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Product Information

Athrombosyn Phytotherapeutic Extract Formulation is designed to attenuate unwanted blood clotting in the cardiovascular system caused by inoculation-based sources. Contains phytotherapeutic extracts of ***Glycyrrihiza galbraith, Salvia miltorrihzia, Coptidis rhizomes, , Silybum marianum, Rehmania glutonius, Zingiber officinale, and Cinnamomum verum.*** This is a synergistic herbal formula known to attenuate blood clots.

Thrombosis occurs when blood clots block your blood vessels. Thrombosis is a serious condition where a clot forms inside a blood vessel (an artery or vein) in your body or sometimes inside of your heart. This is dangerous because clots that form inside blood vessels can block blood flow. They can also break free and travel elsewhere in your body, and if a clot gets stuck in a critical location like your lungs or brain, that can cause life-threatening emergencies. There are 2 main types of thrombosis: **Venous thrombosis** is when the blood clot blocks a vein. Veins carry blood from the body back into the heart. **Arterial thrombosis** is when the blood clot blocks an artery. Arteries carry oxygen-rich blood away from the heart to the body.

Arterial thrombosis may be caused by a hardening of the arteries, called arteriosclerosis, which can occur in the arteries that supply blood to the heart muscle (coronary arteries). This can lead to a heart attack. When arterial thrombosis occurs in a blood vessel in the brain, it can lead to a stroke.

Glycyrrihiza galbraith, Glycyrrhizin (GL), an anti-inflammatory compound isolated from licorice (Glycyrrhiza glabra), has been previously identified as a thrombin inhibitor (Francischetti et al., Biochem Biophys Res Commun 1997;235:259-63). Intravenous administration of GL caused a dose-dependent reduction in thrombus size on a venous thrombosis model that combines stasis and hypercoagulability.
Salvia miltorrihzia, S. miltiorrhiza, is considered to be highly effective in activating circulation, and dispersing stasis or sludging of blood. S. miltiorrhiza has been widely used to treat cardiovascular diseases.
Coptidis rhizomes, is a common component in traditional medicines used to treat CVD associated problems including obesity, diabetes mellitus, hyperlipidemia, hyperglycemia and disorders of lipid metabolism.
Silymarin, Silybum marianum or Milk Thistle, Silymarin (SM), a mixture of flavonoids and polyphenols extracted from *Silybum marianum* (milk thistle), possesses a variety of pharmacological activities including antioxidant and anti-inflammatory/immunomodulatory, hepatoprotective, neuroprotective, renal-protective (against I-R injury), gastroprotective, antibacterial, antiviral, antithrombotic, and vasodilatory properties.
Rehmania glutonius, can regulate hormone metabolism, reduce blood glucose, resist aging, help to sedate patients and promote diuresis.
Zingiber officinalis, is hepatoprotective, anti-inflammatory, antioxidant, antiseptic, and promote gastric secretions.
Cinnamomum verum, Cinnamon health benefits are attributed to its content of a few specific types of antioxidants, including polyphenols, phenolic acid and flavonoids.

Athrombosyn is uniquely extracted from select organic herbs, organic cane alcohol and deep ocean mineral water, as the extraction solvent. Utilizing advanced all-glass apparatus **Athrombosyn**'s ingredients undergo hours of reflux extraction that applies heat and hydroalcohol to enhance the bioavailability of the resultant extraction.

Comparative Study Thromb Res. 2003;112(1-2):93-8. doi: 10.1016/j.thromres.2003.10.014.

Antithrombotic effect of Glycyrrhizin, a plant-derived thrombin inhibitor

Wallace Mendes-Silva [1], Mariane Assafim, Bruno Ruta, Robson Q Monteiro, Jorge A Guimarães, Russolina B Zingali

