Original Article

An Overview of Natural and Synthetic Coumarin Derivatives as Potential Antidiabetic Agents

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Abstract

The common term for cis-o-hydroxy cinnamic acid lactones, which all possess the fundamental structure of the benzo a-pyranone mother nucleus, is coumarins. Especially in *Umbelliferae, Rutaceae, Daphne*, and *Oleaceae*, coumarins are extensively dispersed in the roots, stems, leaves, flowers, fruits, and seeds of higher plants. A few coumarins are also detected in certain microbes and mammals. Certain coumarin molecules may also be synthesized artificially. We have discussed the probable mechanisms behind coumarins' anti-diabetic benefits. Numerous *in vivo* and *in vitro* studies show that coumarins may treat diabetes by reducing inflammation and oxidative stress, enhancing pancreatic function, and reversing aberrant insulin signaling. As a result, they are useful and need further study and development. In conclusion, it is clear that coumarins have a range of biochemical and pharmacological characteristics, some of which have potential therapeutic value that may be useful against diabetes and its consequences. To sum up, improvements in the area have allowed for the isolation or chemical design of novel advantageous compounds with coumarin cores as candidates against diabetes and its consequences; nevertheless, additional study is necessary before safe and effective coumarin medications are employed in the clinic.

Keywords: Coumarin; Diabetes mellitus; DPP-IV; Umbelliferone; Fraxetin

1. INTRODUCTION

Coumarins and their derivatives have received a lot of attention over the years because of their broad range of biological capabilities, including antibacterial, antiviral, anticancer, antioxidant, anti-inflammatory, anti-tuberculosis, anti-influenza, anti-Alzheimer, and anti-hyperlipidemia qualities. These lactones are known as Coumarins because they are all made of the same fundamental skeleton: benzo-a-pyranone mother nucleus. There are several coumarins in higher plants, notably in the *Umbelliferae, Rutaceae, Daphne*, and *Oleaceae*, as well as microbes and animals, although the majority of them are found in plants. Additionally, some of the coumarin molecules may be synthesized in a lab[1,2].

2. REVIEW OF COUMARIN DERIVATIVES AS ANTIDIABETIC AGENTS

There have been hypotheses about the ability of natural items to cure sickness since antiquity. *Aegle marmelos* Corr., a member of the *Rutaceae* family, is frequently used in Indian Ayurvedic medicine to treat diabetes[3,4]. At a dosage of 250 mg/kg, *Aegle marmelos* fruit extract had a greater impact than Glibenclamide[5]. Traditional Chinese medicine suggested Umbelliferae and Oleaceae to treat Xiaoke lesion, or diabetes, by coincidence. For the regulation of Treg differentiation, shift towards Th2 and suppression of lymphocyte proliferation in NOD mice, coumarins from urtica dentate hand inhibited TLR4 signalling pathways and maintained dendritic cells in the immature tolerogenic state, according to Wang et al. This suggests that coumarins could treat T1D[6]. Many active components have been isolated and purified as a result of advances in extraction and separation technologies(**Structure 1**).

Peucedanol glycoside, an extract from *Peucedanum japonicum*, inhibits postprandial hyperglycemia by 39 percent in an oral glucose tolerance test[7]. Hintonia standleyana's ingredients, one of which was confirmed to be 5-O-[beta-D-apiofuranosyl-(1→6)-b-D-glucopyranosyl]-7-methoxy-3',4'-dihydroxy-4-phenylcoumarin in streptozocin-induced diabetic rats[8]. It is difficult to determine whether the coumarins component is the active site because of the complexity of the molecules isolated from plant extracts. Using coumarin's simpler cousin, umbelliferone, blood sugar levels may be brought back to normal[9]. High insulin levels were shown in Ramesh's research to be associated with a decrease in blood glucose levels[10]. Coumarins have been shown to have antihyperglycemic properties by all the data.

3. Effects and Mechanisms of Coumarins on Diabetes

Umbelliferone

To make umbelliferone, Citrus aurantium is used as the primary source of coumarin extraction and purification[11] and Aegle marmelos Correa. In diabetic rats caused by streptozocin (STZ), oral treatment of umbelliferon at dosages of 30 mg/kg reduced fasting blood glucose and glycated haemoglobin type A1c (HbA1c)[12,13]. By increasing the creation of SOD, GSH, and catalase, umbelliferone may help cells survive oxidative stress (CAT)[14]. Bioactivities of glucopyranoside of umbelliferon were found by Kumar et al.[15]. Using a different approach, Ramesh et al. found that umbelliferon inhibits hydroxyproline levels, reducing the synthesis of misfolded collagen, which might be used to treat diabetic nephropathy and diabetic polyneuropathy caused by collagen[10].

