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The Potential of Sorafenib in Preventing Metabolic Syndrome in Rats Fed a High-Fat High-Sucrose Diet

Adnan Iqbal[1], Rahila Najam[1], Shabana Simjee[2], Saira Saeed Khan[1], Azfar Ather Ishaqui[3,4], Salman Ashfaq Ahmed[4], Zeeshan Ahmed[4], Shayan Ahmed[4], Salman Ahmed[5], Muhammad Osama[1], Bilal Jawed[1]

[1] Department of Pharmacology, University of Karachi, Pakistan

[2] HEJ Research Institute of Chemistry, Karachi, Pakistan

[3] Department of Clinical Pharmacy, School of Pharmaceutical Sciences, University Sains Malaysia, Gelugor, Malaysia

[4] Department of Pharmacy, Iqra University, Karachi, Pakistan

[5] Department of Pharmaceutics, University of Sindh, Jamshoro, Pakistan

Abstract: The purpose of this study was to investigate the possible preventive role of sorafenib in preventing obesity, hyperlipidemia, and diabetes by exploring its preventive effects. As there is a rapid increase in the number of people being affected by these diseases, there is a need to find new methods to manage them. Sorafenib has been demonstrated to be a potent inhibitor of ABCC10 transmembrane protein in several studies. A recent study has shown that ABCC10 contributes to the pathogenesis of both hyperglycemia and hyperlipidemia. Additionally, many patients who have cancer also are affected by the metabolic syndrome. Thus, cancer patients must take medicines to control high cholesterol and glucose levels, thus increasing the burden of medicines on cancer patients. As sorafenib is an anti-cancer drug and a potent inhibitor of ABCC10, it may prevent metabolic syndrome in cancer patients, thus reducing the burden of additional medications and their adverse effects. This study's objective was to determine whether sorafenib can lower high lipid and high glucose levels in rats given a high-fat high-sugar diet. There were four groups of the rats: Group I: control (Standard Diet); Group II: diabetic (type-2) rats were given high-fat diet feed and sucrose through drinking water (25% sucrose) for 60 days (HFSD); Group III: diabetic (type-2) rats were given sorafenib 10 mg/kg/d (orally) for 60 days (HFS-S); Group IV: diabetic (type-2) rats were given metformin (50 mg/kg/d). Blood glucose, insulin, triglyceride, cholesterol, and liver enzyme levels were measured. Histopathological analysis of the liver was also conducted using an optical microscope. There was a significant weight reduction when sorafenib was administered to rats. The treatment produces a significant improvement in triglycerides (TG), total cholesterol (TC), and low-density lipoproteins (LDL) ($P < 0.05$). Furthermore, it also lowers blood glucose levels and improves insulin sensitivity ($P < 0.05$). Moreover, hepatic steatosis was also prevented by sorafenib in the histopathological analysis of the liver. According to our study, the effects of sorafenib were significant in improving dyslipidemia, hyperglycemia, and insulin sensitivity, as well as preventing the accumulation of fatty deposits in the rats' liver tissue when sorafenib was administered with a high-fat sucrose diet.

Keywords: sorafenib, ABCC10, cancer, hyperlipidemia, metabolic syndrome.

索拉非尼在预防高脂肪高蔗糖饮食大鼠代谢综合征中的潜力

摘要：本研究的目的是通过探索索拉非尼的预防作用，研究索拉非尼在预防肥胖、高脂血症和糖尿病方面可能的预防作用。由于受这些疾病影响的人数迅速增加，因此需要寻找新的方法来管理它们。在多项研究中，索拉非尼已被证明是一种有效的美国广播公司10跨膜蛋

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About the authors: Adnan Iqbal, Dr. Rahila Najam, Department of Pharmacology, University of Karachi, Pakistan; Dr. Shabana Simjee, HEJ Research Institute of Chemistry, Karachi, Pakistan; Saira Saeed Khan, Department of Pharmacology, University of Karachi, Pakistan; Azfar Ather Ishaqui, Department of Clinical Pharmacy, School of Pharmaceutical Sciences, University Sains Malaysia, Gelugor, Malaysia; Salman Ashfaq Ahmed, Zeeshan Ahmed, Shayan Ahmed, Department of Pharmacy, Iqra University, Karachi, Pakistan; Salman Ahmed, Department of Pharmaceutics, University of Sindh, Jamshoro, Pakistan; Muhammad Osama, Bilal Jawed, Department of Pharmacology, University of Karachi, Pakistan