Affiliations

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Abstract

Glycyrrhizin (GL), an anti-inflammatory compound isolated from licorice (Glycyrrhiza glabra), has been previously identified as a thrombin inhibitor (Francischetti et al., Biochem Biophys Res Commun 1997;235:259-63). Here we report the in vivo effects of GL upon two experimental models of induced thrombosis in rats. Intravenous administration of GL caused a dose-dependent reduction in thrombus size on a venous thrombosis model that combines stasis and hypercoagulability. It was observed that GL doses of 180 mg/kg body weight produced 93% decrease on thrombus weight. This effect showed a time-dependent pattern being significantly reduced when the thrombogenic stimulus was applied 60 min after drug administration. GL was also able to prevent thrombosis using an arteriovenous shunt model. GL doses of 180 and 360 mg/kg decreased the thrombus weight by 35 and 90%, respectively. Accordingly, the APTT ex vivo was enhanced by 1.5- and 4.3-fold at GL doses of 180 and 360 mg/kg, respectively. In addition, GL doses above 90 mg/kg caused significant hemorrhagic effect. In contrast with heparin, GL did not potentiate the inhibitory activity of antithrombin III or heparin cofactor II towards thrombin. Altogether, data indicate that GL is an effective thrombin inhibitor in vivo, which may account for its other known pharmacological properties.

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Original Article

Effects of Preoperative Glycyrrhizin Infusion for the Prevention of Venous Thrombosis on the Tissue Expression of Antithrombin in a Rat Model

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Objective: Using a thrombus model prepared by ligation of the inferior vena cava (IVC), the influences of the glycoside, glycyrrhizin, on plasma antithrombin levels and antithrombin mRNA expression levels in the liver and IVC with the inhibition of venous thrombosis were investigated.
Materials and Methods: The rat IVC was exposed and ligated for 24 h immediately after the intravenous administration of 300 mg/kg glycyrrhizin. Among antithrombotic drugs, the Xa inhibitor, fondaparinux sodium, was used as a control drug.
Results: The mean thrombus weight was significantly smaller in the glycyrrhizin-treated group (18.3 mg) than in the saline-treated group (34.3 mg). In contrast, the inhibition of thrombosis was not observed in the fondaparinux-treated group. Antithrombin mRNA expression levels in the liver were significantly higher in the ligated groups than in the baseline control group. The mean plasma antithrombin level was significantly lower in the glycyrrhizin group (96.6%) than in the saline group (114.4%), but was not significantly different from that in the baseline control group (102.4%).
Conclusion: The pretreatment with glycyrrhizin inhibited venous thrombosis, and antithrombin mRNA expression levels in the liver and IVC as well as plasma antithrombin levels were significantly lower than those in the saline group.

Keywords: glycyrrhizin, antithrombin, DVT

Introduction

Antithrombin is a 58-kD protease inhibitor that is mainly synthesized in the liver and circulates as a plasma protein. It regulates blood coagulation by directly inhibiting the serine proteases of the clotting cascade, with the most important targets being thrombin, factor Xa, and factor IXa. A sequence-specific pentasaccharide present in only a fraction of heparin molecules mediates the high-affinity binding and anticoagulant activation of antithrombin by this polysaccharide.[1)] Antithrombin has lysine binding sites to which heparin binds at a molar ratio of 1:1. The half-life of thrombin is reduced to 20 ms in the presence of a high concentration of heparin, which is an approximately 2000-fold acceleration of this reaction.[2)] Griffith previously identified thrombin-heparin binding as the most important factor for efficient thrombin inhibition by antithrombin.[3)]

P- and E-selectins have been known to mediate the linkage of endothelial cells to neutrophils through the binding to sialyl-Lewis X glycoproteins, which are expressed on the surface of neutrophils.[4,5)] Neutrophils adherent to the endothelium also undergo transendothelial migration, leading to endothelial cell sloughing and exposure of the underlying basement membrane to the accelerated formation of deep vein thrombosis (DVT).[6)]

Glycyrrhizin, which is a natural triterpenoid saponin with a molecular mass of 840 Daltons, has been approved for useful drug for the treatment of allergic disorders and chronic hepatitis in Japan. We previously showed that glycyrrhizin was effective on the prevention of the tissue damage caused by ischemia-reperfusion in the rabbit hind limb.[7)]

Mendes-Silva et al.[8)] were the first to demonstrate that glycyrrhizin exhibits antithrombotic activity *in vivo* and, it has, thus, been characterized as a potential thrombin inhibitor. Assafim et al.[9)] showed that glycyrrhizin was effective in preventing venom-induced thrombus formation through the generation of thrombin by prothrombin activators and platelet-activating components. Glycyrrhizin was previously demonstrated to bind to thrombin exosite I and block the effects of the enzyme on fibrinogen and platelets.[10)]

