RESEARCH ARTICLE

Coumarins and metabolic syndrome: Brief Report

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Abstract

Metabolic syndrome is defined by the presentation of a wide array of interconnected physiological, biochemical, clinical and metabolic abnormalities that mainly increase the risk of type 2 diabetes mellitus and cardiovascular disease, which is commonly recognized as the primary clinical outcome. Pharmacological treatment for those whose risk factors are not adequately reduced with lifestyle changes remains challenging due to the polypharmacy, the risk of side effects and interactions especially in long-term treatments. The aim of this study was a systematic review of the literature published in previous years about the effects of coumarins against metabolic syndrome using *in-vivo* animal models. All studies included where pharmacological treatment was given to animals with obesity or diabetes mellitus. Studies included at least 90% of guidelines of the Gold Standard Publication Checklist (GSPC) for improved design, reporting and scientific quality of animal studies. Twenty studies reporting on the effects of different pharmacological treatments were included. Evidence supports that coumarins derivatives present lipid lowering and antidiabetic effects. However, only animal studies were found, so it is necessary the development of clinical studies with improved trial designs. Especially with the most promising compounds.

Keywords: systematic review, cardiovascular disease, obesity, coumarin, lipid

List of abbreviations

AI- atherogenic index	**LDL-** low density lipoproteins
BMI- body mass index	**LPL-** lipoprotein lipase
b.w- body weight	**MetS-** metabolic syndrome
DM- diabetes mellitus	**OGTT-** oral glucose tolerance test
DMSO- dimethyl sulfoxide	**PL-** phospholipids
FFA- free fatty acids	**PPAR-** peroxisome proliferator-activated receptor
Hb- hemoglobin	**ROS-** reactive oxygen species
HbA1c- glycosylated hemoglobin	**STZ-** streptozotocin
HDL- high-density lipoproteins	**STZ–NA-** streptozotocin–nicotinamide
HFD- high fat diet	**TAG-** total triglyceride
HMG-CoA- 3-hydroxy-3-methylglutaryl coenzyme A	**TC-** total cholesterol
LCAT- lecithin cholesterol acyl transferase	**VLDL-** very low-density lipoproteins

1. Methodology

1.1 Search Strategy

We searched the electronic databases Medline, Embase, Scopus and Scirus (July 2000 to July 2017) using controlled vocabulary and free text terms. The terms ‘‘coumarin’’ was combined with key words for metabolic syndrome, cardiovascular disease, obesity, lipid metabolism and diabetes. Reference lists of all retrieved papers were manually examined for further studies.

1.2 Selection Criteria

Eligible studies assessed the effectiveness and safety of coumarin compounds for the treatment of conditions related to metabolic syndrome. No clinical trials were found in the medical or scientific literature. All studies included where pharmacological treatment was given to animals with obesity or diabetes mellitus. Studies included at least 90% of guidelines of the Gold Standard Publication Checklist (GSPC) for improved design, reporting and scientific quality of animal studies [1].

1.3 Selection of Included Studies

Two parallel reviewers selected the papers independently for inclusion. Titles and abstracts of all suitable articles were screened, and the full text of potentially relevant studies were obtained and fully reviewed. Any disagreements were resolved through discussion, and when consensus was not possible a third reviewer was consulted.

1.4 Data Extraction

Study characteristics and design, experimental model, treatment interventions, source of drugs, details on the control group, and outcome measure used were extracted using a standard data extraction form. The effect of the intervention health outcome were also extracted.

2. Introduction

The term “metabolic syndrome” was first described in the 1920s as the clustering of hypertension, hyperglycaemia, and gout. Later, in 1947, Vague drew attention to upper body adiposity as the obesity phenotype that was commonly associated with metabolic abnormalities such as type 2 diabetes and cardiovascular disease [2-3]. Since then, several MetS definitions