白抑制剂。最近的一项研究表明，美国广播公司10有助于高血糖和高脂血症的发病机制。此外，许多癌症患者也受到代谢综合征的影响。因此，癌症患者必须服用药物来控制高胆固醇和葡萄糖水平，从而增加了癌症患者的药物负担。由于索拉非尼是一种抗癌药物和美国广播公司10的强效抑制剂，它可以预防癌症患者的代谢综合征，从而减少额外药物的负担及其副作用。本研究的目的是确定索拉非尼是否可以降低高脂高糖饮食大鼠的高脂和高血糖水平。有四组大鼠：第一组：对照（标准饮食）；第二组：糖尿病（2型）大鼠通过饮用水（25%蔗糖）给予高脂饲料和蔗糖60天（手足口病）；第三组：糖尿病（2型）大鼠给予索拉非尼10毫克/公斤/天（口服）60天（HFS-
小号）；第四组：糖尿病（2型）大鼠给予二甲双胍（50毫克/公斤/天）。测量了血糖、胰岛素、甘油三酯、胆固醇和肝酶水平。还使用光学显微镜进行肝脏的组织病理学分析。当给大鼠服用索拉非尼时，体重显着减轻。该治疗可显着改善甘油三酯(TG)、总胆固醇(TC)和低密度脂蛋白(低密度脂蛋白)(磷<0.05)。此外，它还可以降低血糖水平并提高胰岛素敏感性（磷<0.05）。此外，在肝脏的组织病理学分析中，索拉非尼还可以预防肝脏脂肪变性。根据我们的研究，当索拉非尼与高脂蔗糖饮食一起给药时，索拉非尼在改善血脂异常、高血糖和胰岛素敏感性以及防止大鼠肝组织中脂肪沉积物的积累方面具有显着的效果。

关键词：索拉非尼，美国广播公司10，癌症，高脂血症，代谢综合征。

1. Introduction

In the last two decades, type II diabetes mellitus (T2DM), obesity, and cancer are becoming more dominant worldwide; identifying novel targets of treatment necessitates a deeper understanding of their links to combat the escalating epidemic [1].

Heredity and external factors, such as diet, may play a role in developing metabolic diseases. Abnormal lipid metabolism is considered one of the primary causes of metabolic disorders. Recent research has identified that a crucial role is played by adenosine triphosphate (ATP)-binding cassette (ABC) transporters in the treatment of the metabolic diseases because of their ability to regulate lipid metabolism [2].

One of the most important superfamilies of transport proteins are the ABC transporters [3]. Additionally, the ABC transporter family consists of 49 members, which can further be divided into 7 subfamilies based on the domain organization and sequence similarity of the members of each subfamily [4, 5]. Transmembrane ABC transporters are proteins located on several different types of organelles and cells, and they are extensively expressed in approximately all organisms. The ABC transporters are predominantly expressed in cancer cells and lipid processing cells, including macrophages, in humans but can also be detected in plants, bacteria, and yeast [6, 7]. Because of their importance in regulating substances' entry and exit from the plasma membrane, ABC transporters play a vital role in the process. Various molecules, comprising proteins, polypeptides, metal ions, sterol, small organic molecules, and small inorganic molecules, can be transported across membranes by ABC transporters when activated by ATP [8, 9]. There are many applications for ABC transporters, including regulating lipid metabolism, one of their primary functions. Mainly, ABC transporters take part in cholesterol uptake, metabolism, and storage, maintaining cholesterol homeostasis [10].

