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REVIEW

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The connection between bile acids and type 2 diabetes mellitus – A review

Luis Jesuino de Oliveira **ANDRADE**[1], Gabriela Correia Matos de **OLIVEIRA**[2] and Luis Matos de **OLIVEIRA**[3]

[1] Universidade Estadual de Santa Cruz, Departamento de Saúde, Ilhéus, BA, Brasil. [2] Programa Saúde da Família, Bahia, BA, Brasil. [3] Escola Bahiana de Medicina e Saúde Pública, Salvador, BA, Brasil.

HIGHLIGHTS

- Bile acids play a significant role in the pathophysiology of type 2 diabetes mellitus by regulating glucose metabolism, lipid metabolism, and cellular energy production.
- Targeting bile acids as a therapeutic approach shows potential in the treatment of type 2 diabetes mellitus, offering innovative and effective options.
- The interactions between bile acids and key metabolic pathways highlight the importance of studying and understanding their role in type 2 diabetes mellitus.

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Corresponding author: Luís Jesuíno de Oliveira Andrade. E-mail: luis_jesuino@yahoo.com.br

ABSTRACT – Background – Bile acids (BAs) are steroid molecules synthesized exclusively in the liver, being end products of cholesterol catabolism. BAs are known to be involved in several metabolic alterations, including metabolic syndrome and type 2 diabetes mellitus (DM2). DM2 is a chronic degenerative disease characterized by insulin resistance, insulin deficiency due to insufficient production of pancreatic ß-cells, and elevated serum glucose levels leading to multiple complications. **Objective –** The objective of this study is to investigate the role of BAs in the pathophysiology of DM2, highlighting the possibilities in the development of therapeutic procedures targeting BAs as an optional pathway in the treatment of DM2. **Methods –** The research was carried out through narrative review and publications on the relationship between BAs and DM2. The databases used for the search include PubMed, Scopus, and Web of Science. The keywords used for the search include bile acids, type 2 diabetes mellitus, metabolic syndrome, and metabolic disorders. **Results –** The studies have reported the involvement of BAs in the pathophysiology of DM2. BAs act as a ligand for the nuclear farnesoid X receptor, regulating glucose metabolism, lipid metabolism, and cellular energy production. Additionally, BAs modulate the production, elimination, and mobilization of BAs through the farnesoid X receptor. BAs also act as a signaling pathway through Takeda G protein-coupled receptor 5, further contributing to metabolic regulation. These findings suggest that targeting BAs may offer a novel therapeutic approach in the treatment of DM2. **Conclusion –** This study highlights the important role of BAs in DM2, specifically through their interactions with key metabolic pathways. Targeting BAs may represent an innovative and effective approach to the treatment of DM2.

Keywords – Bile Acids; hepatobiliary dysfunction; farnesoid X receptor; Takeda G protein-coupled receptor 5; type 2 diabetes mellitus.

INTRODUCTION

Bile acids (BAs) are steroid molecules that have a hydrophilic and a hydrophobic end and are synthesized exclusively in the liver as the end product of cholesterol catabolism. It was originally thought that BAs would act only in the digestion and absorption of lipids in the small intestine[1]. However, in recent years, the action of BAs as metabolic modulators has drawn attention since studies have shown that BAs are essential players in metabolic control, acting as a signaling molecule in the regulation of carbohydrate and lipid metabolism[2].

Currently, it is known that BAs act as a ligand for the nuclear farnesoid X receptor (FXR), a receptor with a vital role in glucose metabolism, lipids, and cellular energy production, as well as the regulation of BAs production, elimination, and mobilization[3]. BAs also act through the Takeda G protein-coupled receptor 5 (TGR5) signaling pathway[4].

FXR is evident in hepatocytes and enterocytes, controlling multiple metabolic pathways by upregulating ileal fibroblast growth factor (FGF) and hepatic heterodimer, thus maintaining BAs homeostasis[5]. Suppressing FXR, on the other hand, promotes glucose homeostasis by inducing glucagon-like peptide-1 (GLP-1) production[6]. TGR5 is present in enteroendocrine cells, brown adipose tissue, and muscle tissue, and its activation stimulates energy expenditure by inducing GLP-1 release that regulates blood glucose and reduces weight gain[7].