have been proposed by different expert groups organizations. Among them, the US National Cholesterol Education Program guidelines have become the most widely used definition because of its ease of use for diagnosing the MetS. According to this organization, MetS is a clustering of at least three of five medical conditions (table 1). Although MetS is a collection of risk factors, it usually appears associated to insulin resistance accompanying abnormal adipose deposition and function. MetS appears to be more common in people who are genetically susceptible, however acquired underlying risk factors (being overweight or obese, physical inactivity, and an atherogenic diet) commonly elicit clinical manifestations. It is generally accepted by all groups that the prevalence of MetS is increasing, in accordance with increasing BMI and age. MetS has become one of the biggest public health issues worldwide, largely as a result of the increase in the prevalence of obesity. In the Western world 20% of adults have MetS [4]. Especially dramatic is the problem of obesity in population of children and adolescents. Approximately today every fifth child and adolescent are obese in the US, while in Europe the prevalence of obesity ranges from 5% to 31% depending on reports from different countries. Childhood obesity usually persists into adulthood, which may result in an increase in cardiovascular morbidity and mortality later in life [5].

The presence of the MetS predicts the future risk of developing diabetes and cardiovascular disease. MetS represents a group that confers a 5-fold increase in the risk of type 2 diabetes mellitus and 2-fold the risk of developing cardiovascular disease over the next 5 to 10 years. Further, patients with the MetS are at 2- to 4-fold increased risk of stroke, a 3- to 4- fold increased risk of myocardial infarction, and 2-fold the risk of dying from such an event compared with those without the syndrome regardless of a previous history of cardiovascular events [6].

Evidence exists to support that initial management of MetS should involve lifestyle modifications, including changes in diet and exercise habits. However, this is insufficient to normalize the risk factors in many patients, who will require pharmacologic interventions, usually for the rest of their lives [7-8]. Clinical management should first focus the underlying risk factor to prevent complications, including premature death [2].

Table 1: Medical conditions of the metabolic syndrome [3].

Medical conditions	Test	Values	
		Male	Female
Glucose intolerance	Fasting plasma glucose	≥ 100 mg/dL	
Insulin resistance			
Central obesity	Waist circumference	> 102 cm	>88 cm
Dyslipidaemia	Blood triglycerides	≥ 150 mg/dL	
	Low HDL cholesterol	< 1.0 mmol/L	<1.3 mmol/L
	HDL-cholesterol	≤ 40 mg/dL	≤50 mg/dL
Hypertension	Blood pressure	≥135/85 mm Hg or medication	

Table 2. Overview of the effects of drugs in the clinical management of MetS [9,10].

Underlying risk factor	Drug	Comments
Blood pressure	Diuretics, ACE inhibitors / ARB, AT_1blockers (ARBs), calcium antagonists	Better metabolic profile than the thiazide diuretics and β-blockers, in particular for the long-term treatment of young patients
Diabetes mellitus	Thiazolidinediones (glitazones)	More favorable metabolic profile tan the classical oral antidiabetic agents.
Lipids	Statins, ezetimibe, fibrates, derivatives of nicotinic acid	
Thrombosis	Acetylsalicylic acid, Clopidogrel	
Obesity	Sibutramine and orlistat	The drugs are difficult to use in the long term. New approaches to the pharmacological treatment of obesity: Modulation of the endocannabinoid system, and hormones involved in the control of b.w. regulation (such as ghrelin, leptin, PYY)

Today there is no single approved drug treatment affecting all components of the syndrome equally (table 2), and so there is growing interest in therapeutic strategies that might target multiple risk factors more effectively, thereby minimizing problems with polypharmacy [9].

According to a review published by van Zwieten *et al*. [10], the drug treatment of hypertension and atherogenic dyslipidemia, can be considered to be satisfactory. The management of type 2 diabetes remains a more difficult and less successful issue, and the drug treatment of obesity also continues to be disappointing.

It is well documented the increase of free radical mediated toxicity in clinical diabetes [11]. The conclusion of a recent review by Gregório *et al*. [12], based on experimental and clinical studies, is that antioxidants compounds exhibit a wide range of effects in protecting the human body against MetS patients, although the underlying mechanisms are not fully elucidated. This idea is supported by Abdali *et al.* [13] who found reasonable evidence about the benefits of supplementation with zinc, lipoic acid, carnitine, cinnamon and green tea, in the management of patients with obesity and type 2 diabetes. However it is important to note that antioxidant supplements are not a panacea and they should be encouraged as part of a nutritional lifestyle change.

