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In-vitro evaluation for antioxidant and anti-inflammatory property of flavanone derivatives

Je-Hyuk Lee

Department of Food and Nutrition, Kongju National University, Yesan, Chungnam 340-702, Korea

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ABSTRACT

The purpose of this study is to evaluate the antioxidant and suppressive activity of flavanone derivatives on the production of nitric oxide (NO) from lipopolysaccharide (LPS)-induced macrophage cells. Flavanone derivatives were prepared by adding one to three methoxy substituents (–OCH_3) to flavanone or chloroflavanone structure. 5-Methoxyflavanones, including 5-methoxyflavanone, 5-methoxy-4′-chloroflavanone, and 5,4′-dimethoxyflavanone, had the best antioxidant activity, as compared to other flavanone derivatives. Anti-inflammatory effect of flavanone derivatives was studied by suppressive activity on NO synthesis from LPS-stimulated macrophages cells. 3′,4′-Dimethoxyflavanone, 5-methoxyflavanone, and 5-methoxy-4′-chloroflavanone showed the potent inhibitory activity on nitrite production. Addition of the methoxy group at 5′-position and 3′,4′-position of flavanone showed a high inhibitory activity of NO production from LPS-macrophage cells, which is one of the typical anti-inflammatory biomarkers. Taken together, the location of the methoxy group in a flavanone structure might have some connection with antioxidant and anti-inflammatory activities.

1. Introduction

Natural plant materials with potential health enhancing and pharmaceutical functions have received considerable attention recently. Phenolic compounds, such as flavavonoids, existing in plant extracts have been regarded as cause substance for health enhancement. Flavonoids, including flavanones, exert the antioxidant, anti-inflammatory, blood lipid-/cholesterol-lowering, and anticarcinogenic activities (Kanaze, Bounartzi, Georgarakis, & Niopas, 2007; Crespo, Galvez, Cruz, Ocete, & Zarzuelo, 1999; Miyake, Yamamoto, Tsujihara, & Osawa, 1998). Flavanone is one of chemically modified metabolic form of flavonoids and the bioavailability and bioactivity of flavanones depends on their chemical modification (Lin, Shen, & Chen, 2005; Middleton, 1998; Ko, Shen, & Chen, 2004).

Nitric oxide (NO) is involved in a progress of inflammatory joint disease and plays an important role in cartilage catabolism through the inflammation. NO is synthesized by nitric oxide synthases (NOSs), which convert L-arginine to L-citrulline. Inducible NOS (iNOS) is activated by inflammatory stimulators, such as bacteria or lipopolysaccharide (LPS) and/or inflammatory cytokines (e.g., TNF-α, IL-1β, IFN-γ) in inflammation, diabetes, and sepsis (Nathan, 1992; Marletta, 1993; Kengatharan, De Kimpe, & Thiemermann, 1996; Jungi, Valentin-Weigand, & Brcic, 1999). Over-produced NO at inflammatory sites for a long time causes chronic inflammation, asthma, neurodegenerative diseases, multiple sclerosis, arthritis and cancer (Lala & Chakraborty, 2001). For these reasons, NO is considered as a target for the production of an anti-inflammatory pharmaceutical.

So far, very few attempts have been made at the roles of flavanone and its chemical derivatives for antioxidants or inhibition of NO synthesis, which is a representative biomarker for anti-inflammation. Many plant extracts and chemical drugs,

E-mail address: leejeh211@kongju.ac.kr

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such as nonsteroidal anti-inflammatory drugs (NSAIDs), have a potent antioxidant activity and anti-inflammatory functions together (Selvam, Jachak, Thilagavathi, & Chakraborti, 2005).

Aim of this study is to evaluate the antioxidant and anti-inflammatory activities of flavanone derivatives by scavenging activity against free radicals and the examination of inhibitory activities on NO production from LPS-stimulated macrophages, respectively.

2. Materials and methods

2.1. Chemicals and reagents

2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), 6-hydroxy-2,5,7,8-tetramethyl- chroman-2-carboxylic acid (Trolox), 2,2′-azobis(2-methylpropionamidine) dihydrochloride (AAPH), fluorescein disodium salt, gallic acid, lipopolysaccaride (LPS, *Escherichia coli* serotype 0127:B8), thiazolyl blue tetrazolium bromide (MTT), and N^G-methyl-L-arginine acetate salt (n-NMMA) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Cell culture media and reagents, such as Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), penicillin/streptomycin, and trypsin-EDTA, were obtained from GIBCO (Invitrogen Inc., NY, USA).