Therefore, BAs, as signaling molecules, play essential endocrine functions in metabolism since they regulate not only their own synthesis but also the metabolic homeostasis, particularly glucose and GLP-1, through the activation of signaling pathways. BAs are related to several metabolic alterations, including metabolic syndrome and type 2 diabetes mellitus (DM2), and may provide an interesting option in DM2 therapy, and could serve as a research target for the development of drugs to treat other metabolic alterations, based on the interconnection between various organs and systems with BAs and their receptors[8].

This manuscript describes the interface between BAs and metabolic disorders, particularly DM2, including discussing therapeutic procedures targeting BAs as an optional pathway in the treatment of metabolic disorders.

Chemistry

The family of BAs integrates a set of molecular categories of acidic steroids with specific biological and physicochemical properties. The BAs belong to a group of chemically diverse steroids which present a core structure constituted of seventeen carbon atoms organized in four linked rings as follows: one five-member cyclopentane ring and three six-member cyclohexane rings, over the course of a five-eight-carbon side-chain which ends with a carboxylic acid and various hydroxyl and methyl groups[9]. BAs molecules are around 20 Å long, with a medium radius of approximately 3.5 Å (FIGURE 1)[10].

Synthesis

The synthesis of BAs takes place only in the liver, where a series of enzymatic reactions occurs in the hepatocyte, transforming the hydrophobic cho-

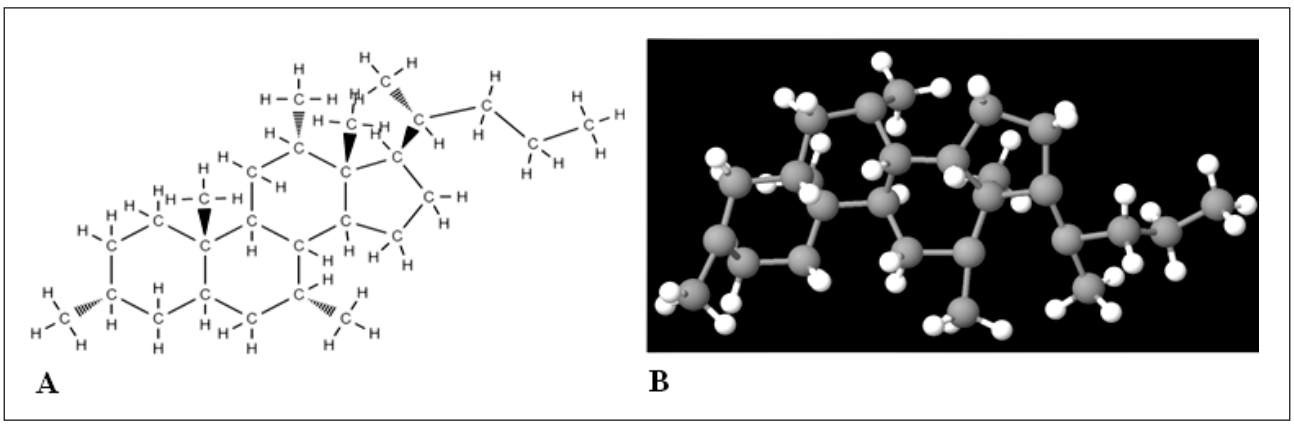

FIGURE 1. Chemical structure (A) and molecular structure (B) of Bas.

lesterol into water-soluble amphipathic groups. The synthesis of BAs occurs through two pathways: the classical pathway and the acidic pathway. The classical pathway results in the development of primary BAs (cholic acid, chenodeoxycholic acid, and deoxycholic acid), and the alternative pathway can be altered by intestinal flora controlled by the enzyme CYP27A1, transforming oxysterols to secondary BAs. BAs are biologically transformed into taurine and glycine conjugates through an amidation reaction stimulated by an acyltransferase. Every day, about 500 mg of cholesterol is transformed into BAs. Physiologically, primary BAs are the main BAs, comprising about 94% of the total Bas[11,12].

In the late 1990s, BAs were recognized as the natural ligands for FXR, which acts as a biological mediator of BAs synthesis through transcriptional stimulation of the small inhibitory nuclear receptor heterodimer and can be stimulated through primary as well as secondary BAs. However, chenodeoxycholic acid is possibly the strongest natural BA ligand[13].