Fraxetin, esculin and esculetin

A traditional Chinese medication known as "cortical faxing" is made up of froxtin and esculin. Extracted from plants such as artemisia capillaris and citrus, Esculetin is aglycone of Esculin. In terms of chemical structure, ffractin, esculin, and esculetin are all quite similar. Thuong et al. found that the phenolic compound fraxetin had both anti-oxidative and antioxidant properties. For example, a modest quantity of fraxetin (1-5 μM) effectively prevented the oxidation of LDL (low density lipoprotein). But at 30 μM of fraxetin, it activated antioxidant enzymes by increasing NF-E2-related factor 2 in the nucleus (Nrf2)[16]. The active sites of antioxidation in fraxetin are 7-OH and 8-OH, according to a structural study of the molecule. Intriguingly, 7-OH has a tendency to build an intramolecular hydrogen bond with 8-OH, making dissociation quicker. Because of this, 7-OH has a higher level of activity[17]. Fructose-1, 6-biphosphatase and glucose-6-phosphatase, two rate-limiting enzymes in glucose metabolism, were boosted by esculetin and fraxetin in vivo in another investigation on glucose metabolism[18]. Tissue glucose consumption might be improved as a result of this. Insulin sensitization may be linked to the anti-hypoglycemic effects of esculin, according to research from the group of Kang et al. in C_2C_{12} cells. Caspase-3 levels in the kidneys of diabetic rats were reduced following esculin treatment[19]. Caspase-3 levels in the kidneys of diabetic rats were reduced following esculin treatment. The antioxidative effects of esculletin on tetrachloromethane-induced hepatic fibrosis are in line with observations that fraxetin reduces oxidative damage to the liver and kidney,[20] by increasing the production of SOD, catalase (CAT), glutathione peroxidase (GPx), and glutathione S transferase (GST)[21]. Esculetin and fraxetin may have comparable pharmacological processes, as shown by the aforementioned investigations.

Osthole and its derivatives

Osthole, which can be found in fructus cnidii and angelica pubescence, dramatically activated PPARγ and PPARα in 3T3-L1 adipocytes in a dose-dependent way. This increased the cells' sensitivity to insulin, which in turn made it easier for fat to be synthesized and stored[22]. Chemically, Osthole differs from thiazolidinediones (TZDs). As PPARγ is activated only partially, it may be a partial rather than a total PPARγ activator. TZD's negative effects, including as edoema, weight gain, and congestive heart failure, may thus be avoided while treating diabetes with this medication. This may be because the synergistic regulation of PPARα/γ-mediated target genes involved in the metabolism of sugars and fatty acids in the liver, fat, and skeletal muscle was discovered by Qi et al. in rats with fatty livers and insulin resistance (IR) produced by high-fat diets[23]. In addition to activating AMPK, osthole has a unique feature. C_2C_{12} and L6 cell glucose absorption and AMPK phosphorylation were increased by osthole, according to Lee et al.[24]. Osthole derivatives, such as NBM-T-BMX-OS01 [25] and N-hydroxycinnamide derivatives [26], have similar effects on AMPK. When it comes to stimulating AMPK, N-hydroxycinnamide derivatives are far more potent than the original compound itself (osthole). Antioxidant and free radical scavenger, Osthole is also. A nuclear factor E2-related factor-2 (Nrf2) signalling pathway was shown to be activated by osthole, which in turn inhibited NF-jB and COX-2 expression, reducing renal cell death[27]. A transcription factor called Nrf2 has also been shown to increase antioxidant synthesis, including that of GPx, CAT, and SOD, therefore protecting cells from oxidative stress. Because of this, it seems to be a promising treatment for diabetic nephropathy.

Scoparone

The inner shell of chestnuts yields a significant amount of scoparone, a coumarin derivative. Previous studies have shown the immunosuppressive, vascular relaxant and anti-diabetic characteristics of scoparone to be very effective[28]. Nitric oxide (NO), COX-2, prostaglandin E2 (PGE2), and factor-alpha (TNF-α), interleukin-1β(IL-1β) levels in RAW 264.7 murine macrophages were also reduced by the treatment[29]. Scoparone, which suppresses the development of 3T3-L1 pre-adipocytes, lowered the level of PPARγ expression, which is an interesting finding[30]. Because of this property, the effectiveness of scoparone in treating diabetes is diminished. Scoparone, on the other hand, gives the impression that it might be utilised to treat obesity and prevent diabetes that is associated to obesity. *In vivo*, it protected pancreatic *β*-cells from the cytotoxicity of IL-1*β* and IFN-γ[31]. More precisely, scoparone defends *β* cells by suppressing NF-κB activation and decreasing NO production through the IL-1*β* and IFN-γ pathways.