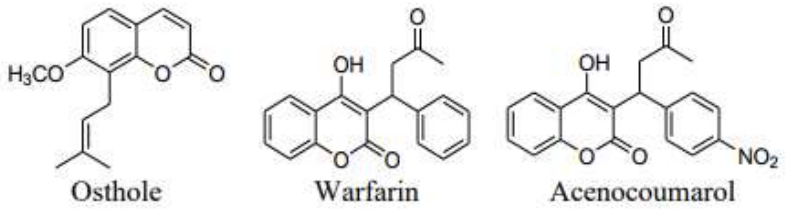

Figure 1. Some lead coumarins with pharmacological properties

At this point, we must highlight the fundamental role that coumarins could play in the development of new drugs for the MetS. Coumarins are secondary metabolites found widely in nature plants (Fig. 1), which are used mainly in anticoagulation and antithrombotic therapy for cardiovascular diseases, usually associated with low toxicity. Some of the coumarin derivatives, which have made their way to clinics, include warfarin (anticoagulant), acenocoumarol (anticoagulant), armillarisin A (antibiotic), hymecromone (choleretic and antispasmodic), carbochromen (coronary disease), phenprocoumon (anticoagulant) and novobiocin (antibiotic). Various coumarin natural or synthetic derivatives, are also found to have antioxidant, antihyperlipidemic, anti-diabetic, and antihypertensive activities [14]. For example, the extract of *Mammea africana*, rich in coumarins, completely prevented the development of arterial hypertension as captopril, and it significantly reduced the left ventricular hypertrophy induced by l-N^{ω}-nitro-l- argininemethyl ester [11]. Osthole, a coumarin isolated from *Cnidium monnieri* (L.) Cusson and *Angelica pubescens*, can reduce blood glucose levels in db/db mice, and it might reduce the triglyceride and free fatty acid levels in serum and hepatic tissue in high fat-induced fatty liver rats and quails or alcoholic-induced fatty liver rats and mice through the PPARα/γ and AMPK pathways [15-16]. The naturally occurring apigenin-coumarin hybrid, 8-(6″-umbelliferyl) apigenin, could promote glucose consumption by 57% in adipocytes, which exhibited similar effect as the positive control metformin at 1 mM [17]. 7-hydroxycoumarin pretreatment of human HepG2 cells significantly attenuates methyl glyoxal-induced cytotoxicity, apoptotic changes and ROS accumulation, due to the induction of the nuclear factor erythroid 2-related factor 2 (Nrf2). These findings highlight the potential of 7-hydroxycoumarin as a novel therapeutic approach towards the progression of diseases in which methyl glyoxal has been implicated, including aging, diabetes, neurodegenerative process as well as diseases that causes hepatic damages [18]. The pre-treatment of rat insulinoma cells (INS-1) with daphnetin (7,8-dihydroxycoumarin) at the concentration of 20 and 40 μM for 24 h resulted in a significant improvement of cell viability (72.0% and 84.1%, respectively); moreover it stimulated insulin secretion by cells in a dose-dependent manner. Daphnetin could suppress apoptosis through up-regulation of anti-apoptotic Bcl-2 protein expression and the down-regulation of pro-apoptotic Bax and nuclear factor NF-κB protein levels [19]. Skimmin, a major active ingredient from

Hydrangea paniculata, decrease significantly the serum creatinine and glucose level in blood of STZ-induced diabetic rats, and increase the creatinine clearance. In histological examination, skimmin-treated rats showed a significant decrease in glomerulus segmented sclerosis and incidence of tubule vacuolar degeneration. This results suggests that the skimmin can suppress diabetic nephropathy in rats effectively, and may slow down the renal fibrosis by regulating the TGF-β1 signal pathway [20].These results are in accordance with the findings of Li, Zheng *et al*. [21] who demonstrated that administration of a novel coumarin–aspirin compound XLF-III-43 to streptozotocin-induced diabetic rats significantly decreased blood urea nitrogen and urinary albumin excretion, it ameliorated kidney hypertrophy, mesangial expansion and glomerulosclerosis relative to untreated model group. All these results suggest that coumarins, of natural and synthetic origin, might be useful for preventing the metabolic síndrome. No clinical trials were found in the medical or scientific literature. For this reason, this review presents a brief critical analysis of various research reports on development of different coumarins from natural and synthetic sources with activities against metabolic syndrome risk factors using *in-vivo* animal models. Due to the average rate of successful translation from animal models to clinical trials is low, all studies included in this review were pharmacological treatments in animals with obesity or diabetes mellitus, which included at least 90% of guidelines of the Gold Standard Publication Checklist (GSPC) for improved design, reporting and scientific quality of animal studies [1]. This comparative information may help to design new effective and safe new pharmacological treatment for the MetS.