Physiology

Studies produced in recent years show that, in addition to their role in the digestive system, BAs regulate a diverse range of metabolic activities from lipid homeostasis to glucose metabolism. Physiological activities of BAs include cholesterol homeostasis, emulsification of fats, metabolism of fat-soluble vitamins, and metabolic regulation[14].

It has been described that BAs have hormonal action through binding to nuclear receptors and modulating the expression of proteins involved in cholesterol homeostasis. Among these nuclear receptors, the FXR is included. Thus, the BA-FXR complex binds to specific genes, stimulating or suppressing their transcription[15]. Thus, activation of FXR at the gut level will stimulate FGF-19 synthesis, and through its downstream effect on FGF-19, it will maintain glucose, lipid, and BA homeostasis (FIGURE 2)[16].

The BAs, also involved in intestinal motility through TGR5, lead to the production of GLP-1 which, in addition to glycemic control by its insulin-stimulating effect on pancreatic ß-cells, inhibits gastric emptying[17].

Interface between bile acids and DM2

DM2 is a chronic degenerative disease with pathophysiology characterized by IR, insulin deficiency due to insufficient production of pancreatic ß-cells, and elevated serum glucose levels leading to multiple complications[18].

As mentioned above, individuals with DM2 have alterations in the metabolism of BAs, such as changes in synthesis, composition, and excretion. Thus, different sizes of BAs have been described in DM2 individuals when comparing treated and untreated individuals. Similarly, the composition of BAs undergoes changes in individuals with DM2[19]. Furthermore, comparative studies between non-diabetic individuals and DM2 patients demonstrated that BAs levels were elevated in DM2[20]. Increases in BAs excretion are associated with glycemic levels in DM2 patients and may represent compensatory elevation in BAs signaling to maintain glucose homeostasis[21].

Bile acids and insulin secretion

The β-cells of the pancreatic islets express TGR5 receptors, which, when activated, increase insulin secretion at both low and high circulating glucose levels[22]. Thus, BAs exhibit an impact on insulin secretion as a function of TGR5-mediated GLP-1 stimulation[23]. In the pancreas, GLP-1 promotes insulin secretion and β-cell enlargement, as well as preventing apoptosis of β-cells[24].

The mechanism of the FXR-dependent insulinotropic effect of BAs includes a block of potassium channels, membrane depolarization, and increased calcium concentration. For the stimulation of insulin secretion, the cytosolic localization of FXR and the BAs-induced interrelation with potassium channels are indispensable[25].

Bile acids and insulin sensitivity

Studies show that BAs activate FXR and TGR5 receptors and improve insulin sensitivity[26]. The positive impact of BAs on glucose metabolism is mediated by means of TGR5. TGR5 has a high expression in the intestine, and its activation in enterocytes stimulates the secretion of the incretin GLP-1, promoting glucose-dependent insulin secretion[27]. GLP-1 is a hormone produced in the intestinal L-cells as a result of food intake that stimulates insulin secretion and blocks glucagon secretion, favoring glucose homeostasis[19].

In summary, after food ingestion, BAs are relea-

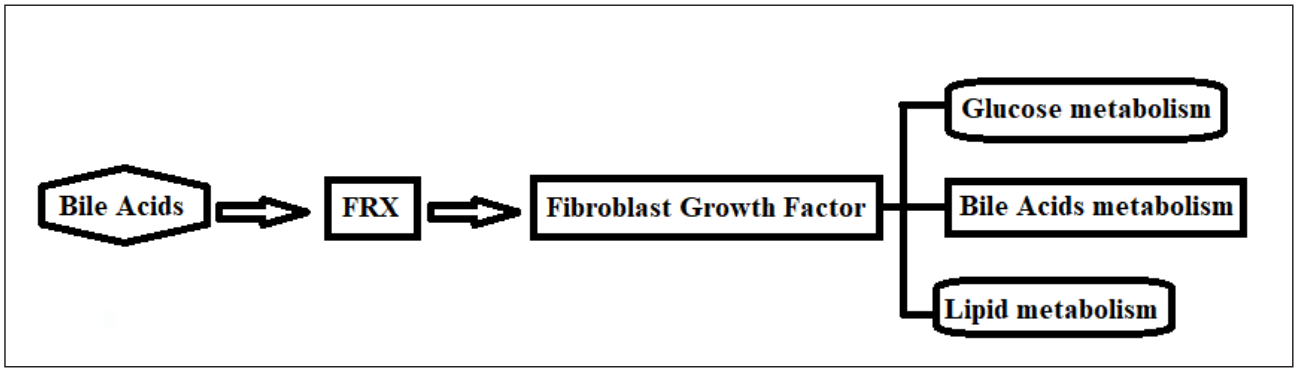

FIGURE 2. Bile acid-mediated modulation in lipid and glucose metabolism.