Furthermore, ABC transporters have also linked metabolic diseases with neoplasms. Moreover, metabolic diseases contribute to the growth of the tumor. Taking the example of epithelial ovarian cancer, metabolic syndrome (MetS) is an evident risk factor for advancing the disease [11]. A significant number of prostate cancer cells lose their homeostasis of cellular cholesterol [12]. It has also been proven that obesity contributes to melanoma's progression and development, and controlling body weight can effectively suppress melanoma [13].

The multi-drug resistance protein family's member, ABCC10, transports various substrates across membranes. Furthermore, it is also a member of the evolutionarily conserved subfamily C of the ABC transporter superfamily [14–16]. As mentioned earlier, this enzyme can contribute to multi-drug resistance in cancer cells by preventing the intracellular accumulation of specific antitumor drugs. The broad spectrum of specificity of ABCC10 transporters

includes the transport of antitumor drugs, for instance, vinca alkaloids, taxanes, cytarabine, and epithilone B. Additionally, it transports modulators of the estrogen pathway, like tamoxifen [17]. This gene has encoded several different isoforms encoded by multiple transcript variants [18]. Several ABCC10 inhibitors have been reported to be effective in overcoming ABCC10 drug resistance mediated by many mechanisms such as sorafenib, cepharanthine, erlotinib, lapatinib, and others [17].

ABCC10 is involved in maintaining the plasma lipid and glucose levels, which provides a rationale for investigating its role in metabolic disorders [19]. The current research focuses on this issue. Thus, we administered the known inhibitor of ABCC10, sorafenib, orally to rats and measured their serum lipid and glucose levels" [20].

Sorafenib is also used as an anti-cancer drug [21]. Metabolic diseases are also common among cancer patients. Considering these findings, sorafenib alone may be able to treat cancer and prevent metabolic diseases in patients with cancer. Therefore, this study will also enable us to explore the therapeutic actions of Sorafenib and minimize the burden of medicines on cancer patients. Moreover, it is necessary to investigate the links between these anti-cancer agents, diabetes, and hyperlipidemia, which justifies conducting this research.

2. Materials and Methods

2.1. Selection of Experimental Animals

Male and Wistar strain rats, weighing approximately 150-175 g, were purchased from the Dow University animal house in Ojha, Karachi, and were acclimated under standard laboratory conditions of (25 ± 2°C) and relative humidity (50 ± 15%). Polypropylene cages (6 per cage) were used to keep the rats (twelve hours light and twelve hours dark: day: night cycle). They were provided and allowed free access to commercial pellet food and tap water. The National research council (NRC) protocol was followed for handling the animals [22]. BASR (Board of Advanced Studies and Research), University of Karachi, approved this research project (ASRB/No./04681/Pharm.).

2.2. Drugs and Experimental Design

High-fat high-sucrose diet (HFSD diet) was given to rats for 60 days, including 1 ml coconut oil, 3 ml Banaspati ghee, and 25% sucrose in their drinking water. A standard Chow diet (NFD Diet) was fed to rats, which consisted of 70% carbohydrate, 20% protein, and 10% fat [23]. For all other chemical reactions, we used analytical-grade chemicals. In all cases, we used distilled water to test the biochemical reactions. After overnight fasting of the rats on the 60th treatment day, the blood glucose levels were checked, and rats whose blood glucose levels were more than 120 mg/dL were considered diabetic type-2 rats [24].

To use in vivo, sorafenib tosylate (Nexavar) tablets were suspended in 1% sodium carboxymethyl cellulose. The tablets were purchased from Byer (Leverkusen, Germany). The following experimental design was framed after acclimatization, and accordingly, the rats underwent two months of treatment. The following groups of adult male Wistar rats were used: Group I: control rats (vehicle-treated) (NFD diet); Group II: Type-2 diabetic rats given a high-fat diet coupled with sucrose drinking water (25%); Group III: Type-2 diabetic rats treated with sorafenib 10 mg/kg/d (orally) for 60 days (HFS-S); Group IV: Type-2 diabetic rats treated with metformin (50 mg/kg/d) orally for 60 days. Two days before the sacrifice of animals, after following overnight fasting, experimental and control rats were subjected to oral glucose tolerance tests. Blood was collected, and the liver was dissected at the end of the experiment for the various parameters assessment [24]. The doses of sorafenib and metformin were determined by a previous study [25, 26]. We weighed rats weekly to monitor changes in body weight, and blood was collected at the experiment's end to measure changes in plasma lipids and glucose. To determine any differences in energy intake, we measured and calculated the daily food intake.