3. Metabolic syndrome factors and coumarins

Coumarins are a group of polyphenolic compounds widely distributed in nature. The richest sources are found in *Rutaceae* and *Umbelliferone*. Both natural and synthetic coumarins belong to the family of benzopyrones, which consists of fused benzene and α-pyrone rings, and according to their chemical structures, these compounds are divided into four subtypes (table 3).

This short review will focus on the effects of natural and synthetic coumarins on the different risk factors defining MetS, although many of these factors can share a mechanism, for example, inflammation related to obesity, diabetes, and hypertension.

3.1 Obesity and coumarins

Obesity is a medical condition which can be defined as abnormal or excessive accumulation of white adipose tissues, and characterized by an abnormal increase of fat- cell number (hyperplasia) and increased fat-cell size [22]. The rising prevalence of overweight and obesity, particularly abdominal obesity, is increasing rapidly and it has been described as a global pandemic. Solid evidence support a correlation between abdominal obesity and adipocyte functions with other risk factors observed in MetS, including type 2 diabetes and dyslipidemia, and atherosclerosis [23]. In addition, excessive fat is responsible for the production of chemical mediators as

reactive oxygen species (ROS) and adipokines, which relate obesity and overweight with inflammation [24].

Antihyperlipidaemic activities of coumarins have been reported (table 4). The action of these compounds at a molecular level is unclear but could be related to the inhibition of hydroxymethylglutaryl-coenzyme A reductase activity as reported by Sashidhara *et al*. [25]. This biological mechanism is the same used by the statins compounds, which are the main treatment for hyperlipidemia, however these compunds have some side effects like liver damage, muscle fatigue and digestive problems [26]. Hyperglycaemia-mediated oxidative stress of LDL plays a crucial role in diabetic complications, as atherosclerosis. Esculetin inhibits adipogenesis in 3T3-L1 cells, via the reduction of the ROS. Moreover, it showed a protective effect in diabetes by attenuating hyperglycaemia-mediated oxidative stress in both hepatic and renal tissues via antioxidant competence. Its nontoxic characteristics make this compound a great candidate to prevent atherosclerosis effectively [27]. When administered to hyperlipidaemic diabetic rabbits, scoparone (the major constituent of the Chinese herb *Artemisia capillaries*) protects against some alterations of plasma lipoproteins [significantly reduced the TC (73.3%), TAG (48.3%), VLDL (66.0%), LDL (55.7%) and HDL (79.5%)], vascular morphology and vascular reactivity [28]. In a culture of primary hepatocytes, 1.8 μg/mL of scoparone can significantly alter metabolism, evidencing that this natural compound may have biological effects on liver cells [29]. Suksdorfin, coumarin isolated from *Lomatium suksdorfii*, significantly promoted adipocyte differentiation and enhanced production of adiponectin, an anti-diabetic adipokine. This compound activates peroxisome proliferator-activated receptor gamma (PPARγ), a regulator of adipogenesis [30]. Coumarins isolated from *Peucedanum japonicum* Thunb, a subtropical medicinal plant from southern Japan, China, and Taiwan, has shown its applicability for the treatment of obesity and diabetes activity. The studies demonstrated that these compounds plays the key role in regulating the lipid metabolism-related gene network and improving energy production [31].

In summary, there is evidence to attribute an effect of coumarins on major end-points of obesity. However, further clinical studies are necessary.

Table 3. Classification of coumarins.

Coumarin Subtypes	Structural features	Coumarin Osthole
Simple Cumarins	Hydroxylated, alkoxylated or alkylated benzane ring	Osthole, Umbelliferone
Furocoumarins	Furan ring attached to benzene ring	
Pyranocoumarins	Pyran ring attached to benzene ring	Seselin, Xanthylein
Pyrone-Substituted Coumarins	Substitution on pyrone ring	Warfarin, Dicoumarol

Table 4. Summary of the lipid lowering effects of coumarins derivatives.