sed into the intestine activating FXR and TGR5. FXR activation activates the FGF-19 that contributes to glycogen synthesis and gluconeogenesis. Thus, the activation of TGR5 raises GLP-1 levels, promoting insulin secretion and reducing blood glucose levels. BAs returning via the enterohepatic circulation stimulate FXR in the liver, which will also participate in glycolysis and gluconeogenesis. FXR signaling, although it does not affect hepatic insulin sensitivity, does act on insulin sensitivity in skeletal muscle and brown adipose tissue (FIGURE 3)[28].

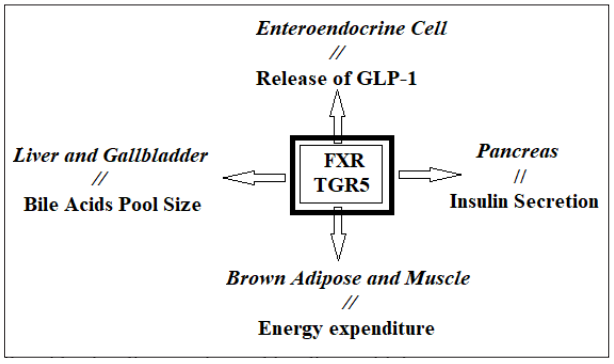

FIGURE 3. Bile acids - insulin secretion and insulin sensitivity.

Bile acids and DM2

DM2 arises from both genetic and environmental factors and is characterized by an inappropriate insulin reaction. Insulin becomes ineffective at activating glucose absorption in peripheral tissues, such as muscle and fat, leading to IR. This decreased insulin sensitivity results in hyperglycemia due to reduced secretion of insulin by pancreatic ß-cells[29].

As previously described, the BAs play a pleiotropic role in regulating metabolism, including insulin secretion by the pancreas and stimulating incretins. Thus, BAs could serve as a potential marker of ß-cell performance in DM2. Changes in the profile of circulating BAs can alter the homeostasis of metabolism and contribute to the pathogenesis of IR and DM2[30].

DM2 is associated with an elevation in the hydrophobicity of circulating BAs in humans, and deregulation of BAs maintains the hyperglycemic state and pancreatic ß-cell degeneration[24]. The accumulation of toxic BAs leads to inflammatory damage to pancreatic ß-cells, which has been linked to the onset of DM2.

Bas, TGR5 and FXR signaling modulate glucose homeostasis at the hepatic level, which is crucial for glycemic metabolism and energy production. Alterations in BAs signaling, associated with dysbiosis, contribute to the onset or decompensation of DM2. Thus, regulating BAs signaling pathways plays a vital role in metabolic control and may contribute to the treatment of DM2 (FIGURE 4).

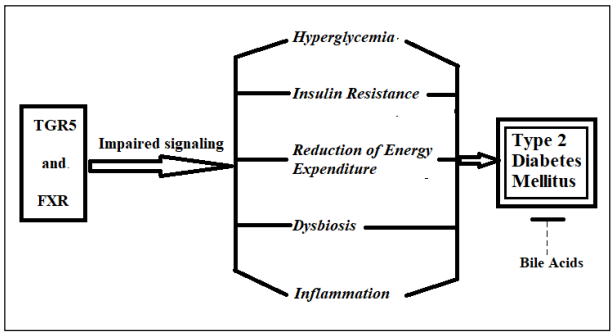

FIGURE 4. Bile acids and type 2 diabetes mellitus.

Treatment options for DM2 with BAs

The relationship between glycemic levels and serum levels of BAs makes BAs a viable option for treating DM2. BAs have been used in the treatment of DM2 for some years due to their ability to activate intestinal FXR and TGR5 receptors, leading to incre-

ased insulin secretion and GLP-1 with consequent glycemic control[31].