2.3. Blood Sugar Levels after Fasting (FBG)

After overnight fasting, glucose levels in the blood were measured using a glucometer (Accu-chek, Roche, Switzerland). By nicking a rat's tail tip, blood glucose levels were measured as mg/dL [24].

2.4. OGTT Test

An oral glucose load was given for different periods (60, 120, and 180 min) of 10 mL/kg, 50% w/v after a glucometer (Accu-chek, Roche, Switzerland) was used to estimate blood glucose levels. Before administering glucose, the blood glucose value is considered 0 min. Measurements are in milligrams per deciliter [27].

2.5. Fasting Serum Insulin

Crystal ChemInc (Illinois, USA) provided an ultrasensitive rat insulin ELISA kit to measure serum insulin. The detection range was between 0.1 and 64 ng/ml. Insulin antibody exhibits 100% cross-reactivity with rat insulin. In nanograms per milliliter, the results were reported [28].

2.6. Insulin Resistance (HOMA-IR)

It was determined by multiplying serum insulin in fasted state and blood glucose fasting by 405 [29].

2.7. Lipid Parameters and Liver Enzymes (LFTs)

Test kits purchased from HUMAN Diagnostic, Germany, were used to measure HDL, ALT, AST, LDL, TG, and serum cholesterol.

2.8. Histopathological Analysis

The rats were euthanized with a ketamine overdose (7 mg/kg) at the end of the protocol. The blood was collected by cardiac puncture, and the livers were surgically removed. Using the Haug & Hostmark method, liver samples were analyzed for hepatic lipids [30]. The hepatic tissue from each rat was homogenized in isopropanol at 5% (wt/vol). After keeping the homogenate at 4°C for two days, the homogenate was centrifuged at 3000 rpm for 10 min. to extract the triglycerides. Using the same commercial kits used for serum lipid analysis, we quantified hepatic triglycerides in aliquots of the supernatants. Hematoxylin and eosin (H & E) staining of liver samples was used to study the histopathology of liver slices fixed in 10% concentration of formalin and paraffin wax was used as an embedding agent. An optical microscope was used to examine the samples (Olympus Optical, Japan).

2.9. Analysis of Statistical Data

The data gathered from the study are stated as means + standard deviations (SD). Additionally, the significance of statistics was compared between groups by using the one-way analysis of variance (ANOVA) using SPSS 21.0 software, and differences among groups were examined using Tukey's multiple comparisons test. The value of the significance level was set at $P < 0.05$.

3. Results

3.1. Evaluation of Sorafenib Effectiveness in Treating Obesity

To study the effects of sorafenib on obesity, rats were kept on an HFSD diet. No significant difference was observed in the animals' initial weights ($P > 0.05$) Rats receiving sorafenib possessed considerably lower weights of the body, compared to rats in the high-fat group ($P < 0.01$) (Fig. 1). The caloric intake of rats who consume high fat is higher than that of rats who consume sorafenib. Rats in all groups consumed nearly the same amount of food, with no significant differences ($P > 0.05$).

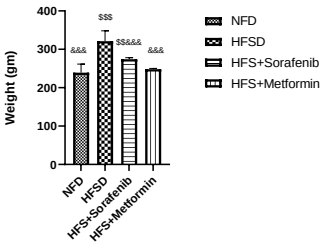


Fig. 1 Effects of HFS-S on rat body weight
$^{\&}P \leq 0.05$; $^{\&\&}P \leq 0.01$; $^{\&\&\&}p \leq 0.001$ significant differences compared with the HFSD group of rats
$^{\$}P \leq 0.05$; $^{\$\$}P \leq 0.01$; $^{\$\$\$}P \leq 0.001$ significant differences compared with the NFD group of rats
n = six rats/group

3.2. Effect of Sorafenib on Lipid Profile

Upon completing the experiment, serum lipid concentrations were measured. Taking the HFSD diet resulted in higher levels of TG, cholesterol, and LDL than rats taking sorafenib ($P < 0.05$) (Table 1). In contrast, sorafenib did not significantly affect HDL serum levels in our study compared with the HFSD group.

