

## **Micro Nano Bio Aspects**



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# Novel formulations of Kaempferol and its monosaccharide derivatives for healing cancers and microbial infections

Natural compounds isolated from plant species have a potential pharmacological capability and is now

regarded to be an alternative therapeutic agent. Flavonoid metabolites have exhibited significant antioxidant,

anti-inflammatory, antimicrobial, and anticancer properties. Kaempferol and its monosaccharide derivatives

such as kaempferol-3-glucoside and kaempferol 7-O-glucoside as a well-studied bioactive compound have

shown remarkable therapeutic activities. As a major therapeutic limitation, this plant-derived metabolite is

soluble in ethanol and slightly soluble in aqueous solvents. This property can hinder the clinical application

of kaempferol, as recent studies have tried to discovery effective micro and nano formations. In this way, this mini-review has discussed efficacy of these novel formulations in recent years. This study has shown micro and nanocarriers can improve bioavailability property of kaempferol and its monosaccharide



<sup>1</sup>Department of Biology, Faculty of Science, Razi University, Kermanshah, Iran <sup>2</sup>Unit of Genomics Research, Digestive Diseases Research Center, Ardabil University of Medical Sciences, Ardabil, Iran

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#### ABSTRACT

derivative derivatives.

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**DOI:** https://doi.org/10.22034/mnba.2023.401346.1036 **Introduction** 

In the recent years, bioactive compounds have achieved significant achievements in the treatment of various microbial infections and cancers [1]. This inspired scientists to continuously evaluate new formulations of bioactive agents isolated from various natural sources, specifically medical plant species [2-4]. The therapeutic application of natural compounds has gained a lot of attention because of acceptable biocompatibility and biodegradability of these bioactive compounds in physiological conditions [5-7]. Kaempferol (3,4',5,7-tetrahydroxyflavone  $(C_{15}H_{10}O_6))$ is a natural flavonol related to flavonoid group (Figure 1), which can be isolated from variety of plant species such as Capparis spinosa [8], Crocus sativus [9], Eruca vesicaria [10], Brassica oleracea [11], Brassica juncea [12], Zingiber officinale [13], Phaseolus vulgaris [14], and Brassica rapa [15]. Furthermore, this polyphenol compound is opulently found in fruits, vegetables and medicinal plant-derived beverages [15].

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It has been reported that kampferol has some health benefits including antioxidant, anti-inflammatory, antimicrobial, lipolytic, anti-hypertensive, anti-diabetic and anticancer activities [16, 17].

Kaempferol biosynthesis is polyphenol compounds which is structurally composed of diphenylpropane. This bioactive metabolite synthesized through condensation process by chalcone synthase that combine three molecules of malonyl-CoA and one molecule of 4-coumaroyl-CoA and producing naringenin chalcone. Naringenin chalcone was converted into naringenin flavanone and thereby dihydrokaempferol produced. In the last step, flavonol synthase make double bound in C2–C3 of dihydrokaempferol and producing kaempferol [18]. Cancer-related activities and processes including cell cycle, apoptosis, oxidative stress, proliferation, angiogenesis, and metastasis can be affected by

angiogenesis, and metastasis can be affected by kaempferol [19]. Kaempferol acts as bioactive compound and effect on a range of intracellular as well as extracellular targets involved in the cell signaling pathways that in turn are known to regulate the hallmarks of cancer growth progressions like apoptosis, cell cycle, invasion or metastasis, angiogenesis and inflammation. This herbal material is soluble in dimethyl sulfoxide (DMSO), ethanol, and ethers and poorly soluble aqueous solvents [20]. Therefore, new strategies such as polytherapy or combination therapy and nonoformulations can improve the half-life and healing activities of kaempferol. On the other hand, the issue of the poor bioavailability of kaempferol has been resolved by nanotechnology. In this way, this minireview has tried to cover these aspects of formulations based on recent studies.