Therapeutic plans for elevating BAs levels for glucose homeostasis in DM2 may include targeting FXR, TGR5 targeting, and BAs sequestrants.

Targeting FXR

FXR, cloned in 1995, was shown to regulate several metabolic pathways affecting serum glucose levels[32]. GLP-1 is one of the pathways that connect FXR to glucose homeostasis. The stimulation of FXR agonists causes changes in the gut microbiome, leading to the expression of TGR5 agonists, which in turn stimulates enhanced secretion of GLP-1. The upregulation of GLP-1 contributes to reduced blood glucose levels during FXR inactivation[33]. Thus, simultaneous stimulation of FXR and TGR5 with GLP-1 activation appears to be an effective strategy for metabolic control in DM2.

FXR inhibits gluconeogenesis through the FXR-FGF-19 pathway. FXR activation also enhances gluconeogenesis gene transcription and promotes gluconeogenesis in hepatocytes through glucagon, thereby restoring glucose homeostasis[34]. Moreover, FXR interferes with insulin signaling by increasing both insulin secretion and insulin sensitivity. FXR acts on insulin signaling through the FXR-Kruppel-like factor 11 pathway, contributing to the preservation of pancreatic β-cell function[35]. Studies have shown that the treatment with an FXR agonist causes an increase in insulin secretion by inhibiting membrane potassium channels and leading to an increased calcium flux through calcium channels in the pancreatic β-cells, resulting in an enhanced glucose-induced insulin secretion[36]. Furthermore, FXR agonists have been found to improve insulin sensitivity and IR in individuals with DM2 through FXR-specific activation. FXR agonists have been shown to restore insulin sensitivity by reducing IRS phosphorylation on Ser(312) and increasing AKT phosphorylation on Ser(437) at both the muscle and liver level, thus triggering the transcription and release of insulin[37].

Therefore, the action of FXR agonists on glucose homeostasis in DM2 constitutes an important therapeutic prospect for treating this disease and could also serve as a basis for the development of new drugs.

TGR5 targeting

Although treatment with TGR5 agonists requires further evaluation, published studies have pointed to the possibility of therapeutic outcomes in relation to TGR5 modulation, thus making it an interesting therapeutic target for the treatment of DM2.

TGR5 is a G protein-coupled receptor that is associated with stimulatory G protein which is activated by BAs. TGR5 is present in several tissues, including the liver, gallbladder, brown adipose tissue, and the intestine. TGR5 activation in macrophages can enhance insulin action and prevent IR. In L cells of the intestine, TGR5 stimulates the secretion of GLP-1 and the anorectic hormone peptide YY[38]. Hence, TGR5 may play a crucial role in controlling DM2, and several chemical compounds with diverse chemical structures have been described as TGR5 agonists for the treatment of DM2.

One of the most important roles of TGR5 is to maintain normal glucose levels and increase energy expenditure. Among the eleven forms of BAs, taurolithocholic acid, as well as fexaramine, activate TGR5 agonists, which improve IR and glucose tolerance. Furthermore, the activation of TGR5 in muscle and brown adipocytes will activate the enzyme deiodinase 2, converting thyroxine into triiodothyronine, stimulating energy expenditure[39].

Studies have shown that using TGR5 agonists on high-fat food-induced intestinal GLP-1 secretion restores normal glycemic levels. Thus, TGR5 agonist therapy may represent an alternative to the use of incretin and dipeptidyl peptidase IV inhibitors in the treatment of DM2[40].

What has been shown in the literature is that TGR5 agonists in hyperglycemic situations rearrange pancreatic α-cell to produce GLP-1 and increase β-cell mass, resulting physiologically in improved insulin sensitivity, weight reduction, and improved IR. Thus, TGR5 agonists present a novel mechanism in glucose homeostasis in DM2 patients.

BAs sequestrants

BA sequestrants are also involved in the normalization of glycemic feedback in DM2. The impacts of BAs sequestrants, which interfere with both glucose levels and the profile of BAs, were especially evidenced by the collaboration of BAs. BAs are non-absorba-

ble resins prescribed for dyslipidemia and surprisingly showed favorable results on glucose homeostasis and insulin sensitivity in individuals with DM2[41]. Of the sequestrants, only colesevelam is approved by the US Food and Drug Administration and by the European Medical Agency for the treatment of DM2.

