JOURNAL OF FOOD AND DRUG ANALYSIS 25 (2017) 71–83

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfda-online.com

Review Article

Chemistry and health effects of furanocoumarins in grapefruit

Wei-Lun Hung, Joon Hyuk Suh, Yu Wang[*]

Citrus Research and Education Center, Department of Food Science and Human Nutrition, University of Florida, Lake Alfred, FL, USA

ARTICLE INFO

Article history:
Received 1 September 2016
Received in revised form
2 November 2016
Accepted 3 November 2016
Available online 6 December 2016

Keywords:
anticancer activity
bergamottin
bone health
furanocoumarins
grapefruit

ABSTRACT

Furanocoumarins are a specific group of secondary metabolites that commonly present in higher plants, such as citrus plants. The major furanocoumarins found in grapefruits (*Citrus paradisi*) include bergamottin, epoxybergamottin, and 6′,7′-dihydroxybergamottin. During biosynthesis of these furanocoumarins, coumarins undergo biochemical modifications corresponding to a prenylation reaction catalyzed by the cytochrome P450 enzymes with the subsequent formation of furan rings. Because of undesirable interactions with several medications, many studies have developed methods for grapefruit furanocoumarin quantification that include high-performance liquid chromatography coupled with UV detector or mass spectrometry. The distribution of furanocoumarins in grapefruits is affected by several environmental conditions, such as processing techniques, storage temperature, and packing materials. In the past few years, grapefruit furanocoumarins have been demonstrated to exhibit several biological activities including antioxidative, -inflammatory, and -cancer activities as well as bone health promotion both *in vitro* and *in vivo*. Notably, furanocoumarins potently exerted antiproliferative activities against cancer cell growth through modulation of several molecular pathways, such as regulation of the signal transducer and activator of transcription 3, nuclear factor-κB, phosphatidylinositol-3-kinase/AKT, and mitogen-activated protein kinase expression. Therefore, based on this review, we suggest furanocoumarins may serve as bioactive components that contribute, at least in part, to the health benefits of grapefruit.

1. Introduction

Citrus fruits, belonging to the family Rutaceae, genus *Citrus*, are believed to originate from certain regions of Southeast Asia and are mainly cultivated in the regions in the Northern Hemisphere [1]. Citrus crops are one of the major fruit crops in the world and it is estimated that more than 135 million tons were produced in 2013 [2]. The leading citrus fruit-producing countries in the world include China, Brazil, the United

---

[*] *Corresponding author*. Department of Food Science and Human Nutrition, Citrus Research and Education Center, University of Florida, 700 Experiment Station Road, Lake Alfred, FL 33850, USA.
E-mail address: yu.wang@ufl.edu (Y. Wang).

http://dx.doi.org/10.1016/j.jfda.2016.11.008

States, India, Mexico, and Spain, which collectively account for two-thirds of the global production [3]. Citrus taxonomy remains controversial. However, the four core ancestral *Citrus* taxa including *Citrus medica* (citron), *Citrus reticulata* (mandarin), *Citrus maxima* (pummelo), and *Citrus micrantha* (papeda) have been recognized as the ancestors of all cultivated citrus fruits [4,5]. The major *Citrus* fruits consumed worldwide are oranges, mandarins, lemons, grapefruits, as well as limes. Owing to a pleasing flavor and aroma as well as desirable taste, citrus species are widely consumed as fresh or used as raw materials for juice. Citrus fruits are not only a particular rich source of vitamin C, but are also abundant in nutrients such as dietary fiber, sugar, and minerals. Along with a high nutrition value, the secondary metabolites of citrus fruits, including flavonoids, limonoids, and coumarins, they are also known to possess several health benefits such as antioxidative, anti-inflammatory, anticancer and neuroprotective activities.

