antimicrobial activities. Several cell signal transduction pathways of cancer cells can be hindered by combination therapy based on naringin and naringenin [1]. The physicochemical properties of naringenin and naringin have been presented in Table 1. As shown in Table 1, the flexibility of naringin is greater than naringenin by values of 0.20 and 0.056, respectively. In addition, naringenin has a smaller Van der Waals volume of 267.823 A^3 compared to naringin with a molecular volume amount of 537.374 A^3. Naringin as a large and flexible compound with more rotatable bonds is interested in pharmaceutical

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programs considering at docking of protein targets. In this regard, naringin shows different values compared to naringenin for a given conformation-dependent physicochemical property [7]. The molecular polar surface areas as the main determinant factor of bioavailability were 86.990 and 225.060 $Å^2$ $molecule^{-1}$ for naringenin and naringin, respectively (Table 1). In the case of naringenin, low bioavailability can be caused by its water solubility of ~46 µg/mL [8]. For naringin, the oral bioavailability of naringin is ~5–9% at a concentration of 50 mg of aglycone [9]. To overcome this clinical limitation, combined therapy and the application of micro and nano-formulation can be promising approaches. Organic and synthetic nanomaterials such as liposomes, metal/metal oxide nanoparticles, and polymeric nanoparticles in a wide range of shapes and structures have been employed for the loading and encapsulation of therapeutic compounds [10, 11]. Metallic nanoparticles, polymeric, and lipidic nanoparticles are well-known types of nanomaterials [12, 13]. According above information, we have tried to discuss the antineoplastic activity of naringenin and naringin based on cellular and molecular mechanisms.

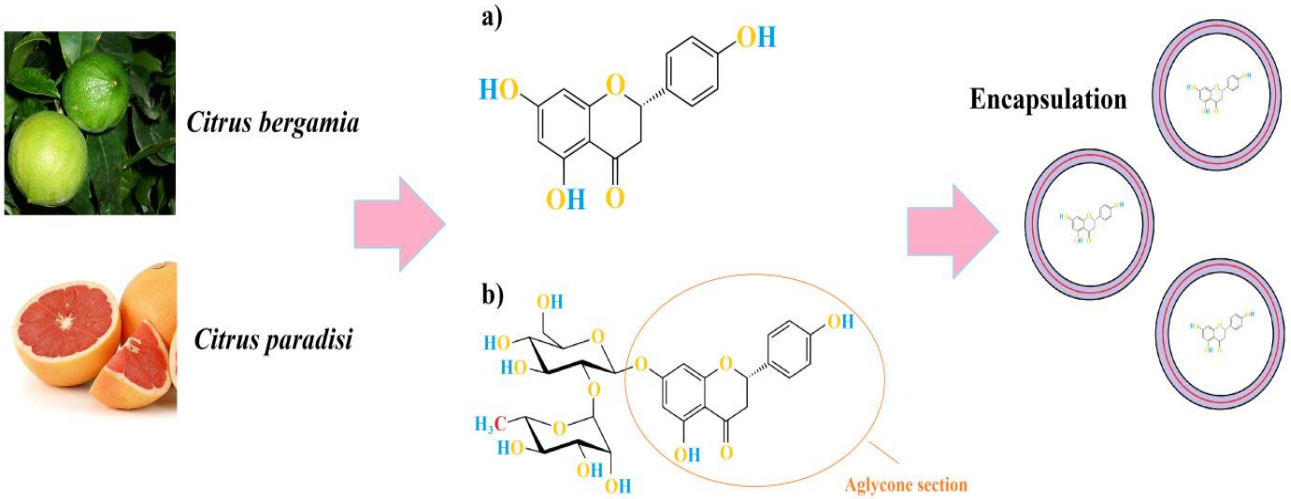

Fig. 1. The main plant sources and chemical structures of naringenin (a) and naringin (b) with their encapsulation in micro or nanoformulations (chemical structures have been extracted and modified from PubChem).