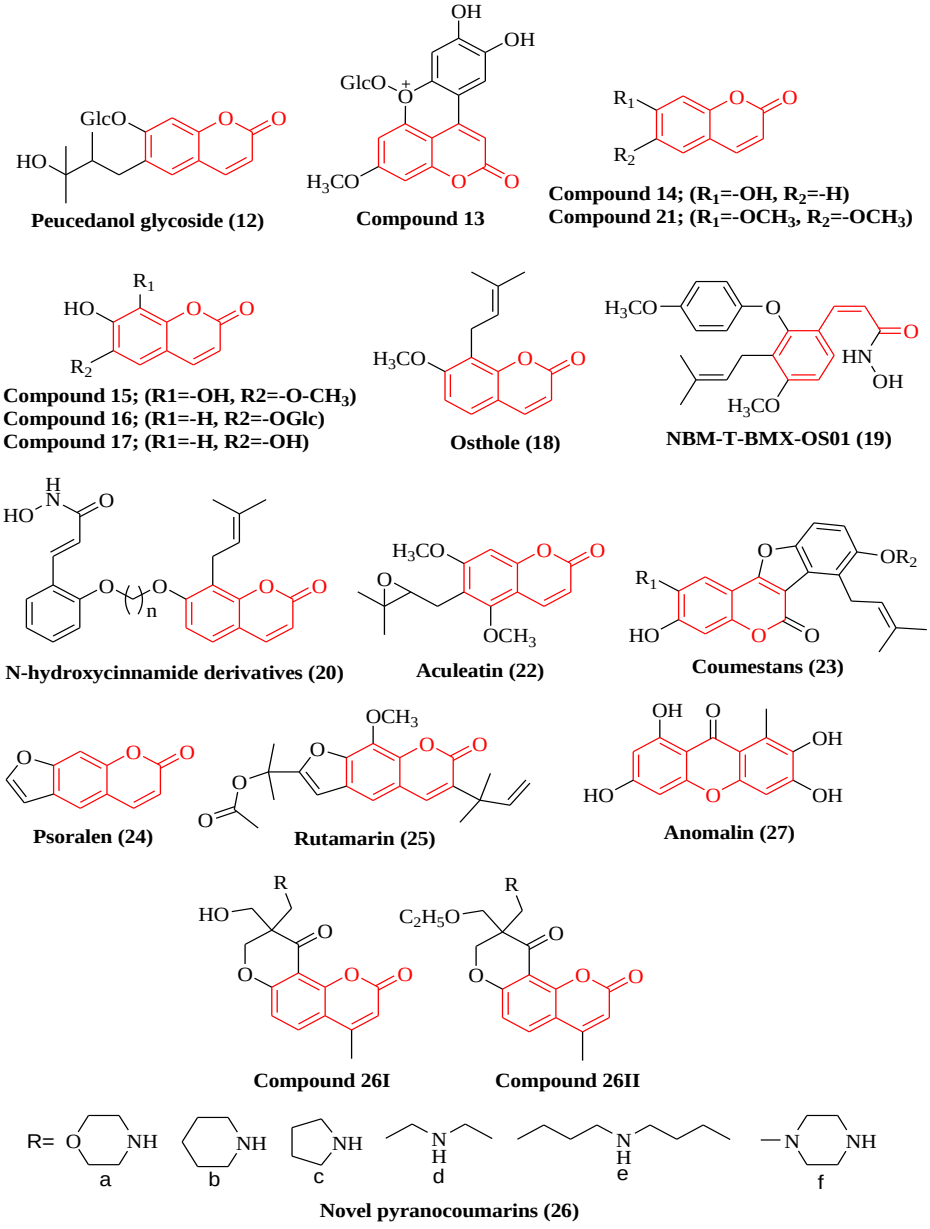
Aculeate

An ethanolic extract of *Toddalia asiatica*, which has antioxidative and antihyperglycemic properties, is where aculeatin is obtained from[32]. Upregulation of PPARγ target genes by Aculeatin, downregulation of inflammatory gene expression by *Mcp1*, *Ccl6*, and *Il6*, and an increase in 3T3-L1 adipocyte differentiation and lipolysis are only a few of the effects of this compound. As a result, this chemical may be used to treat lipid problems as well as diabetes[33]. There is little doubt that obesity and type 2 diabetes are exacerbated by chronic inflammation. Infiltration of macrophages, which release

inflammatory proteins including MCP-1 and IL-6, is characteristic of adipose tissue with obesity-associated diabetes. Insulin resistance may be exacerbated by inhibiting IRS phosphorylation, which MCP-1 and IL-6 may do[34].