The mechanism of action of colesevelam in reducing plasma glucose levels has several hypotheses. However, it has been shown that colesevelam increases GLP-1 levels mediated by activation of TGR5, activates FRX, which increases peripheral glucose uptake and reduces gluconeogenesis, and reduces glucose uptake at the intestinal level[42]. Guidelines from the American Diabetes Association, American College of Endocrinology, and Association of Clinical Endocrinologists include colesevelam as therapy to aid in the management of DM2[43,44].

The clinical effectiveness of colesevelam as a complementary drug to the treatment of DM2 has been evaluated in association with the various treatment options recommended for DM2, including metformin, SGLT-2 inhibitors, DPP-IV inhibitors, GLP-1 receptor agonists, thiazolidinedione, and insulin. However, the ADA mentions colesevelam as a drug to be prescribed in selected patients due to limiting side effects and modest efficacy[45].

CONCLUSION

This study highlights the important role of BAs in DM2, specifically through their interactions with key metabolic pathways. Targeting BAs may represent an innovative and effective approach to the treatment of DM2.

The great discussions on the use of BAs in the treatment of DM2 would be to what extent their effects have clinical relevance, that is, to what extent the activation of TGR5 and FRX, although we already have the theoretical rationale, will promote glycemic control, what would be the potential adverse effects of this modulation, the use of selective drugs that will act on TGR5 or will act on FRX, or a drug that will modulate all these receptors. Therefore, the great difficulty is the production of a molecule that acts on the BAs signaling in a tissue-specific way that has the ability to significantly normalize glycemic homeostasis without significant side effects.

Orcid

Luis J de Oliveira Andrade: 0000-0002-7714-0330.
Gabriela CM de Oliveira: 0000-0002-8042-0261.
Luis Matos de Oliveira: 0000-0003-4854-6910.

Andrade LJO, Oliveira GCM, Oliveira LM. A conexão entre ácidos biliares e diabetes mellitus tipo 2 – Uma revisão. Arq gastroenterol. 2023;60(4):536-42.

RESUMO – Contexto – Os ácidos biliares (ABs) são moléculas esteróides sintetizadas exclusivamente no fígado, sendo produtos finais do catabolismo do colesterol. Os ABs são conhecidos por estarem envolvidos em várias alterações metabólicas, incluindo a síndrome metabólica e o diabetes mellitus tipo 2 (DM2). A DM2 é uma doença crônica degenerativa caracterizada pela resistência insulínica, deficiência de insulina devido à produção insuficiente de células ß pancreáticas e hiperglicemia levando a múltiplas complicações. **Objetivo –** O objetivo deste estudo é investigar o papel dos ABs na fisiopatologia da DM2, destacando as possibilidades no desenvolvimento de procedimentos terapêuticos visando os ABs como uma via opcional no tratamento da DM2. **Métodos –** A pesquisa foi realizada por meio de revisão narrativa e publicações sobre a relação entre ABs e DM2. As bases de dados usadas para a pesquisa incluem PubMed, Scopus e Web of Science. As palavras-chave usadas para a pesquisa incluíram: ácidos biliares, diabetes mellitus tipo 2, síndrome metabólica e distúrbios metabólicos. **Resultados** – Os estudos relataram o envolvimento dos ABs na fisiopatologia da DM2. Os ABs atuam como ligantes para o receptor nuclear farnesoide X, regulando o metabolismo da glicose, metabolismo lipídico e produção de energia celular. Além disso, os ABs regulam a produção, eliminação e mobilização de ABs através do receptor farnesoide X. Os ABs também atuam como uma via de sinalização através do receptor acoplado à proteína G Takeda 5, contribuindo ainda mais para a regulação metabólica. Esses achados sugerem que o ABs pode oferecer uma nova abordagem terapêutica no tratamento da DM2. **Conclusão –** Este estudo destaca o papel importante do ABs na DM2, especificamente por meio de suas interações com vias metabólicas-chave. O redirecionamento ao ABs pode representar uma abordagem inovadora e eficaz para o tratamento da DM2.

Palavras-chave – Ácidos biliares; disfunção hepatobiliar; receptor farnesoide X; receptor acoplado à proteína G Takeda 5; diabetes mellitus tipo 2.

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