Table 1. Physicochemical properties of naringenin and naringin based on ADMETlab.

Physicochemical properties	**Naringenin**	**Naringin**
Molecular Weight (MW (g/mol))	272.070	580.180
Volume (Van der Waals volume (A^3))	267.823	537.374
Density (MW / Volume)	1.016	1.080
nHA (Number of hydrogen bond acceptors)	5	14
nHD (Number of hydrogen bond donors)	3	8
nRot (Number of rotatable bonds)	1	6
nRing (Number of rings)	3	5
MaxRing (Number of atoms in the biggest ring)	10	10
nHet (Number of non-carbon atoms)	5	14
fChar (Formal charge)	0	0
nRig (Number of rigid bonds)	18	30
Flexibility (nRot / nRig)	0.056	0.200
Stereo Centers (Number of stereocenters)	1	11
TPSA (Topological polar surface area ($Å^2$ $molecule^{-1}$))	86.990	225.060
logS (The logarithm of aqueous solubility value)	-4.024	-4.189
logP (The logarithm of the n-octanol/water distribution coefficient)	2.596	0.589
logD (The logarithm of the n-octanol/water distribution coefficients at pH=7.4)	2.491	0.047

Naringenin

One of the most deadly skin cancers is malignant melanoma with metastasis and aggressive proliferation features [14]. Naringenin hindered cell proliferation and migration in a dose-dependent way in SK-MEL-28 human melanoma cells and B16F10 murine by reduction of phosphorylation of the extracellular signal-regulated kinase 1/2 (ERK1/2) and the c-Jun N-terminal kinase (JNK) pathway a signaling cassette of the mitogen-activated protein kinase (MAPK) signaling pathway. Moreover, the protein expression of activated caspase 3 and poly (ADP-ribose) polymerase (PARP) in B16F10 and SK-MEL-28 cells were upregulated in SK-MEL-28 and B16F10 cells upon treatment by this metabolite [15]. Pectin as a water-soluble polysaccharide can enhance the bioavalibility of naringenin. Dimethylaminopyridine and dicyclohexylcarbodiimide were utilized to prepare the pectin–naringenin conjugates. These conjugates illustrated significant anticancer activity against NIH: OVCAR-5 cells (epithelial cells isolated from adenocarcinoma of the ovary) [16].

As explained in the introduction section, nanomaterials have unique abilities to loading, encapsulation, and sustained-release of therapeutic agents in physiological conditions. For instance, lyotropic liquid crystalline nanoparticles (LCNs) are self-assembled drug delivery systems that behave both like a solid and a liquid crystal [17]. These amphiphilic LCNs were loaded by naringenin to target human lung epithelial carcinoma (A549) cell lines and human airway epithelium-derived basal cells (BCi-NS1.1). As anti-inflammatory mechanisms, expression of tumor necrosis factor α (TNFα), interleukin-1β (IL-1β), interleukin-8 (IL-8), and interleukin-6 (IL-6) was reduced in lipopolysaccharide-induced BCi-NS1.1 cells. In the case of the cancer cell line of A549, proliferation, migration, and colony formation were inhibited by this nanoformulation [18]. Nanostructured lipid carriers (NLCs) are drug-delivery systems in an aqueous solution composed of both liquid (oil) and solid lipids as a core matrix surrounded by a surfactant [19]. Co-encapsulation of naringenin and oxaliplatin by NLCs with an average particle size of 98 nm led to the induction of apoptosis in colon cancer cells (HT-29). These nanoformulations augmented the apoptosis process from 31% up to 50%. In addition to an increase in pro-apoptotic factor Bid mRNA expression, there was a remarkable reduction in anti-apoptotic factors of cyclin-B1, Nrf2, and survival in cancer cells [20]. The redox potential of antioxidant naringenin is a critical factor in hindering cancer prevention and progression [21]. Phytocompounds of naringenin and baicalein were encapsulated in polymeric nano-micelles by two methods including solvent evaporation and direct dissolution. The amounts of encapsulated naringenin were 19.2 and 0.95 mg/mL by solvent evaporation and direct dissolution methods, respectively. This formulation showed an increase in antioxidant activities compared to each phyto-drug alone [22].