3.3. Effects of Sorafenib on Liver

This study shows that rats that consumed only fat and sucrose exhibited higher SGPT levels than those receiving sorafenib ($P < 0.05$). HFSD-fed rats gained a fatty liver with an increased amount of hepatic swelling, as shown in Fig. 3. Moreover, rats on sorafenib have lower liver triglyceride levels than rats on the HFSD diet (Table 1). The livers of the rats on sorafenib showed normal appearance with normal cell size.

3.4. Efficacy of Sorafenib in the Prevention of Diabetes

Compared with the HFSD group, rats on Sorafenib showed improved glucose and insulin tolerance (Table 2). In calculating insulin resistance, fasting serum insulin levels and blood glucose levels were used as a reference. HFSD group animals were seen to have high insulin resistance, which was partially improved after treatment with sorafenib (Table 2).

3.5. OGTT

The glucose concentration increased right after the glucose load in control rats and reached the highest level within an hour after the glucose load. It declined after a short period and was restored to its normal range within 3 h. However, in the HFSD group, the level rose within 1 h. The level did not decrease after 2 h, and it did not return to its fasting level within 3 h. Blood glucose significantly increased during the OGT test in the group with diabetes compared with control levels at basal and other time points. The rise in blood glucose level after 1 h in the group who received sorafenib administration was gradually reduced after 2 h and reached its fasting blood glucose range after 3 h (Fig. 2).

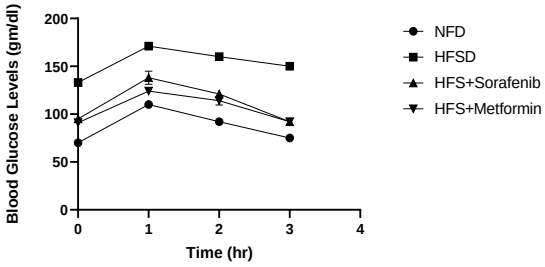
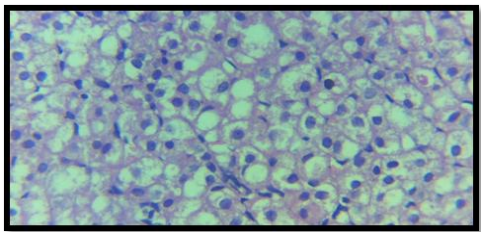
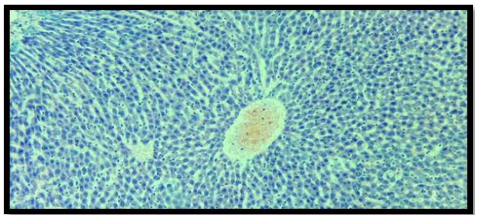


Fig. 2 Effect of sorafenib on OGTT test



A



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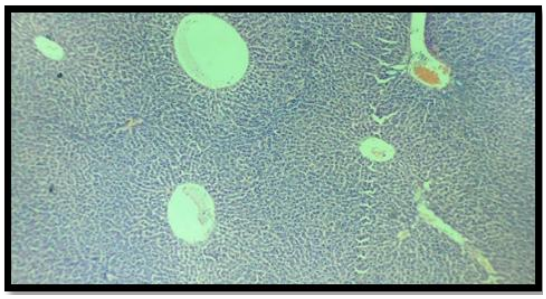

C

Fig. 3 Light microscopic histopathological photographs of the liver from male adult rats (HE × 40). The section of liver tissue (A) shows lipid droplets. The liver tissue section (B and C) shows liver parenchyma with normal architecture. A - HFSD group, B - HFS-S group, C - NFD group

Table 1 Hepatic triglyceride levels and HFS-S influence on TG, TC, HDL-C, LDL-C, ALT, AST, and HDL-C

