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Original Article

Screening of hepatoprotective compounds from licorice against carbon tetrachloride and acetaminophen induced HepG2 cells injury

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ABSTRACT

Background: Licorice and its constituents, especially licorice flavonoids have been reported to possess significant hepatoprotective activities. However, previous studies mainly focus on the extract and major compounds, and few reports are available on other licorice compounds.

Purpose: This work aims to evaluate the *in vitro* hepatoprotective activities of licorice compounds and screen active compounds, and to establish the structure–activity relationship.

Methods: A compound library consisting of 180 compounds from three medicinal licorice species, *Glycyrrhiza uralensis, G. glabra* and *G. inflata* was established. HepG2 cells were incubated with the compounds, together with the treatment of 0.35% CCl_4 for 6 h and 14 mM APAP for 24 h, respectively.

Results: A total of 62 compounds at 10 μM showed protective effects against CCl_4 to improve cell viability from 52.5% to >60%, and compounds **5** (licoflavone A), **104** (3,4-didehydroglabridin), **107** (isoliquiritigenin), **108** (3,4,3′,4′-tetrahydroxychalcone), and **111** (licochalcone B) showed the most potent activities, improving cell viability to >80%. And 64 compounds showed protective effects against APAP to improve cell viability from 52.0% to >60%, and compounds **47** (derrone), **76** (xambioona), **77** ((2S)-abyssinone I), **107** (isoliquiritigenin), **118** (licoagrochalcone A), and **144** (2′-*O*-demethybidwillol B) showed the most potent activities, improving cell viability to >80%. Preliminary structure–activity analysis indicated that free phenolics compounds especially chalcones showed relatively stronger protective activities than other types of compounds.

Conclusion: Compounds **5, 76, 104, 107, 111, 118** and **144** possess potent activities against both CCl_4 and APAP, and **5, 76** and **118** were reported for the first time. They could be the major active compounds of licorice for the treatment of liver injury.

Introduction

Natural products are valuable resources to screen bioactive compounds due to their high diversity of chemical structures and biological functions (Yuan et al., 2016). Licorice is one of the most popular herbal medicines worldwide. It is derived from the roots and rhizomes of *Glycyrrhiza* species (Leguminosae family). Three species, *Glycyrrhiza uralensis, G. glabra* and *G. inflata* are officially used in China (Chinese Pharmacopeia Commission, 2005). Licorice shows a variety of therapeutic effects for liver ailments, fever, sore throat, asthma, bronchitis, dyspepsia, gastric ulcers, Addison's disease, and rheumatoid arthritis (Asl and Hosseinzadeh, 2008). Thus, more than 400 compounds have been isolated from licorice, including flavonoids and saponins (Zhang and Ye, 2009). In modern research, increasing attention is being paid to licorice flavonoids because of their significant biological activities including antioxidant, anti-inflammatory, antimicrobial, antispasmodic, antitumor, and metabolic syndrome preventive activities (Hosseinzadeh and Nassiri-Asl, 2015).

Liver is the central organ in the metabolism and detoxification of xenobiotics in human body, and liver diseases are one of the riskiest causes of death worldwide (Bleibel et al., 2007; Losser and Payen, 1996). Herbal medicines offer a number of bioactive compounds for liver diseases therapy, including, glycyrrhizin and silymarin (Hong et al., 2015).

Licorice has been used for the treatment of liver ailments for a long history. Saponins and flavonoids may play the major role (Zhang and Ye, 2009). However, the bioactive compounds have not been systematically clarified yet. Only the major constituents such as glycyrrhizic acid, glycyrrhetinic acid and isoliquiritigenin have been investigated for their hepatoprotective activities (Orazizadeh et al., 2014; Chen et al., 2014; Zhao et al., 2015). In this study, 130 flavonoids and 50 other compounds (including saponins) isolated from *Glycyrrhiza*

Abbreviations: CCl_4, carbon tetrachloride; APAP, acetaminophen; DMSO, dimethyl sulfoxide; FBS, fetal bovine serum