Silk fibroin (SF) isolated from the *Bombyx mori* silkworm is a biodegradable and protein-based biomacromolecule ((Gly–Ala–Gly–Ala–Gly–Ser)n) with desirable physicochemical properties suitable for preparation of drug delivery systems with a controlled release [23]. This biocompatible polymer can be employed as nanoparticles to load bioactive compounds such as naringenin due to the increase in its bioavailability. Naringenin-loaded SF nanoparticles exhibited the first-order kinetic of naringenin release and remarkable anticancer effects on HeLa cancer cells [24]. Smart or stimuli-responsive polymeric nanoparticles can be synthesized from an organic or synthetic polymer [25]. Smart polymeric nanoparticles composed mainly of N-isopropyl acrylamide and vinyl imidazole with thermo and pH-sensitive properties were used for the encapsulation of naringenin. These nanoparticles induced apoptosis and inhibited the cell cycle and proliferation in breast cancer lines [26].

Naringin

Combination therapy can improve the antineoplastic capacities of the formulation. The complex of naringin and oxovanadium was used to hinder the growth of adenocarcinoma human alveolar basal epithelial cells. This complex showed a 20% decrease in cancer cell viability after 24 h incubation by promoting apoptosis and production of intracellular reactive oxygen species (ROS) as an oxidative stress mechanism. In addition, as the histological changes, elongated lamellipodia, and cytoplasmic shrinkage were observed compared to the control after 24 h incubation (Figure 2) [27].

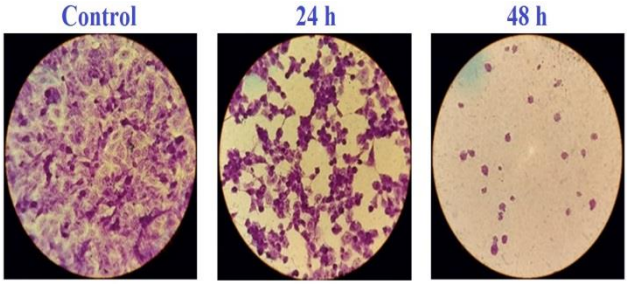

Fig. 2. Morphological changes in A549 cells after 24 and 48 h incubation under the complex of naringin and oxovanadium with a concentration of 100 µM. Apoptotic bodies were formed after 48 h incubation (Extracted and modified from [27]).

The efficacy of chemotherapeutic agents can be diminished by the emergence of multidrug resistance in cancer cells. Several mechanisms include a decrease of drug uptake by influx transporters, an increase in expression of drug efflux by ATP-binding cassette (ABC) transporters, mutation of drug target, alterations in drug metabolism, and DNA damage repair [28]. The most common cancer among women is breast cancer with 25% of all female malignancies [26]. A mixed micellar system was used for co-encapsulation and co-delivery of paclitaxel with naringin against breast cancer cells. This formulation synergistically ameliorated intracellular uptake of paclitaxel and 65% cytotoxicity at its lower concentration of 15 µg/mL [29]. It should be noted that programmed cell death 5 (PDCD5) can interact with the tumor protein p53 (p53) to induce cell apoptosis. Dextrin as a small polysaccharide in nanoformulation was employed to load naringin against human hepatocellular carcinoma cell lines. These nanostructures increased the apoptosis process by a decrease in the expression levels of B-cell lymphoma-2 and an increase in the expression levels of caspase-3, p53, Bcl-2-associated X protein, caspase-9, and PDCD5 under ROS generation [30]. Inorganic nanomaterials such as carbon nanotubes (CNTs) and metallic nanoparticles have unique physicochemical properties compared to micro-materials suitable for the delivery of therapeutic agents. For increasing the biocompatibility of CNTs, oxidation treatment of the CNT by acids provides the incorporation of functional groups (-OH and -COOH) on the surface of these nanotubes. Naringenin modification of these types of CNTs exhibited a 50% cytotoxicity inhibitory concentration (CC_{50}) of 82.6 µg/mL compared to CNTs and naringenin with values of 106.4 and 129.3 µg/mL, respectively against malignant lung cells (A549). The total release of naringenin at first 8 h in the tumor pH environment (at pH 5.5) was 54.4% compared to 71.8% at pH 7.4 [31]. Silk fibroin as a biocompatible and biodegradable protein approved by the Food and Drug Administration (FDA) can attract and adsorb various compounds via hydrophobic/hydrophilic and hydrogen interactions due to its amino acid sequence and chemical structure [32, 33]. Naringenin loaded by silk fibroin nanoparticles in a size range of 148-180 nm and zeta potential of −30.5 - −39.1 mV showed higher cytotoxic effects compared to silk fibroin nanoparticles and naringenin against the tumor cell lines of HeLa [24].