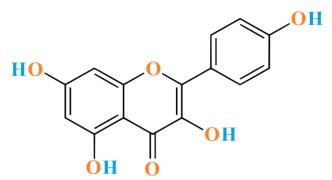


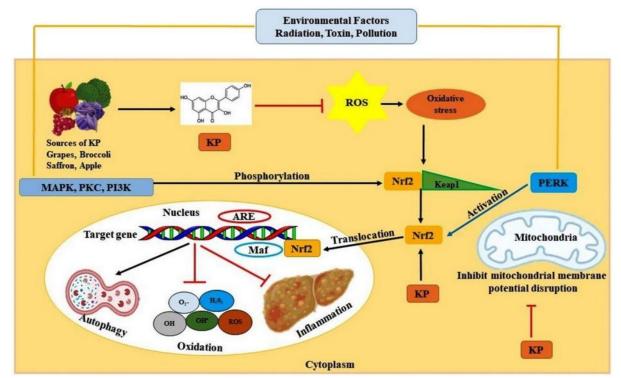
Fig. 1. Chemical structure of kaempferol.

#### **Anticancer effects**

Plant-derived flavonoids are regarded natural bioactive compounds and have been widely used as treatments different types of cancers, such as bladder cancer, bone cancer, breast cancer, cervical cancer, colon cancer, gastric cancer, endometrial cancer, liver cancer, lung cancer, ovarian cancer, nervous system cancer, pancreatic cancer, prostate cancer, skin cancer, nervous system cancer and leukemia [21]. Kaempferol can modulate cell signaling pathways and various cancerrelated processes including angiogenesis, proliferation, tumor suppressor gene, oxidative stress, cell cycle, apoptosis, autophagy and metastasis [22, 23]. Cell cycle arrest can be resulted from kaempferol treatment by increasing and decreasing of p53 and c-Myc (A multifunctional transcription factor), respectively [24]. In the case of angiogenesis, kaempferol reduce a level of HIF-1 (hypoxia inducible factor-1) VEGF (vascular endothelial growth factor), and ESRRA (estrogen related receptor alpha) [25]. Breast cancer is introduced as one of the deadliest cancer in women, which there are conventional methods including radiation, surgery, and medicine (anthracyclines, antiestrogen drugs, aromatase inhibitors, monoclonal antibody drugs, and anti-angiogenesis drugs) therapy for treatment it [26]. Three main ways involving blocking the growth (at G2/M stage via downregulation of CDK1), inducing the apoptosis (by induction of the cleavage of poly-ADP ribose polymerase (PARP) expression), and inhibiting migration and invasion (through inhibition of triclosaninduced epithelial-mesenchymal transition (EMT) and metastatic proteins) of breast cancer cells have been indicated for anticancer mechanisms of kaempferol [27]. In a comparative study, kaempferol showed higher antitumor activity than kaempferol-7-Okaempferol-3-O-rhamnoside, glucoside, and kaempferol-3-O-rutinoside. In addition, kaempferol promoted caspase-dependent apoptosis and inhibited AMPK and AKT signaling pathways in liver cancer cells [28]. In other nano-formulations, metal or metal oxide nanoparticles have been used to loading various natural compounds [29, 30]. As an example, kaempferol-coated AgNPs showed remarkable anticancer effects on liver cancer (HepG2) cells through cell cycle arrest and oxidative stress-mediated apoptosis [31].

#### Antioxidant and anti-inflammatory effects

Reactive oxygen species (ROS) such as free radicals of superoxide  $(O_2^{-*})$  and hydroxyl radical  $(OH^*)$  or nonradical species, such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) in prolonged oxidative stress can lead to mutations and uncontrolled cell division [32]. Acting on the Nrf2-Keap1 complex is the main antioxidant mechanism of kaempferol. In this regard, the level of Nrf2 is augmented by this polyphenol antioxidant (Figure 2) [19]. Kaempferol plays a promising role in combatting cancer by modulating the Nrf2 transcriptional pathway and decrease cell redox homeostasis [33]. Kaempferol and three glycoside derivatives including kaempferol-3-O-rutinoside, kaempferol-7-O-glucoside, and kaempferol-3-O-rhamnoside blocked the proliferation of activated T cells in a dose and time-dependent manner. Moreover, kaempferol hindered lipopolysaccharide (LPS)-induced ROS production in a concentration-dependent manner [28].



**Fig. 2.** Antioxidant effects of kaempferol (KP) via KP via Nrf2-Keap1 pathway. Nrf2 (nuclear factor erythroid 2 related factors 2), Keap1 (Kelch-like ECH-associated protein 1), Maf (musculoaponeurotic fibrosarcoma) transcription factor, ARE (the antioxidant response element sequence) (adopted and modified from [19]).