Other coumarins and their derivatives

In C_2C_{12} cells, coumestans may increase the expression of AMPK and acetyl-CoA carboxylases (ACCs). However, it is possible to attribute the coumarin fragment's capacity to benzofurans to other chemicals, and this would reduce their activity greatly[35]. Furocoumarins, including psoralen, have been shown to enhance blood glucose levels and glucose tolerance in diabetic rats by Seo et al.[36]. When exposed to high levels of oxygen, oxidative stress activates the stress-related proteins p-AMPK, SOD, and GPx, whereas apoptotic proteins such as JNK and p-p38 are downregulated. Glucose control in diabetic mice was improved by rutamarin, which was shown to inhibit PTP1B and induce GLUT4 translocation in CHO-K1/GLUT4 cells[37]. Furocoumarin derivatives increased glucose absorption and fat production in 3T3-L1 adipocytes[38]. Atul et al. designed and screened a series of furocoumarins based on natural antidiabetic scaffolds including Sanggenone C, Rutamarin[37], and Luvangetin[39], which exhibited promising antidiabetic activity. In sucrose-loaded animals, many new pyranocoumarins (**26Ia, 26Ic, 26IIa, 26IIb, 26IIc, 26IIe, 26IIf**) might likewise reduce blood glucose and inhibit PTP1B. Apart from that, rats with triton-induced dyslipidemia responded well to their antidyslipidemic effects[40]. It has been shown that the pyranocoumarin-rich extract of Angelica gigas Nakai (AGN) may activate the IRS-1/PI3K/GLUT4 pathway and boost PPARc expression in 3T3-L1 cell lines[41] and pyranocoumarins separated from Clausena harmandiana stimulated glucose uptake in L6 myotubes[42]. Anomaline **(27)**, a pyranocoumarin derivative, boosted HO-1 and Nrf2 mRNA expression and reduced alterations in mitochondrial membrane potential in terms of antioxidation and anti-inflammation. This was accomplished by decreasing the levels of TNF-a, IL-6, and IL-1b, which were also decreased by Anomalin's ability to adversely regulate iNOS and Cox-2[43]. Coumarins such as pyranocoumarins, bi- and tri-coumarins, as well as the more complex ones, may all block alpha-glucosidase. **Structure 1** depicts the structures of all of the coumarins mentioned above.



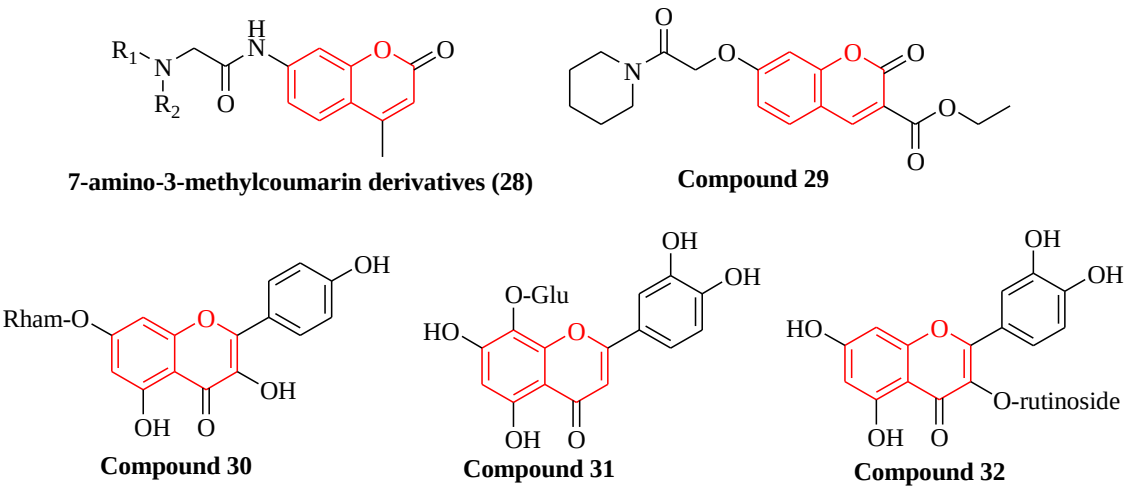
Structure 1. Structures of Coumarins reported as antidiabetic agents