Conclusions

Different cell signal transduction pathways of cancer cells can be blocked by combination therapy based on naringin and naringenin. Naringin is a larger and more flexible compound with more rotatable bonds than naringenin, which is interesting in pharmaceutical programs considering at docking of protein targets. Naringin compared to naringenin shows different values for a given conformation-dependent physicochemical property. Low bioavailability of naringin and naringenin can hinder the transition of these natural compounds from preclinical to clinical application. Two main approaches based on a combination of these compounds with conventional drugs and encapsulation or loading by nanostructures may diminish the clinical limitations and ameliorate therapeutic outcomes. Co-encapsulation and co-delivery of naringin with paclitaxel and oxaliplatin showed synergistic anti-neoplastic activity against breast cancer cells and colon cancer cells, respectively. In addition, the load of naringenin by the LCNs drug delivery system resulted in the inhibition of anti-proliferation, anti-migration, and anti-colony formation of human lung epithelial carcinoma cell lines. Induction of apoptosis in human hepatocellular carcinoma cells can be resulted from cell cycle arrest, DNA fragmentation, and ROS generation via naringin-dextrin nanoformulation. The prolonged release of anticancer agents in the tumor environment is a critical factor in maximizing therapeutic results. Naringenin-CNTs showed sustained release of naringenin in pH 5.5 as pH-responsive behavior.

Study Highlights

- Naringin compared to naringenin shows different values for a given conformation-dependent physicochemical property.
- Low bioavailability of naringin and naringenin can hinder the transition of these natural compounds from preclinical to clinical application.
- Co-delivery of naringin with paclitaxel showed synergistic anti-neoplastic activity against breast cancer cells.
- Induction of apoptosis in cancer cells can be caused by naringin-dextrin nanoformulation.
- The prolonged release of anticancer agents in the tumor environment is a critical factor in maximizing therapeutic results.
- Naringenin-CNTs exhibited sustained release of naringenin in pH 5.5.

Abbreviations

CC_{50}: 50% cytotoxicity inhibitory concentration
ERK1/2: Extracellular signal-regulated kinase 1/2
FDA: Food and drug administration
IL-1β: Interleukin-1β
IL-6: Interleukin-6
IL-8: Interleukin-8
JNK: c-Jun N-terminal kinase
MAPK: Mitogen-activated protein kinase
p53: Tumor protein p53
PARP: Poly (ADP-ribose) polymerase
PDCD5: Programmed cell death 5
ROS: Reactive oxygen species
SF: Silk fibroin
TNFα: Tumor necrosis factor α

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:
Kahrizi D, Mohammadi MR, Amini S. Micro and nano formulas of phyto-drugs naringenin and naringin with antineoplastic activity: Cellular and molecular aspects. Micro Nano Bio Aspects. 2023; 2(2): 27-33.
doi: https://doi.org/10.22034/mnba.2023.401317.1035