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Key Words
Syringic acid, hepatoprotection, inflammation, hepatocellular carcinoma, apoptosis, hepG2, oxidative stress

Corresponding Author
Burak Batuhan Laçin,
Department of Physiology, Faculty of Veterinary Medicine, Atatürk University, Erzurum, Turkey

Received: 18 February 2023
Accepted: 11 March 2023
Published: 18 March 2023

Citation: Burak Batuhan Laçin and Ali Çınar, 2023. Syringic Acid and Liver Damage. J. Anim. Vet. Adv., 22: 8-14, doi: 10.59218/makjava.2023.8.14

Syringic Acid and Liver Damage

Burak Batuhan Laçin and Ali Çınar
Department of Physiology, Faculty of Veterinary Medicine, Atatürk University, Erzurum, Turkey

ABSTRACT
Data from valuable literature information on the impact of syringic acid (SA) values on health. Studies have succeeded in pointing out that with vanillic acid, SA members can suppress hepatic fibrosis in chronic artifacts and instead point to its potential to mitigate widespread damage. It is also impressive that it effectively alleviates SA ammonia penalties and thioacetamide-induced hepatic tattooing of commonly occurring tattoo markers such as AST, ALT, ALP and LDH. SA showed promise in alleviating diabetic diabetes complications and protecting against renal, neuronal, cardiac and hepatic damage in rats. Contrary to these positive effects, another study shows that SA can induce the effects shown in clinical trials and emphasizes that the side effects of its effects are spent and affect more.

INTRODUCTION

Herbal metabolites are accepted as the source of natural products with different structures and biological effects. Recently, there has been a growing interest among researchers in the use of natural polyphenols as potential therapeutic phytochemicals due to their biological properties. Phenolic acids are the major polyphenols found in plants[1-5].

Syringic acid (SA) has antioxidant[1], anti-inflammatory[2], neuroprotective[3], hepatoprotective[4], cardioprotective[5], nephroprotective and anti-cancer properties[6,7]. The antidiabetic[8-10], antiglycator[11], antisteatosis-anti-inflammatory[12], antihypertensive[13,14] and antibacterial-antimicrobial properties of SA have been reported[1,15]. Thanks to its neuroprotective[16-21] and hepatoprotective properties[22,23], it ameliorates diabetic cataracts by suppressing the aldose reductase enzyme. It has also been stated that SA is used to make dental cement[22]. SA reduces acute thromboembolism and clot formation in mice[24]. SA is a derivative of 4-hydroxy-3,5-dimethoxybenzoic acid and hydroxybenzoic acid (Fig. 1). It is found in different plants such as Herba dendrobii, Radix isatidis and Alpinia calcarata Roscoe[25-27]. SA has also been proven to protect the heart, liver and brain[4,6-9,23,28-29]. SA acts as a free radical scavenger and can fight against reactive oxygen species (ROS). It also has the potential to regulate enzyme activity, transcription factors, growth factors and signaling pathways[4]. In addition, no adverse effects were observed in toxicological studies with SA[30].

The efficacy of antioxidants in reducing the risk of diabetic complications is remarkable[31,32]. Diabetes mellitus is a metabolic disease characterized by insufficient insulin secretion[33,34] . These pathological conditions can lead to irregular carbohydrate, protein and lipid metabolism[35]. The kidneys, eyes, nerves, liver, blood vessels and heart are the organs most affected by abnormal hyperglycemia[33]. The increase in diabetes, which is estimated to reach 53.1 million by 2025, is significant[36]. According to Rashedinia *et al.*[37]. They reported that dietary supplementation of SA

