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Chemistry and bioactivity of nobiletin and its metabolites

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ABSTRACT

The studies of nobiletin and other polymethoxyflavones from citrus peels become prevalent in recent years due to many well-established evidences showing their multiple efficacious biological activities. The biotransformation study of polymethoxyflavones, particularly nobiletin has emerged along with the significant findings of nobiletin bioactivity. Major nobiletin metabolites from rodent biofluids have been successfully characterized, isolated or synthesized for the evaluation of their biological activities and subsequently revealed that nobiletin metabolites demonstrate similar efficacies or more potent anti-oxidant activity and scavenging property against free radicals and in the inhibition of inflammation and cancer growth, and the prevention of metabolic syndrome and cardiovascular diseases. This review starts with basic chemistry of nobiletin and other polymethoxyflavones, highlights their biological properties and recent findings and summarizes nobiletin's biotransformation and biological activities of the main nobiletin metabolites.

Contents

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1. Introduction

Abundantly existed in the peels of citrus genus, polymethoxyflavones (PMFs) are a unique group of poly-methylated flavonoids and have been shown many health-promoting effects in animal studies. Accumulative evidence has indicated that PMFs exhibit various biological activities, such as anti-carcinogenic, anti-inflammatory, anti-viral, anti-atherogenic and anti-diabetic properties (Assini, Mulvill, & Hurf, 2013; Li et al., 2009; Miyata et al., 2011; Onda, Horike, Suzuki, & Hirano, 2013; Pan, Lai, Wu, & Ho, 2011; Qiu et al., 2011) *etc*. Furthermore, multiple metabolites of PMFs have been identified and their biological activity examined showing that they possess similar or more effective biological activities (Li et al., 2007; Oshitari et al., 2011; Su et al., 2012). Previously, we have reviewed studies in the anti-tumor and anti-inflammatory activity of PMFs including nobiletin, tangeretin, and 3,5,6,7,8,3′,4′-heptamethoxyflavone (Li et al., 2009). In this paper, we summarize the biological activities of one of the most abundant PMFs, nobiletin and its major known metabolites.

1.1. Chemistry of nobiletin

Nobiletin is a flavonoid, or O-methylated flavonoid by conventional flavonoid definition in which flavonoids are polyphenolic compounds having a basic C6–C3–C6 15-carbon skeleton with multiple hydroxyl groups on the three-ring system. Flavonoids from citrus fruits are embedded with a benzo-γ-pyrone structure and have phenyl substitutions at the C3 position. The citrus flavonoids include a class of glycosides, namely hesperidin and naringin, and another class of O-methylated aglycones of flavones such as nobiletin and tangeretin, which are relatively common two polymethoxylated flavones (PMFs), both present in the peels of tangerine (*Citrus tangerina*), sweet orange (*Citrus sinensis*) and bitter orange (*Citrus aurantium*).

Nobiletin, likely named after *Citrus nobilis* represented by tangerine, mandarin *etc*. easy-peel citrus, is the most prevalent flavone exclusively existing in citrus genus and particularly copious in citrus peels. It has six methoxyl groups on the flavone core distributed at the 5, 6, 7, 8-positions of A-ring and 3′, 4′- positions of B-ring (Fig. 1). Hence, its IUPAC name is 2-(3,4-dimethoxyphenyl)-5,6,7,8-tetramethoxychromen-4-one, and other common names are 2-(3,4-dimethoxyphenyl)-5,6,7, 8-tetramethoxy-4H-1-benzopyran-4-one, and 5,6,7,8, 3′,4′-hexamethoxyflavone.

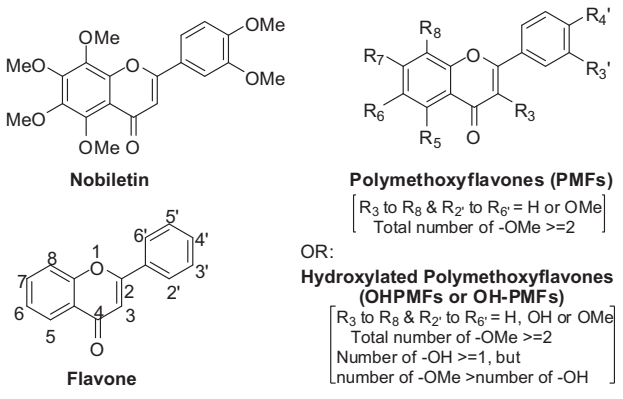

Fig. 1 – Nomenclature of nobiletin and its relatives.

1.2. Chemical analysis of nobiletin in citrus peels

Currently there are more than twenty polymethoxylated flavones being isolated and identified from different tissues of citrus plants with citrus peels being the most abundant resource. The isomers and content of PMFs vary dramatically among different variety of citrus species. Hence the variety and amount of PMFs should be studied thoroughly and results obtained can serve for taxonomic purposes in botanical and agricultural sciences.

The co-existence of multiple polymethoxyflavones and mono- or di-desmethyl-polymethoxyflavones creates difficult hurdles for identification and quantification of individual PMFs or OHPMFs including nobiletin and its related compounds. Fortunately, with the help of modern advanced analytical techniques such as HPLC, LC/MS/MS and NMR *etc*., the disentanglement of the complex phyto-mixture becomes enabling in isolation and characterization of virtually any phytochemicals in plants or plant extracts. In the analysis of nobiletin containing PMFs in citrus peels, there were several reported methodologies such as GC, GC/MS, HPLC and LC/MS. But the standardized research of identification and quantification of nobiletin and its class of PMFs did not gained its popularity until the report of a validated HPLC analysis method of six individual PMFs in citrus peel extracts (CPEs) with nobiletin being a major components in the measured CPEs (Wang, Li, Ferguson, Goodnow, & Ho, 2008). The application of these analytical techniques in combination with cell and molecular bioassays enable identification of key bioactive components such as nobiletin that help to establish the SAR (structure–activity relationship), and consequently guide the study direction towards chemically defined and biologically confirmed components as targeted screening and standardized control in natural product research.

Nobiletin is ubiquitous and abundant in most reported PMF containing CPEs. For example, in sweet orange peels, the major PMFs are nobiletin, tangeretin, 3,5,6,7,8,3′,4′-heptamethoxyflavone and 3,5,6,7,3′,4′-hexamethoxyflavone, (Li et al., 2006a; Li, Lo, & Ho, 2006b). Overall, the most common PMFs in high yielding citrus are two polymethoxylated flavones, nobiletin and tangeretin. Both PMFs are presented in sweet orange peel (*Citrus sinensis*) and in bitter orange peel (*Citrus aurantium*) with nobiletin has the highest weight content (Li et al., 2006a, 2006b; Wang et al. 2008). The HPLC traces of the peel extracts of sweet orange, tangerine and bitter