Glycyrrhizin, an agent with a chemical structure analogous to that of sialyl-Lewis X and the ability to bind P- and L-selectins, may be useful for blocking the P-selectin-mediated thrombotic cascade due to its competitive binding to sialyl-Lewis X oligosaccharides on neutrophils and subsequent blocking of neutrophil adhesion to the vascular endothelium.[7,11)]

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Case Report

Licorice Root Associated With Intracranial Hemorrhagic Stroke and Cerebral Microbleeds

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Hannah Shin, BS[1], Matthew Chung, MD[2], and David Z. Rose, MD[2]

Abstract

Chinese Licorice root "gan zao" (*Glycyrrhiza uralensis*) is an ancient, medicinal herb utilized in Traditional Chinese Medicine for its presumably antiulcer, anti-inflammatory, antiviral, antibacterial, and expectorant properties. One of the major biologically active components is glycyrrhizin, which when hydrolyzed to glycyrrhetinic acid in the human body, possesses significant hypertensive effects due to interaction with the enzyme 11-β-hydroxysteroid dehydrogenase-2.[1] Glycyrrhizin and glycyrrhetinic acid also show antithrombotic properties, as orally active, direct inhibitors of blood coagulation factor Xa as well as of thrombin.[2] To our knowledge, this is the first reported case of intracranial hemorrhagic stroke associated with Chinese Licorice Root, and first reported case of cerebral microbleeds (CMB) associated with it as well.

Keywords

licorice root, intracranial hemorrhage, stroke, cerebral microbleeds, hypertension

Case Report

A 68-year-old Chinese-American woman without previous medical history was presented to the hospital with acute dysarthria and right hemiparesis, and a blood pressure of 219/123. Computed tomography of the head demonstrated a 3.9 cm × 2.5 cm left basal ganglia intraparenchymal hemorrhage (IPH).

Electrocardiogram showed normal sinus rhythm without signs of left ventricle hypertrophy, and serum laboratories were grossly unremarkable. Urine toxicology was negative for drugs of abuse. Computed tomography angiography of the head and neck showed no evidence of extravasation, arteriovenous malformation, aneurysm, vasculopathy, or high-grade stenosis. Magnetic resonance imaging (MRI) of the brain confirmed stability of the IPH but also uncovered supratentorial microhemorrhages/cerebral microbleeds (CMB) in deep structures bilaterally on Susceptibility-weighted imaging (SWI) sequences (Figure 1). With low-dose intravenous nicardipine, used intermittently, over 4 days, blood pressure fell quickly to 133/86 and she was discharged home with amlodipine 5 mg only.

Performing a meticulous rereview of her social history revealed that she had been dabbling in TCM over the last 40 years and occasionally consuming a Chinese herbal supplement containing Licorice Root for a panoply of sporadic gastrointestinal complaints.

However, because of a recent 2-week bout of dyspepsia and indigestion, she increased her consumption to every single day for 2 weeks straight. The ingredients are listed in Figure 2 and include "Chinese Licorice (gan zao) Root 800 mg."

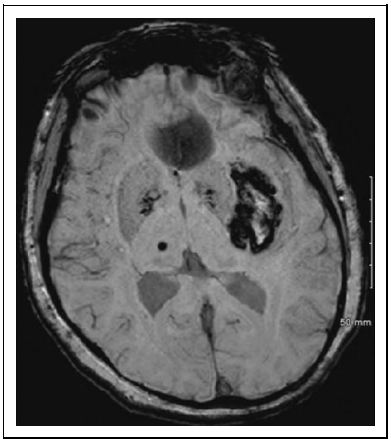

Figure 1. Axial SWI sequence on brain MRI demonstrates blood products in the left basal ganglia as well as cerebral microbleeds (CMB) involving the deep brain structures. MRI indicates magnetic resonance imaging.

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The potential of glycyrrhizin and licorice extract in combating COVID-19 and associated conditions

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ABSTRACT

Background: Several recent studies have stated that glycyrrhizin and licorice extract are present in most traditional Chinese medicine formulas used against SARS-CoV-2 in China. Significant data are showing that glycyrrhizin and licorice extract have multiple beneficial activities in combating most features of SARS-CoV-2.

Purpose: The aim of current review was to highlight recent progresses in research that showed the evidence of the potential use of glycyrrhizin and licorice extract against COVID-19.

