Structure-Hepatoprotective Activity Relationship Study of Iridoids: A QSAR Analysis

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ABSTRACT

Iridoids, the largest class of monoterpenoids, are widespread group of substances present in various plant organisms. This study is devoted to investigation of the hepatoprotective activity of a series of iridoid compounds with application of a quantitative structure-activity relationship (QSAR) analysis. The investigated activity was based on in vitro experimental data, where iridoids’ effects on CCl\textsubscript{4}-induced hepatocytes’ damage were obtained. The QSAR analysis was carried out using a combination of genetic algorithm for variable selection and multiple linear regression analysis. A set of calculated descriptors was used for modeling, including quantum-chemical descriptors. Several high-performance models were developed and the best model describing the hepatoprotective activity of iridoids is proposed. The model obtained in this study shows not only a statistical significance, but also excellent predictive ability. The obtained model can be used to estimate the hepatoprotective activity of new substituted iridoids.

KEYWORDS

Hepatoprotective Activity, In Vitro, Iridoids, Natural Compounds, Predictive Model, QSAR, Quantum-Chemical Descriptors, Structure-Activity Relationship

1. INTRODUCTION

Iridoids represent a large group of cyclopenta[c]pyran monoterpenoids found in a number of folk medicinal plants and used as hypotensives, cough medicines, bitter tonics, sedatives, antipyretics, remedies for wound sand skin disorders (Tietze et al., 1983). This fact encouraged scientists to investigate the bioactivities of these plant compounds. Additional studies during recent years revealed that iridoids exhibit a wide range of bioactivity: neuroprotective, antitumor, anti-inflammatory, antioxidant, cardiovascular, antihepatotoxic, choleric, hypoglycemic, hypolipidemic, antispasmodic,
antiviral, antimicrobial, immunomodulator, antiallergic, anti-leishmanial and molluscicidal effects (Ghisalberti et al., 1998, Usmanov et al., 2019). Naturally occurring iridoid compounds were classified into different sub-groups on the basis of their demonstrated or postulated biosynthesis pathway as well as on the basis of chemical properties. According to Hegnauer’s classification (Hegnauer, 1986), natural iridoids in the broadest sense are represented by nine structural groups, consisting of cyclopentanoid monoterpines and secoiridoids in general characterized by the structural feature of a 7,8-seco ring including pseudo alkaloids, as well as complex indole- and isoquinoline-type alkaloids. In another study, the iridoid glycosides were summarized (El-Naggar et al., 1980), which are mainly containing a glucose, secoiridoid glucosides and non-glycosidic compounds, while all nitrogen-containing iridoids were omitted. Also, simple pseudoalkaloids were considered as artefacts, where they were formed by replacement of oxygen by nitrogen in iridoids, during ammonia treatment at extraction.

Oxidative stress, chronic liver inflammation from viral and chemical toxicity, and accumulation of fats in liver from insulin resistance are the key factors for liver diseases. Several pro-inflammatory cytokines such as TNF-a, IL-1b, and IL-6 and endothelial growth factors are over-expressed by liver kupffer cells in the inflammation site, which in turn initiate an inflammation cascade to produce TGF-b1 and other growth factors and chemokines for remedial measure. The growth factor TGF-b1 induces the activation of hepatic stellate cells for transformation into myofibroblasts, which initiate apoptosis of hepatocytes in liver tissues. The pro-inflammatory genes, TNF-a, IL-1b, IL-6, IL-8, and IL-17 are considered as key players to elevate obesity and fat-related inflammation in liver (Andrade et al., 2015; Czaja et al., 2014; Tilg et al., 2010). Therefore, search for new effective medicinal compounds with hepatoprotective properties is an important task. Pathology and functional disorders of the liver are almost always combined with pathology of the gallbladder and biliary tract, and therefore the most successful therapy is aimed at improving the metabolic processes in the liver, increasing its resistance to pathogenic effects, accelerating the recovery of its functions during various injuries and to eliminate dysfunctional disorders of the biliary tract.

Some of iridoids from *P. scandens var tomentosa* possess a notable hepatoprotective activity, mainly via the process of decreasing the oxidative stress level in liver tissues. Total sum of iridoid glycosides can therefore be regarded as a promising candidate agent for protecting again statucorchronic liver injury (Peng et al., 2015). The iridoids, secoiridoids and analog glycosides from a *Gentianaceae* herb Gentian may be responsible for the hepatoprotective effect of this kind of food additive or medicine. The regulation of the expression levels of hepatic CYP450 systems and improvement of mitochondrial functions are the potential hepatoprotective mechanisms. Among computational methods, molecular docking analysis provides useful information on structure–activity relationships between CYPs and the naturally found iridoids, secoiridoids and analog glycosides. Further experimental validation of the hepatoprotective effect of amarogentin on aconitine-induced stress in HepG2 cells reveals a functional relationship between amarogentin and the CYP3A4 enzyme (Dai et al., 2018). Such iridoid as picroliv has been shown to have a pronounced hepatoprotective activity against many hepatotoxic compounds such as alcohol, aflatoxin B1 and oxytetracycline (Saraswat et al., 1997; Rastogi et al., 2000; Rastogi et al., 2001). This effect has been attributed to a stabilizing action on the cell membrane of the hepatocytes, which was possibly related to the ability of picroliv to act as an oxygen free-radical scavenger that limits the lipid-peroxidation involved in membrane damage elicited by hepatotoxins. The hepatoprotective activity of picroliv to provide protection against the biochemical alterations produced by CCl4 and *E. histolytica* was also previously evaluated (Singh et al., 2005).

For the last decade, iridoids have been the objects of considerable interest for quantitative structure-activity relationship (QSAR) investigations since there is a growing need for more effective hepatoprotective drugs. There are limited number of publications available that report QSAR studies to predict hepatoprotective activity (Jaqua et al., 2005; Paukku et al., 2009; Bartalis et al., 2011; Vinholes et al, 2014; Kondeva-Burdina et al., 2019). These QSAR models were developed for other class of compounds, such as sesquiterpenes (Paukku et al., 2009; Vinholes et al, 2014), cucurbitacin
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