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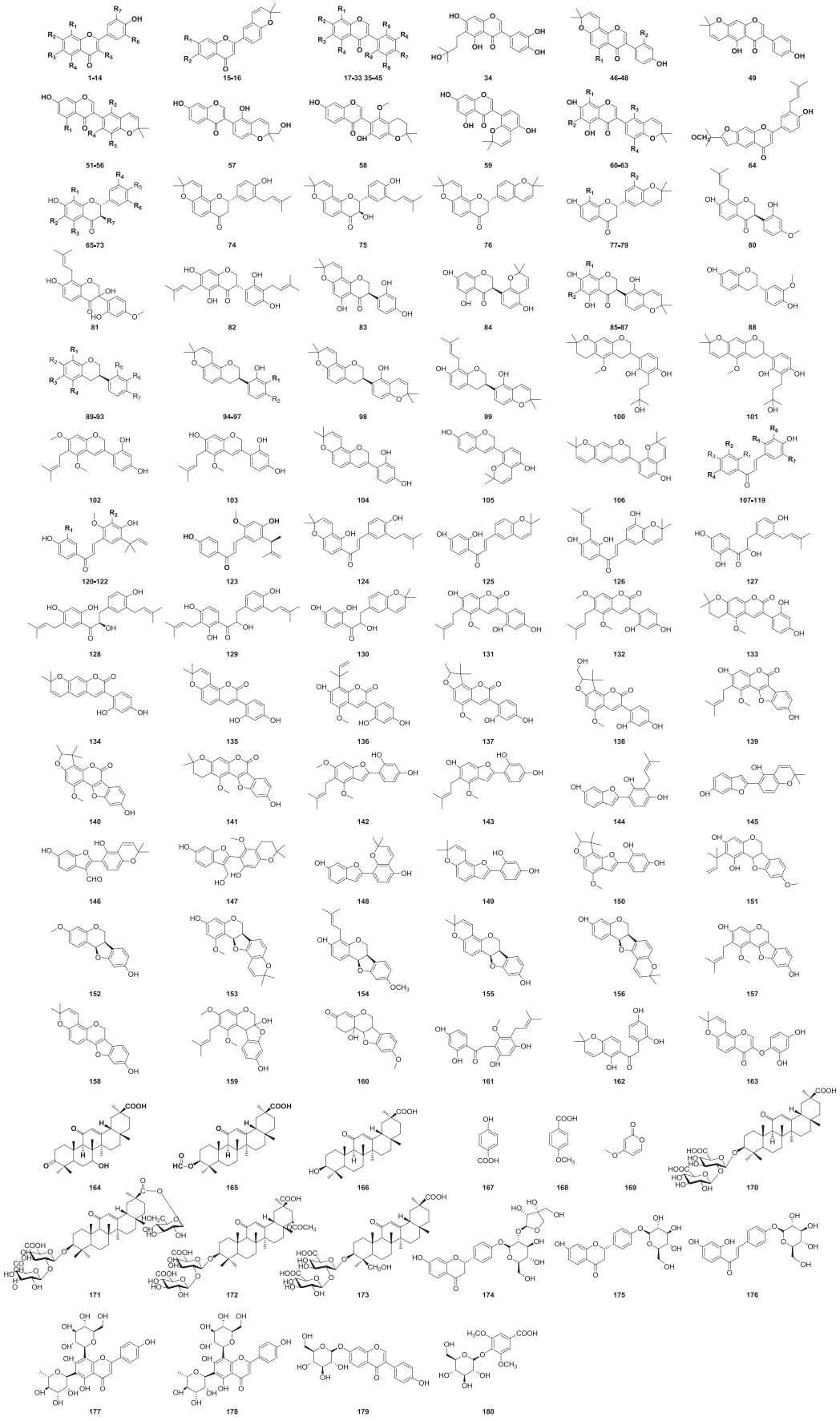

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