Choi, 2013 [32]	
Experimental model	20 Groups/8 rats group/4 weeks Male Sprague-Dawley rats (wt. 200−220 g)
Experimental treatment	Scoparone analogues (50 mg/kg) orally administered in water
Source of drugs	Synthetic derivatives
Control treatment	Simvastatin, atorvastatin (50 mg/kg)
Health outcomes	The compounds recovered the AI, cardiac risk factor, and liver index to levels similar to the normal groups
Comments	The histological analysis showed a clear relationship between the drug treatment and cholesterol-lowering activity Results comparable with simvastatin and atorvastatin
Iwase, 2017 [30]	
Experimental model	4 Groups / 14 days Four-week-old male KK-A^y mice
Experimental treatment	Two groups of HFD with 0.05% and 0.1% suksdorfin (w/w)
Source of drugs	Suksdorfin was purified from the ethyl acetate extract of *Ligusticum involucratum* roots
Control treatment	HFD with 0.01% pioglitazone, a synthetic PPARγ agonist
Health outcomes	Plasma glucose and TAG levels were decreased Suksdorfin had no effect on body and fat weight The plasma insulin levels were unaffected by suksdorfin intake
Comments	Suksdorfin activated PPARγ, reduce adipocyte size, and improved glucose metabolism in obese-diabetic mice
Li, 2017 [33]	
Experimental model	3 Groups/ 8 mice group /4 week Male Kun Ming mice (wt. 20 ± 2 g)
Experimental treatment	Intragastric administration of isofraxidin (20 mg/kg/day) suspended in 0.5% carboxymethyl cellulose
Source of drugs	Commercial available natural isofraxidin
Control treatment	—
Health outcomes	Anti-lipotoxicity effect via inhibition of lipid production and inflammation. The mechanisms involved lipogenesis reduction via activation of the AMPK phosphorylation and down- regulation of FAS and HMGCR protein expression Moreover, IF treatment resulted in reduced inflammatory cell infiltration by inhibiting the TLR4/NF-κB pathway
Comments	The liver index (liver mass relative to total body mass) in high-fat diet plus isofraxidin fed mice were significantly decreased by approximately 11.6% compared to the high-fat diet group
Madhavan, 2003 [34]	
Experimental model	18 Groups / 5 mice group / 6 days Swiss Albino Mice (wt. 21–29 g)
Experimental treatment	Novel heterocyclic coumarin derivatives (3 mg/kg/day)
Source of drugs	New synthetic derivatives

Control treatment	Fenofibrate (3 mg/kg/day)
Health outcomes	Tested compounds decrease the TAG by 25-45%.
Comments	Fenofibrate (30 mg/kg/day) decrease the TAG by 36%
Ogawa, 2005 [35]	
Experimental model	2 Groups/6 rats group/7 weeks Spontaneously Hypertensive Stroke Prone rats
Experimental treatment	Addition of 0.1% laserpitin to the control diet
Source of drugs	Laserpitin was isolated from the juice from stems of *Angelica keiskei* Koidzumi ('Ashitaba' in Japanese)
Control treatment	—
Health outcomes	It produced an increase of HDL levels, and decreases in the hepatic TAG. It reduced bodyweight after 4 weeks
Comments	It produced a significant increase in serum levels of TC and PL
Pari, 2014 [36]	
Experimental model	5 Groups/6 rats group/45 days (STZ–NA-induced DM) Male albino Wistar rats (wt. 200–220 g)
Experimental treatment	Coumarin,100 mg/ kg b.w. dissolved in corn oil
Source of drugs	Commercial available coumarin
Control treatment	—
Health outcomes	Significant antihyperglycemic effect. Decreased TC, TAG, FFA, PL, LDL-C, VLDL-C
Comments	An increase in the activity of HMG-CoA reductase in tissues and decrease in the activities of LPL and LCAT in plasma
Ramesh, 2005 [37]	
Experimental model	5 Groups/6 rats group/45 days (Streptozotocin-induced DM) Male albino Wistar rats (wt. 180–200 g)
Experimental treatment	Solution of Umbelliferone in 10% DMSO (30 mg/kg/day) administered intraperitoneally
Source of drugs	Commercial available
Control treatment	Glibenclamide (0.6mg/kg)
Health outcomes	Umbelliferone has an antidiabetic (it decreases blood glucose, elevated plasma insulin, protein profile and albumin) and hypolipidemic effect (it decreases TC, TAG, LDL-C, VLDL-C, FFA, and PL, and elevate HDL-C) to near normal levels
Comments	Umbelliferone increased b. w. and food intake to near normalcy. Results comparable with glibenclamide
Sashidhara, 2010 [25]	
Experimental model	15 Groups/8 rats group/45 days High fat diet fed dyslipidemic male Golden Syrian hamsters (*Mesocricetus auratus*), 12 week old (wt. 110±10 g)
Experimental treatment	Coumarin bisindole hybrids orally at a dose of 10 mg/kg/day b.w (vehicle, 0.1% acacia gum)
Source of drugs	New synthetic derivatives
Control treatment	Atorvastatin and Lovastatin
Health outcomes	The best compound showed antihyperlipidemic activity, a decrease of TAG (55%), TC (20%), and an increase of HDL-C/TC ratio (42%)