2.2. Flavanones derivatives

Derivatives of flavanone were synthesized from 2-hydroxybenzoic acids according to the reports (Lee, Jung, & Jung, 2007). Briefly, lithium diisopropylamide (2.0 M, 4.2 mL, 8.4 mmol) was added in a solution of 2′-hydroxyacetophenone (545 mg, 4.0 mmol), synthesized by treatment of 2-hydroxybenzoic acids and 3 equiv of CH_3Li, in THF (12 mL)

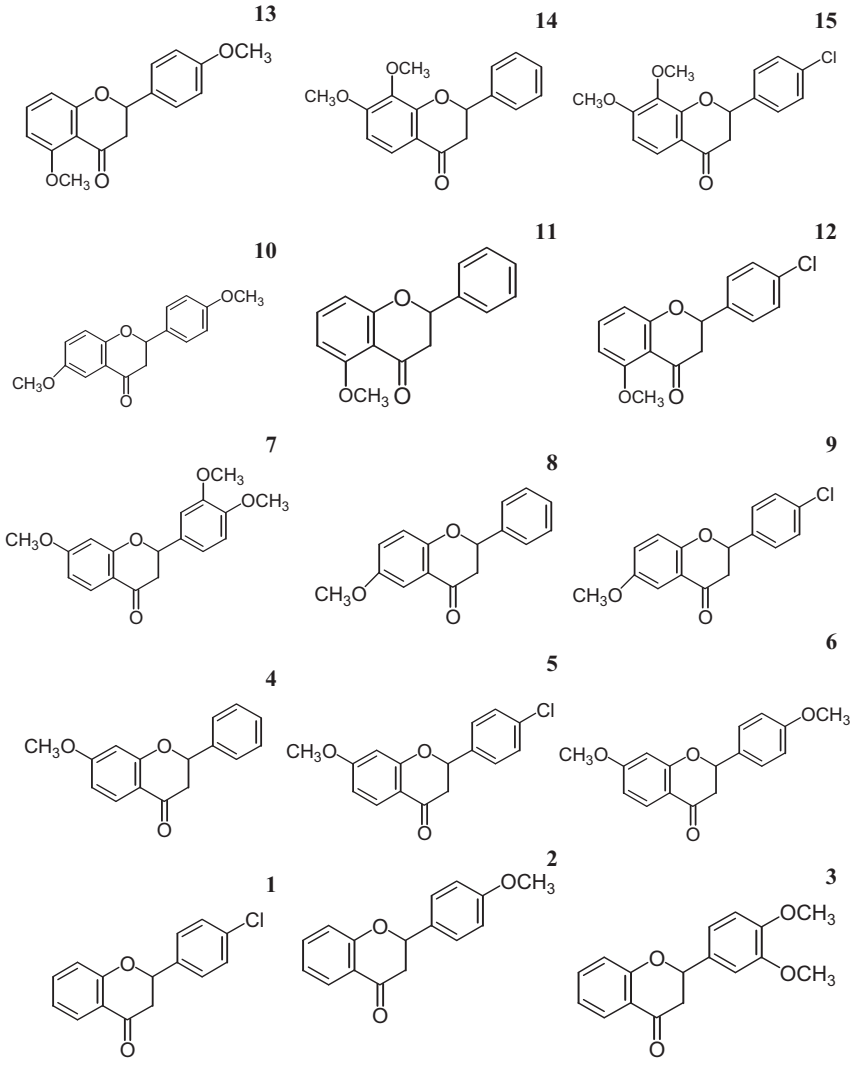

Fig. 1 – Chemical structures of flavanone and its derivatives. (1) 4′-Chloroflavanone; (2) 4′-Methoxyflavanone; (3) 3′, 4′-Dimethoxyflavanone; (4) 7-Methoxylflavanone; (5) 7-Methoxy-4′-chloroflavanone; (6) 7,4′-Dimethoxyflava-none; (7) 7,3′, 4′-Trimethoxyflavanone; (8) 6-Methoxyflavanone; (9) 6-Methoxy-4′-chloroflavanone; (10) 6, 4′-Dimethoxyflavanone; (11) 5-Methoxyflavanone; (12) 5-Methoxy-4′-chloroflavanone; (13) 5,4′-Dimethoxyflavanone; (14) 7,8-Dimethoxy-flavanone; (15) 7,8-Dimethoxy-4′-chloroflavanone.