Methodology: We have reviewed the information published from 1979 to October 2020. These studies demonstrated the effects , use and safety of glycyrrhizin and icorice extract against viral infections,bacterial infections, inflammatory disorders of lung (in vitro and in vivo). These studies were collated through online electronic databases research (Academic libraries as PubMed, Scopus, Web of Science and Egyptian Knowledge Bank).

Results: Pooled effect size of articles provides information about the rationale for using glycyrrhizin and licorice extract to treat COVID-19. Fifty studies demonstrate antiviral activity of glycyrrhizin and licorice extract. The most frequent mechanism of the antiviral activity is due to disrupting viral uptake into the host cells and disrupting the interaction between receptor- binding domain (RBD) of SARS-COV2 and ACE2 in recent articles. Fifty studies indicate that glycyrrhizin and licorice extract have significant antioxidant, anti-inflammatory and immunomodulatory effects. Twenty five studies provide evidence for the protective effect of glycyrrhizin and licorice extract against inflammation-induced acute lung injury and cardiovascular disorders.

Conclusion: The current study showed several evidence regarding the beneficial effects of glycyrrhizin and licorice extract in combating COVID-19. More randomized clinical trials are needed to obtain a precise conclusion.

Introduction

Coronavirus disease 2019 (COVID-19), is a kind of viral pneumonia caused by a novel coronavirus named Severe Acute Respiratory Syndrome. The pathogen that causes COVID-19 disease is a SARS-CoV2 or new coronavirus that has similar genetic structures with the other coronavirus as SARS-CoV . The SARS-CoV-2 shares 79.5% of genetic sequence and the same cell entry receptor, angiotensin-converting enzyme II (ACE2), with SARS-CoV (Zhou et al., 2020). It has an envelope spike (S) protein that is important for receptor binding and membrane fusion of coronavirus. Angiotensin-converting enzyme II (ACE2) is the cell receptor for SARS-CoV2 similar to SARS-CoV (Xu et al., 2020).

The S protein of SARS-CoV-2 has an affinity property to binds ACE2 10- to 20-fold greater than S protein of SARS-CoV. This high affinity of S protein for human ACE2 probably the reason for the rapid spread of SARS-CoV-2 (Wan et al., 2020). Hirano and Murakami (2020) documented that ACE2 as the SARS-CoV-2 receptor for cellular is critical for the virus entry. The targeting ACE2 has a promise for the prevention of SARS-CoV-2 infection during the initial phase of disease (Letko and Munster, 2020). In the later stages, a reduction of ACE2 enzyme, which

Abbreviations: : ACE2, angiotensin-converting enzyme 2; ALI, acute lung injury; ARDS, acute Respiratory Distress Syndrome; DCs, dendritic cells; COVID-19, Coronavirus disease 2019; COX-2, cyclooxygenase-2; 18β-GA, 18β-glycyrrhetinic acid; Gl, glycyrrhizin; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HMGB1, high-mobility group box 1; h, hour; IL, interleukin; iNOS, inducible nitric oxide synthase; licorice extract, LE; MAPKs, mitogen-activated protein kinases; MERS, Middle East respiratory syndrome; MR, mineralocorticoid receptor; MRSA, Methicillin-resistant *Staphylococcus aureus*; NO, nitric oxide; RBD, receptor-binding domain; ROS, reactive oxygen species; S, Spike; SARS, severe acute respiratory syndrome; TCM, traditional Chinese medicine; TLR, toll-like receptor; TNF-α, tumor necrosis factor alpha; TMPRSS2, type 2 transmembrane serine protease.

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Anti-thrombotic activity of phenolic acids obtained from *Salvia miltiorrhiza* f. alba in TNF-α-stimulated endothelial cells via the NF-κB/JNK/p38 MAPK signaling pathway

Xianjing Zheng, Haimei Liu, Maoqiang Ma, Jianbo Ji, Faliang Zhu & Longru Sun

Archives of Pharmacal Research **44**, 427–438 (2021)

Abstract

Over the past 100 years, *Salvia miltiorrhiza* f. alba (Lamiaceae) (RSMA) roots have been used to cure thromboangiitis obliterans (TAO) in local clinics. This study aimed to confirm the anti-thrombotic efficacy of 12 phenolic acids obtained from RSMA and to clarify the possible underlying mechanisms. The results of quantitative real-time polymerase chain reaction (qRT-PCR) and enzyme-linked immunosorbent assay (ELISA) experiments demonstrated that most of the phenolic acids markedly inhibited PAI-1 protein and mRNA levels but increased t-PA protein and mRNA levels in TNF-α-induced EA.hy926 cells ($P < 0.05$ or 0.001), with