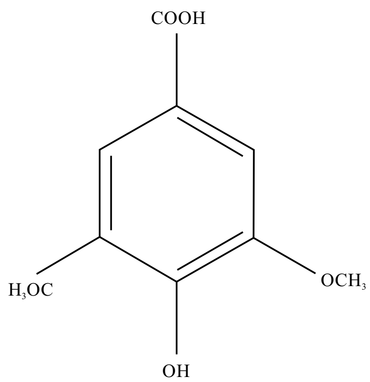

Fig. 1: Chemical structure of SA

protects hepatic tissue against hyperglycemia and lipid peroxidation. They also determined that SA provided protection by improving the deterioration in mitochondrial biogenesis in diabetic rats. The results of this study demonstrate the role of SA in mitochondrial biogenesis and its antioxidant activity in diabetes complications. It induces oxidative stress by increasing the level of reactive oxygen species (ROS) produced due to hyperglycemia, excessive mitochondrial activity and stimulation of the NF-κB signaling pathway in phagocytes. Oxidative stress plays a critical role in diabetic complications due to its adverse effects on vital biomacromolecules such as proteins, lipids and DNA[38]. These cellular damages can lead to cell death via apoptosis and necrosis[39]. The liver plays a central role in carbohydrate metabolism and maintenance of normal glucose levels. In diabetic conditions, chronic hyperglycemia, insulin resistance and decreased peripheral glucose uptake lead to an increase in lipogenesis as well as hepatic glucose output[40]. There is a strong correlation between diabetes and alteration in mitochondrial function. Decreased mitochondrial density, ATP production and decreased mitochondrial mRNA levels are other complications in diabetes and insulin resistance[41]. Mitochondrial biogenesis is a process affected by hyperglycemia and insulin resistance. Therefore, mitochondrial biogenesis is considered in the latest treatment strategies[42].

Type 2 diabetes mellitus is a non-communicable metabolic disease characterized by severe and persistent hyperglycemia due to decreased insulin secretion and increased insulin resistance. Poor control of hyperglycemia in diabetic patients often results in severe microvascular (diabetic nephropathy, neuropathy and cardiomyopathy) and macrovascular (peripheral vascular disease and cerebrovascular disease) complications[43-45]. Ghule *et al.*[46] and Shang *et al.*[47] emphasized that diabetic nephropathy, manifested as microalbuminuria, impaired urinary creatinine clearance rate, renal hypertrophy and glomerular sclerosis, is the most common cause of end-stage renal disease worldwide. Painful diabetic neuropathy affects all types of peripheral nerves, affecting almost all systems and organs in the body, including the long somatosensory nerves in the extremities, where it often causes sensory loss[48]. In addition, diabetic patients are 2-5 times more likely to experience cardiac dysfunction than non-diabetic patients [49]. Various structural abnormalities that result in left ventricular hypertrophy, systolic and diastolic dysfunction, or a combination thereof, are the main manifestations of diabetic cardiomyopathy[50]. In addition, hyperglycemia causes liver dysfunction, a common secondary diabetic complication[51,52]. According to Mirza *et al.*[53] reported that SA reduced hyperglycemia, polydipsia, polyphagia, polyuria, relative organ weight, cardiac hypertrophic indices, inflammatory markers, cell injury markers, glycosylated hemoglobin, histopathological score and oxidative stress. However, they found that it increased the Na/K ATPase activity. In conclusion, they found that SA could significantly reduce diabetic complications and renal, neuronal, cardiac and hepatic damage in streptozotocin-induced neonatal (nSTZ) diabetic rats. Hepatic encephalopathy (HE) is a complex syndrome with neuropsychiatric abnormalities associated with acute liver dysfunctions such as cirrhosis[54]. The incidence of cirrhosis increases with time and cirrhosis is the most common risk factor for HE, particularly in patients with alcoholic liver failure and portal hypertension[55]. HE affects brain function and includes a wide variety of symptoms, including altered consciousness, cognitive impairment, sensory abnormalities, altered motor activity and personality defects, as well as spatial memory dysfunction[56-68]. The most prominent current theory regarding the pathogenesis of HE is the accumulation of ammonia and other neurotoxic substances in the central nervous system due to impaired liver function[59]. The effects of ammonia on astrocytes in the brain are largely notable for its role in neuronal damage and eventual cognitive and motor symptoms[60]. In addition, as a potent free radical generator, ammonia induces free radical formation in astrocytes and impairs the antioxidant capacity of astrocytes[61-62]. Okkay *et al*.[63] Effectively attenuates thioacetamide-induced liver injury through reduction in SA ammonia, AST, ALT, ALP, LDH and reduction in oxidative stress (low MDA, ROS and increased SOD and GSH), as well as TNF-α, IL-1β and decreased inflammatory damage by suppressing NF-kB and increasing IL-10. It has also been stated that SA reduces the aggravating effects of thioacetamide. In conclusion, syringic acid has been reported to exert hepatoprotective and neuroprotective effects against hepatic encephalopathy by reducing hepatotoxicity biomarkers, suppressing hyperammonemia, as well as exerting antioxidant and anti-inflammatory effects.