Group	TG (mg/dl)	TC (mg/dl)	HDL-C` (mg/dl)	LDL-C (mg/dl)	ALT (U/L)	AST (U/L)	Hepatic Triglycerides
NFD	$90 \pm 5.5^{\&\&\&}$	$65.5 \pm 7.0^{\&\&\&}$	22.1 ± 1.6	$27.5 \pm 2.7^{\&\&\&}$	$134.1 \pm 4.1^{\&\&\&}$	168 ± 3.6	$928 \pm 92.8^{\&\&\&\$\$\$}$
HFS-S	$107 \pm 13.4^{\$\$\$}$	$75 \pm 2.2^{\&\$}$	22.1 ± 1.2	$29 \pm 2.7^{\&\&\&}$	$126 \pm 4.4^{\&\&\&}$	$184 \pm 6.1^{\&\&\$\$}$	$1690 \pm 28.2^{\&\&\&\$\$\$}$
HFSD	$192.1 \pm 12.8^{\&\&\&\$}$	$85.3 \pm 6.8^{\$\$\$}$	24 ± 1.2	$41.8 \pm 4.7^{\$\$\$}$	$162.6 \pm 10.1^{\$\$\$}$	166.8 ± 8.2	$2123 \pm 211.8^{\&\&\&\$\$\$}$

Notes: The outcomes were shown as mean ± SD in every group (n = 6 rats/group).
$^{\&}P \le 0.05$; $^{\&\&}P \le 0.01$; $^{\&\&\&}p \le 0.001$ significant differences compared with the HFSD group of rats
$^{\$}P \le 0.05$; $^{\$\$}P \le 0.01$; $^{\$\$\$}P \le 0.001$ significant differences compared with the NFD group of rats

Table 2 Influence of high fat on serum glucose and insulin levels

Group	Fasting Blood Glucose (mg/dl)	Fasting Insulin (ng/ml)	HOMA-IR
NFD	$80 \pm 1.87^{\&\&\&}$	$0.43 \pm 1.21^{\&\&\&}$	$0.09 \pm 0.02^{\&\&\&}$
HFSD	$130 \pm 3.38^{\$\$\$}$	$1.43 \pm 1.2^{\$\$\$}$	$0.46 \pm 0.05^{\$\$\$}$
HFS+S	$105 \pm 2.31^{\&\&\&\$\$\$}$	$0.70 \pm 0.089^{\&\&\&\$\$}$	$0.18 \pm 0.02^{\&\&\&\$\$\$}$
HFS+M	$94 \pm 2.87^{\&\&\&\$\$\$}$	$0.78 \pm 0.116^{\&\&\&\$\$\$}$	$0.18 \pm 0.03^{\&\&\&\$\$\$}$

Notes: The outcomes were shown as mean ± SD in every group (n = 6 rats/group).
$^{\&}P \le 0.05$; $^{\&\&}P \le 0.01$; $^{\&\&\&}p \le 0.001$ significant differences compared with the HFSD group of rats
$^{\$}P \le 0.05$; $^{\$\$}P \le 0.01$; $^{\$\$\$}P \le 0.001$ significant differences compared with the NFD group of rats

4. Discussion

Cancer, obesity and diabetes are the diseases that are rapidly increasing worldwide. Increasingly, clinicians need to treat patients with both cancer and T2DM, cancer, or both cancer and obesity. Cancer patients who are obese before diagnosis and gain weight after diagnosis have a worse prognosis [1]. How the risk and outcomes of the cancer are affected by diabetes and its treatment is complex and controversial [31]. Weight loss is a known adverse prognostic factor for cancer patients [32]; Nevertheless, the Cancer Prevention Study II data show that, at the time of diagnosis of various types of cancer, a high BMI is associated with augmented all-cause mortality [33]. Certain cancer treatments cause toxicities in the body, including hyperglycemia, which may limit the dosage of a few patients, exclusively the ones with diabetes pre-existing [31]. Based on these findings, it is important to research or repurpose drugs to manage these diseases.