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Salvia miltiorrhiza prevents deep vein thrombosis via antioxidative effects in endothelial cells

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Abstract

Deep vein thrombosis (DVT) is a common clinical problem, which represents a significant clinical and economic burden. The present study investigated whether Salvia miltiorrhiza (S. miltiorrhiza) could prevent DVT. A total of 30 rabbits were randomly divided into three groups (n=10 per group): The control, model and Salvia groups. A ligation model was used, where the femoral veins of rabbits were exposed and ligated. Measurements of coagulation function, blood rheological parameters, antioxidative function and effects on endothelial cells were conducted. Treatment with S. miltiorrhiza one week prior to generation of the ligation model did not affect the coagulation function much, except to increase the prothrombin time. There was a statistically significant difference (P<0.05) in whole blood viscosity (1/s, 5/s, 30/s) on the third and seventh days (1/s, 5/s, 30/s and 200/s) following generation of the model. S.

frontiers in Pharmacology

MINI REVIEW
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Rhizoma Coptidis: A Potential Cardiovascular Protective Agent

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Cardiovascular diseases (CVDs) are among the leading causes of morbidity and mortality in both the developed and developing world. Rhizoma coptidis (RC), known as Huang Lian in China, is the dried rhizome of medicinal plants from the family Ranunculaceae, such as *Coptis chinensis* Franch, *C. deltoidea* C.Y. Cheng et Hsiao, and *C. teeta* Wall which has been used by Chinese medicinal physicians for more than 2000 years. In China, RC is a common component in traditional medicines used to treat CVD associated problems including obesity, diabetes mellitus, hyperlipidemia, hyperglycemia and disorders of lipid metabolism. In recent years, numerous scientific studies have sought to investigate the biological properties of RC to provide scientific evidence for its traditional medical uses. RC has been found to exert significant beneficial effects on major risk factors for CVDs including anti-atherosclerotic effect, lipid-lowering effect, anti-obesity effect and anti-hepatic steatosis effect. It also has myocardioprotective effect as it provides protection from myocardial ischemia-reperfusion injury. These properties have been attributed to the presence of bioactive compounds contained in RC such as berberine, coptisine, palmatine, epiberberine, jatrorrhizine, and magnoflorine; all of which have been demonstrated to have cardioprotective effects on the various parameters contributing to the occurrence of CVD through a variety of pathways. The evidence available in the published literature indicates that RC is a herb with tremendous potential to reduce the risks of CVDs, and this review aims to summarize the cardioprotective properties of RC with reference to the published literature which overall indicates that RC is a herb with remarkable potential to reduce the risks and damage caused by CVDs.

Keywords: coptis root, Huang Lian, *Coptis chinensis* Franch, cardiovascular diseases, ethnopharmacology

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INTRODUCTION

Cardiovascular diseases (CVDs) appears set to continue as the largest cause of death and disease burden across the globe. They include a wide spectrum of life-threatening disorders such as coronary heart disease (CHD), cerebrovascular disease and peripheral arterial disease, all of which result from impairment to the heart and blood vessels (Wallace, 2011). Among the risk factors

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Original Article

Radix Rehmannia Glutinosa inhibits the development of renal fibrosis by regulating miR-122-5p/PKM axis