Grapefruits (*Citrus paradisi*) are medium-sized, subtropical fruit trees that belong to the family of Rutaceae. Grapefruit, a hybrid of pomelos (*C. maxima*) and sweet oranges (*Citrus sinensis*) was first discovered in the 18th century. Different varieties of grapefruits vary in hue from white to red depending on the presence or absence of lycopene [6]. According to the data from the Food and Agricultural Organization of the United Nations, China and the United States are the leading grapefruit producers worldwide. In China, a total of 3.8 million metric tons of grapefruit was reportedly produced in 2013 [3]. The major varieties of grapefruit include Pink, Ruby Red, Star Ruby, Thompson, and White Marsh. Owing to several bioactive phytochemicals, such as flavonoids, carotenoids, coumarins, and organic acids, grapefruit possesses several health-promoting properties such as anti-inflammatory, -cancer, and -obesity effects [7–9]. Flavonoids are considered the most important bioactive components present in grapefruit. The major flavonoids found in grapefruit, including hesperetin, naringenin, narirutin, and didymin, have been extensively studied both *in vitro* and *in vivo* to confirm their role in benefiting human health [10,11]. Although these phytochemicals exhibit bioactive activities, some compounds have been shown to interact with numerous medications causing adverse effects known as the "grapefruit juice effect." Furanocoumarins and flavanones are the major culprits responsible for grapefruit juice causing these drug interactions. Several studies have reported that furanocoumarins present in grapefruit interact with medications by interfering with the haptic and intestinal enzyme cytochrome P450 [12]. Several studies have developed different processing methods for the removal of furanocoumarins from grapefruits such as heat treatment, UV irradiation, and autoclaved fungi [13–15]. Until now, numerous comprehensive reviews summarized the grapefruit juice–drug interaction mechanisms mainly focusing on discussion of the adverse effects of furanocoumarins [16–18]. Although furanocoumarins can cause undesirable effects because of interactions with certain medications, recent evidence has emerged from several *in vitro* and *in vivo* studies suggesting that furanocoumarins possess additional biological activities, such as antioxidative, -proliferative, -inflammatory, and bone health promoting effects. As grapefruit juice is one of the most popular fruit juices worldwide, grapefruit furanocoumarins deserve more attention with regard to their health benefits. Thus, this review first summarizes the biosynthetic pathway, analytical methods, and distribution of grapefruit furanocoumarins, and then provides a comprehensive view of their health benefits.

2. Biosynthetic pathway of furanocoumarins in grapefruit

Furanocoumarins, a subclass of organic chemical compounds, are the secondary metabolites produced in citrus and are involved in the plant's defenses against insects, pathogens, and other organisms [19]. Their structure is characterized by a furan ring attached to carbon 6 and 7 (linear type) or 7 and 8 (angular type) of a benzo-α-pyrone (coumarin). Linear furanocoumarins are practically distributed into four families of higher plants that include Rutaceae, Moraceae, Leguminosae, and Apiaceae, whereas the angular furanocoumarins are primarily confined to Apiaceae and Leguminosae [19]. The most abundant linear furanocoumarins existing in higher plants are psoralen, xanthotoxin, bergapten, and isopimpinellin.

Citrus plants synthesize both coumarins and furanocoumarins with grapefruit considered the major dietary source of furanocoumarins in the Western diet. It is estimated that the average consumption of furanocoumarins in the United States and Germany is 1.3 mg/d and 0.562 mg/d, respectively, and grapefruit juice contributes to ~73% of furanocoumarin intake from foods [20,21]. The major furanocoumarins found in grapefruits are bergamottin, epoxybergamottin, and 6′,7′-dihydroxybergamottin. The pathway of furanocoumarin biosynthesis was confirmed and characterized using radiolabeled compounds during 1960–1980 [22–24]. This biosynthetic pathway in higher plants use umbelliferone, also known as 7-hydroxycoumarin, as the precursor of these furanocoumarins. In the first step of coumarin synthesis, several phenylpropanoid intermediates are synthesized from phenylalanine (Figure 1). Through a deamination reaction by phenylalanine ammonia-lyase, phenylalanine is first converted to *trans*-cinnamic acid. This is subsequently catalyzed by cinnamate 4-hydrolase (C4H), an essential enzyme involved in phenylalanine metabolism, to form *p*-coumaric acid. C4H, a member of cytochrome P450 monooxygenase from CYP73A family, can catalyze monooxylation of various substrates within organisms [25,26]. *p*-Coumaric acid is further catalyzed through thioesterification by 4-coumarate-CoA ligase, and *p*-coumaroyl-CoA is then produced. In the phenylpropanoid pathway, coumaroyl-CoA is the pivotal intermediate of not only coumarins, but also a broad range of metabolites, such as flavonoids, anthocyanins, tannins, and lignans [27,28]. Next, the *ortho*-hydroxylation of *p*-coumaroyl-CoA catalyzed by cinnamoyl-CoA 2′-hydroxylase (C2′H) leads to synthesis of 2,4-dihyroxycinnamoyl CoA. *ortho*-Hydroxylation is a key step of coumarin biosynthesis, and a previous study of *Lavandula officinalis* demonstrated that *para*-hydroxylation was a prerequisite for *ortho*-hydroxylation [23]. Finally, nonenzymatic lactonization results in