We are repurposing the role of sorafenib in diabetes and dyslipidemia in our research. We tested the sorafenib effects on rats, which are on a high-fat high-sucrose diet. Compared with rats taking an HFSD diet, sorafenib at a dose of 10 mg/kg/day significantly reduced triglyceride levels. Furthermore, it prevented the rise of serum LDL and cholesterol in rats and lowered triglyceride levels. Additionally, inflammatory cell infiltration and hepatic lipid accumulation in the liver were decreased by treatment of sorafenib compared to the treatment in HFSD group rats, which suggests that sorafenib helps prevent diet-induced steatosis in the liver.

In recent decades, non-alcoholic steatohepatitis (NASH) has been considered one of the significant reasons for end-stage liver disease, such as liver failure, cirrhosis, and non-Hodgkin lymphoma [34, 35]. NASH is expected to become the foremost reason for liver transplants by 2030 [36, 37]. Multiple pathogenic factors contribute to the NASH development, namely hepatic ballooning, hepatic steatosis, lobular inflammation, and fibrosis [38–40]. As a result, new therapies are needed to combat these diseases. Our study is essential for exploring new treatment options for metabolic disorders and hepatic steatosis.

Many malignancies are currently treated with tyrosine kinase inhibitors (TKIs). Based on increasing numbers of studies, therapy with TKI can result in

either decreased or increased levels of blood glucose, based upon clinical context and the used agent [41, 42]. It has been reported that hyperglycemia comprises the common adverse effect of TKIs in some settings [43]. However, TKIs lower the glucose levels and improve or increase glycemic control. In [44], diabetic and nondiabetic patients experienced hypoglycemic effects from sunitinib, sorafenib, dasatinib, and imatinib, but the exact mechanisms remain unknown. For the patients consisting T2DM, this effect can be beneficial by allowing them to discontinue their antidiabetic medications. In the abovementioned research [44], the TKI treatment achieved glycaemic control in eight of the seventeen patients with diabetes (47%), allowing some patients to stop taking their anti-diabetic medications, including insulin.

In our study, we have also observed that sorafenib prevents the rise in blood sugar levels and improves insulin sensitivity. Fasting blood glucose and insulin were dropped significantly in rats treated with sorafenib compared with the rats fed with the HFSD diet ($P < 0.05$). Strongly, these data advocate that low-dose sorafenib consists of a protective effect in contrast to type 2 diabetes mellitus.

Previous research has established that oral administration of sorafenib may reduce dyslipidemia and hepatic steatosis through AMPK activation [45]. Due to the well-established role of ABCC10 in the development of dyslipidemia and making insulin resistance [19], sorafenib inhibition of ABCC10 protects rats against metabolic syndrome. Due to these findings and actions of sorafenib, our study is unique in examining the new aspects of this drug in managing metabolic syndrome and cancer.

5. Conclusion

Cancer patients tend to develop diabetes, hyperlipidemia, and cardiovascular disease, which increases the patient's stress, as well as the likelihood of poor prognosis for the patient. According to these results, sorafenib alone may be effective in treating cancer in individuals with cancer as well as preventing metabolic diseases in those individuals with cancer. The prognosis of cancer would also be improved because of this. This study will therefore also enable us to explore the therapeutic actions of Sorafenib and reduce the burden of medicines on patients with cancer by allowing us to investigate its therapeutic actions. There has never been any research of this type done on sorafenib before. In terms of curbing metabolic diseases, the results of this research are very motivating and open up new horizons and methods for the future.

Our study demonstrated that sorafenib reduced serum lipid profiles and blood glucose levels, increased insulin responses, and prevented weight gain in the animals. Sorafenib is one of the potential drugs used to manage obesity, hyperlipidemia, and type 2 diabetes mellitus.

Currently, we have seen only a protective effect of sorafenib on hyperlipidemic rats using a rat model that is pre-clinical. Further research is needed to investigate the role of sorafenib in preventing metabolic diseases associated with cancer, both in vitro and clinically. To determine the mechanism by which sorafenib prevents metabolic disease, further research is needed.

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