4. REVIEW OF COUMARIN DERIVATIVES AS DPP-IV INHIBITORS

Antioxidant properties of quercetin and coumarin were studied by **Anand Krishna Singh** et al. The IC_{50} values of diprotin A, quercetin, coumarin, and sitagliptin were determined to be 0.653, 4.02, 54.83, and 5.49 nmol/mL, respectively, in the DPP-IV inhibition tests, respectively. The drug-likeness and docking efficiency of quercetin and coumarin to the DPP-IV protein, as well as their ex vivo anti-peroxidative potential, were studied in silico as was their anti-peroxidative potential. Quercetin's DPP-IV inhibitory capability was found to be somewhat greater than that of sitagliptin in this investigation. Virtual docking indicated that quercetin and DPP-IV protein form a strong bond. *In vitro* and *ex vivo*, quercetin and coumarin lowered oxidative stress. Both compounds were shown to inhibit DPP-IV and had antioxidant action for the first time, making them potential functional dietary additives for diabetes prevention[44].

Rina Soni and **Shubhangi S. Soman** have found that the 7-amino-3-methylcoumarin derivative, compound 28 (**Structure 2**), might be a potential inhibitor of the DPP-IV pathway. At 25 µM, one of the drugs showed a 52.90% inhibition of DPP-IV. Chromen-2-one derivatives were shown to be DPP-IV inhibitors in another work by same researchers. As a consequence of the docking investigations, compounds containing aromatic and cyclic secondary amines residue bind in the large and small pockets of DPP-IV enzymes, respectively. A number of coumarin derivatives have been produced and their structures have been studied by researchers. Two of the synthesised compounds exhibited potential DPP-IV inhibitory action at a dose of 10 µM, despite their lower activity than conventional medicines Vildagliptin and Sitagliptin. Compound 29 (**Structure 2**) was particularly active, inhibiting the enzyme at a concentration of 10 µM at a rate of 56.8%[45].

This study identified two novel flavonoids from the leaves of Smilax china L., bismilachinone and smilachinin. Spectroscopic approaches were used to discover their structures. Compounds were tested at the molecular level for their inhibitory effects on PTP1B, α-glucosidase, and DPP-IV. Compounds 30, 31, and 32 (**Structure 2**) demonstrated moderate DPP-IV inhibitory effects with IC50 values of 20.81, 33.12, and 32.93 µM, respectively.



Structure 2. The Coumarin derivatives reported as DPP-IV inhibitors

5. CONCLUSION

In the fight against diabetes and its consequences, finding medications that are both effective and safe has long been a priority for medical researchers. In light of the fact that type 2 diabetes (T2D) accounts for nearly all cases of the disease, more and more attention is being paid to treatments for T2D that improve insulin resistance, restore beta-cell function, or enhance the incretin system. These include insulin sensitizers and insulin mimetics. Inhibition of SGLT2 has been proposed as a new approach to limit glucose absorption in the renal tubules, hence increasing glucose excretion in the urine and decreasing blood glucose levels.

The anti-diabetic properties of coumarins and the methods by which they work have been examined. Coumarins' antioxidative and anti-inflammatory properties, as well as their effects on pancreatic function and insulin signalling, have all been shown in both *in vivo* and *in vitro* studies. As a result, they are useful and need further investigation and development. A number of biochemical and pharmacological features found in coumarins have been shown to be beneficial in the treatment of diabetes and its complications. In light of the complex pathophysiology of diabetes, the variety of coumarin targets is advantageous for antidiabetic use. In the context of integrative medicine, coumarins might be utilized to treat diabetes and cardiovascular problems or as an auxiliary to other antidiabetic drugs based on evidence-based complementary treatments. The development of novel beneficial compounds with coumarin cores as candidates against diabetes and its consequences has been made possible by breakthroughs in the area, but more study is needed before safe and effective coumarin medications may be utilized in the clinic. It was so determined that certain coumarin compounds could be useful in the treatment of diabetes.

Conflicts of Interests

Declared none

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All the authors have contributed equally in this study.

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