Hepatocellular carcinoma is the second most common cause of cancer death in the world and its incidence has increased significantly worldwide over the past two decades. Its incidence is increasing and is an important public health problem[64]. Recently, the International Agency for Research on Cancer, a specialized cancer organization of the World Health Organization, found that hepatocellular carcinoma is now the second leading cause of death worldwide. As the causes of hepatocellular carcinoma; chronic alcohol consumption, hepatitis B and C virus infections, non-alcoholic fatty liver diseases, foods contaminated with aflatoxin B1, etc., takes place[65]. The most common treatment modalities in current practice for hepatocellular carcinoma are surgery, ablation and liver transplantation[66]. Sorafenib, a mitogen-activated protein kinase pathway inhibitor, is currently the only therapeutic agent approved for systemic use in hepatocellular carcinoma patients, although it has several adverse effects including hyperbilirubinemia, hand and foot skin reactions and fatigue[67]. Despite advances in the diagnosis and treatment of hepatocellular carcinoma, its incidence and mortality continue to increase. Therefore, there is a need for effective treatment options with fewer or possibly no side effects for patients with advanced hepatocellular carcinoma. Research into the efficacy of plant-based drugs has received increasing attention due to their little or no side effects. It has been reported that natural bioactive substances alter the redox state and interfere with essential cellular functions such as cell cycle, apoptosis, inflammation, angiogenesis[68].

Several studies have shown that plant-derived phytocompounds have a broad spectrum of biological activity, including anti-inflammatory, antioxidant, antimutagenic and anticancer properties[69]. There are studies showing that SA has a cytotoxic effect on the human HepG2 cell line and is a promising agent in anticancer research. According to Itoh *et al*.[70] reported that administration of syringing acid and vanillic acid significantly reduced transaminase activity on concanavalin A (ConA)-induced liver injury in mice. In addition, they stated that the administration of syringe acid and vanillic acid significantly suppressed cytokine levels. It has also been stated that SA treatment causes significant cytotoxicity and ROS release in HepG2 cells. Gheena and Ezhilarasan[71] reported that SA has a cytotoxic effect on the human HepG2 cell line and can be used as a promising agent in anticancer research.

Drug-induced liver injury is increasingly recognized as one of the leading causes of acute liver failure and the need for liver transplantation[72]. Drug-induced liver injury is one of the common reasons for withdrawal of drugs from the market and clinical trials. For example, acetaminophen, amoxicillin/clavulanate, dapsone, isoniazid and methotrexate are the most common causes of DILI[73-74]. Gheena *et al*.[75] reported that SA could be a promising herbal medicine that can prevent Sodium valproate-induced hepatotoxicity when administered together due to its potential anti-inflammatory effects.

Obesity, which is risk factors for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, diabetes and related pathologies, is associated with insulin resistance and adipose tissue distribution[76]. Ham *et al*.[77] reported that SA decreased body weight, visceral fat mass, serum levels of leptin, TNFα, IFNγ, IL-6 and MCP-1, insulin resistance, hepatic lipid content and early fibrosis, while increasing adiponectin circulation. They stated that SA has anti-obesity, anti-inflammatory and anti-steatotic effects through regulation of lipid metabolic and inflammatory genes. They also stated that SA could be a new natural therapeutic agent for obesity or non-alcoholic liver disease.

In conclusion, the immunomodulatory properties of SA are also believed to play a role in the suppression of liver damage caused by the activation of T cells. Furthermore, a study conducted on rats fed a high-fat diet showed that SA has beneficial effects on diet-induced hepatic dysfunction and further supports its potential as a liver health protective agent. In general, studies have been conducted suggesting its promising effects in alleviating liver diseases and inflammation, as well as protecting against oxidative damage in SA diabetic cases. More research is needed to fully understand the mechanisms underlying these effects and to identify potential therapeutic applications of SA on liver health.

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