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Abstract: Objective: It is acknowledged that Radix Rehmanniae Praeparata (RR) can regulate hormone metabolism, reduce blood glucose, resist aging, help to sedate patients and promote diuresis. The study aims to investigate the mechanism of how RR influences the development of renal fibrosis by regulating the miR-122-5p/PKM axis. Methods: Unilateral ureteral obstruction (UUO) was applied to induce renal fibrosis in mice *in vivo*, and human tubular epithelial HK2 cells treated by transforming growth factor-β (TGF-β1) were used to induce renal fibrosis *in vitro*. Interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) in mouse serum were detected by Enzyme-linked immunosorbent assay (ELISA); fibronectin (FN) and type I collagen (Col-I) in renal tissue were detected by Western blotting; serum creatinine (Cr) and blood urea nitrogen (BUN) were analyzed by kits. Hematoxylin-eosin (HE) staining and Masson staining were utilized to assess the degree of pathological damage and fibrosis. Cell viability and apoptosis in the *in vitro* model were detected by MTT and Flow cytometry. Dual-luciferase reporter assay was performed to determine intermolecular targeting relationships. Results: RR could inhibit IL-6 and TNF-α levels, decrease the levels of FN and Col-I and improve the renal function indexes (serum Cr and BUN) in UUO mice (all $P<0.05$). In addition, RR was able to promote the up-regulation of miR-122-5p expression in UUO mice *in vivo* ($P<0.05$). MiR-122-5p expression was down-regulated and PKM expression was up-regulated in HK2 cells treated with TGF-β1 (all $P<0.05$). RR inhibited renal fibrosis progression by regulating the miR-122-5p/PKM axis. Inhibition of miR-122-5p or overexpression of PKM could promote apoptosis of TGF-β1-treated HK2 cells, inhibit their viability, aggravate fibrosis, and attenuate the protective effect of RR on the cells. The protective effect of RR promoted by overexpression of miR-122-5p was partially counteracted by PKM. Conclusion: RR can inhibit renal fibrosis progression by regulating the miR-122-5p/PKM axis.

Keywords: Radix Rehmannia Glutinosa, renal fibrosis, miR-122-5p, PKM

Introduction

Renal fibrosis is prevalent in end-stage renal diseases and it is a major cause of renal failure [1, 2]. Renal fibrosis is mainly characterized by tubular atrophy and extracellular matrix accumulation [3]. At present, the incidence of primary or concurrent renal diseases continues to increase [4]. This study strives to explore new molecular pathways and potential targets for the prevention and treatment of renal fibrosis. Radix Rehmanniae Praeparata (RR) is made from Radix Rehmanniae after steaming and further-processing, which belongs to the Scrophulariaceae family. It has been used as a medicine for more than 3000 years [5, 6]. Studies have demonstrated that RR has pharmaceutical effects such as anti-osteoporosis, anti-diabetes, anti-cardiovascular disease and anti-oxidative stress [7-10]. It has also been found that RR and Cornus officinalis can reduce symptoms of diabetic nephropathy via AGE-RAGE signaling pathway [11]. In this study, we further investigated the molecular mechanism of RR.

MiRNAs are a kind of single-stranded non-coding small RNAs that play a regulatory role during gene expression after transcription [12]. Many studies have suggested that miRNAs are involved in the pathogenesis of renal fibrosis. For example, miRNA let-7i-5p aggravates renal

nutrients

MDPI

Article

The Effect of Silymarin Flavonolignans and Their Sulfated Conjugates on Platelet Aggregation and Blood Vessels Ex Vivo

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Abstract: Silymarin is a traditional drug and food supplement employed for numerous liver disorders. The available studies indicate that its activities may be broader, in particular due to claimed benefits in some cardiovascular diseases, but the contributions of individual silymarin components are unclear. Therefore, we tested silymarin flavonolignans as pure diastereomers as well as their sulfated metabolites for potential vasorelaxant and antiplatelet effects in isolated rat aorta and in human blood, respectively. Eleven compounds from a panel of 17 tested exhibited a vasorelaxant effect, with half maximal effective concentrations (EC_{50}) ranging from 20 to 100 μM, and some substances retained certain activity even in the range of hundreds of nM. Stereomers A were generally more potent as vasorelaxants than stereomers B. Interestingly, the most active compound was a metabolite—silychristin-19-*O*-sulfate. Although initial experiments showed that silybin, 2,3-dehydrosilybin, and 2,3-dehydrosilychristin were able to substantially block platelet aggregation, their effects were rapidly abolished with decreasing concentration, and were negligible at concentrations ≤100 μM. In conclusion, metabolites of silymarin flavonolignans seem to have biologically relevant vasodilatory properties, but the effect of silymarin components on platelets is low or negligible.

Keywords: milk thistle; *Silybum marianum*; sulfates; metabolites; vasorelaxant; aorta; thrombocytes; blood coagulation

1. Introduction

The dietary utilization of the milk thistle (*Silybum marianum* (L.) Gaertn., Asteraceae) was probably first mentioned by the ancient Greeks (Theophrastus of Eresos, ca. 371–287 BC and Pedanios Dioscurides, ca. 40–90 AD), with medicinal properties being described even in medieval times (Hildegard von Bingen). Liver protection has been the most popular application, encompassing traditional use against