#### Antimicrobial effects

In the case of implanted medical devices, the most common bacterial infections are resulted from the biofilm formation on surfaces by Staphylococcus aureus. Kaempferol at a concentration of 64 µg/mL (at sub-inhibitory concentration) inhibited biofilm formation of bacteria by 80%. Reduction in fibrous protrusions on the surface of S. aureus was found as the major antibiofilm mechanism of kaempferol [34]. Encapsulation or loading of therapeutic agents including natural compounds or drugs by nanomaterials such as liposomes, polymeric nanoparticles, and metallic nanoparticles can promote healing processes [35, 36]. In the case of polymeric nanomaterials, cellulose and chitosan are two main biocompatible polysaccharides applicable to a wide range of therapeutic nano-formulations [37]. Chitosan as a polycation linear polysaccharide ( $\beta$ -(1 $\rightarrow$ 4)-linked D-glucosamine and N-acetyl-D-glucosamine) can be isolated from the chitin shells of shrimp or other crustaceans [38]. Chitosan/sodium tripolyphosphate NPs were produced by the electrostatic self-assembly method. Quorum sensing Chromobacterium violaceum CV026 bacteria was inhibited by kaemperol loaded on chitosan/sodium tripolyphosphate nanoparticles with a

diameter of 192.27 nm [39]. Nanotechnology has obtained high attention owing to the unique physicochemical, biological, and biomedical properties of organic and inorganic nanomaterials [40]. Among the inorganic nanomaterials, silver (Ag) NPs have been employed in various fields, such as catalysis, biosensors, anticancer, and antimicrobials agents. These NPs have shown antimicrobial activity in a broad-spectrum against bacteria, fungi, parasites, and viruses [41]. Conjugation of AgNPs with kaempferol and hydrocortisone resulted in NPs with spherical shape in a size range of 10-30 nm. These NPs showed remarkable stability and strong antibacterial activity against Bacillus subtilis, Escherichia coli, and Staphylococcus aureus. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of these NPs against E. coli were 62.5 and 125 µg/mL, respectively. Production of ROS and lipid peroxidation were indicated the main antibacterial mechanisms of AgNPs-kaempferol-hydrocortisone [42].

#### Conclusions

The main barrier for the clinical application of kaempferol is its low solubility in aqueous solutions. Two approaches encompassing the combined therapy

and novel biocompatible micro and nano-formulations can reduce this limitation. Both organic and inorganic nanomaterials have been employed to obtaining acceptable therapeutic outcomes. For example, nanoformulation of kaempferol using organic polymers such as chitosan has demonstrated a significant antiquorum sensing activity against C. violaceum. In a kaempferol-3-O-rutinoside, comparative way, kaempferol-7-O-glucoside, and kaempferol-3-Orhamnoside showed poor anticancer. antiinflammatory, and antioxidant activities than kaempferol. The major antibiofilm mechanism of kaempferol was reduction in fibrous protrusions on the surface of S. aureus. For nanoformulations of AgNPskaempferol-hydrocortisone, production of ROS and lipid peroxidation were the main antibacterial mechanisms.

#### **Study Highlights**

- The main barrier for the clinical application of kaempferol is its low solubility in aqueous solutions.
- Nanoformulation of kaempferol using organic polymers such as chitosan has demonstrated a significant anti-quorum sensing activity against *C. violaceum*.
- Kaempferol-3-O-rutinoside, kaempferol-7-Oglucoside, and kaempferol-3-O-rhamnoside showed poor anticancer, anti-inflammatory, and antioxidant activities compared to kaempferol.
- The major antibiofilm mechanism of kaempferol was reduction in fibrous protrusions on the surface of *S. aureus*.
- Nanoformulations of AgNPs-kaempferolhydrocortisone, production of ROS and lipid peroxidation were the main antibacterial mechanisms.

#### Abbreviations

ARE: Antioxidant response element sequence c-Myc: A multifunctional transcription factor EMT: Epithelial-mesenchymal transition ESRRA: Estrogen related receptor alpha HIF-1: Hypoxia inducible factor-1 Keap1: Kelch-like ECH-associated protein 1 LPS: Lipopolysaccharide Maf: Musculoaponeurotic fibrosarcoma MBC: Minimum bactericidal concentration MIC: Minimum inhibitory concentration Nrf2: Nuclear factor erythroid 2 related factors 2
PARP: Poly-ADP ribose polymerase
ROS: Reactive oxygen species
VEGF: Vascular endothelial growth factor
AMPK: AMP-activated protein kinase

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#### **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.

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