Comments	Lovastatin (25 mg/kg b.w.) decreased the TAG (29%), TC (9%), and an increase in HDL-C/TC ratio (12%) Initial studies indicate compounds to be devoid of cytotoxicity in normal cells
Sashidhara, 2013 [38]	
Experimental model	12 Groups/6 rats group/18 h (triton WR-1339 induced hyperlipidemic) Male Charles Foster Rats (wt. 200–225 g)
Experimental treatment	Coumarin chalcone fibrates (100 mg/kg) administrated intraperitoneally as acacia gum suspension in water (0.2% w/v)
Source of drugs	New synthetic derivatives
Control treatment	Gemfibrozil (100 mg/kg)
Health outcomes	Compounds decreased TC (6-26%), PL (7-24%) and TAG (8- 25%). The best compound significantly reversed the levels of VLDL, LDL and HDL also increased the LPL activity
Comments	Results comparable with gemfibrozil (100 mg/kg)
Taira, 2017 [31]	
Experimental model	2 Groups/6 mice group/4 weeks Twelve 4-week-old male C57BL/6 mice
Experimental treatment	Addition of 0.1-0.2% coumarin concentrate to the control diet
Source of drugs	Coumarin concentrate was obtained from the ethanolic extract of *Peucedanum japonicum* Thunb leaves
Control treatment	—
Health outcomes	Coumarin concentrate group gained significantly lesser body weight (26%) than the control group (40%). Relative weights of epididymal, omental, and subcutaneous white adipose tissue were significantly lower than those of the control mice
Comments	The pure compounds significantly inhibited lipid accumulation and lipogenic-related gene expressions in 3T3-L1 adipocytes cells

3.2 Insulin resistance and coumarins

In accordance with the American Diabetes Association, the three main types of diabetes (type 1,type 2 and gestational diabetes) are characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism that occur when the body cannot produce enough insulin or cannot use it effectively, or both (table 5) [39]. DM is one of the most common chronic diseases in nearly all countries, and it has been considered as 1 of the 3 leading causes of death. IDF's Diabetes Atlas reported that the number of people with diabetes is predicted to rise from over 415 million in 2015 to 642 million by 2040. The total global health expenditure due to diabetes was estimated at 673 billion US dollars in 2015 [40-41].

The modern hypoglycemic synthetic drugs as sulphonylurea, biguanide, thiazolidinedione and α-glycosidase inhibitors, have been associated to several undesirable side effects and contraindications when they are used for long-term therapy [42]. Moreover, their high prices limit their usage. For these reasons,even with great advances in modern medicine and therapeutic

Table 5. Classification and observations on types of DM.

Feature	Type 1	Type 2	Gestational
Age of onset	Usually during childhood or puberty	Frequently after the age of 35	2^{o} or 3^{o} trimester of pregnancy
Pattern of onset	Abrupt – Symptoms develop rapidly	Slow – Symptoms appear gradually	Aggressive clinical progress
Prevalence	10% of diagnosed cases	90% of diagnosed cases	2-5% of pregnant women
Genetic predisposition	Moderate	Very strong	
Nutrition	Undernourished	Mostly obese	
Biochemical defect	Autoimmune destruction of ß-cells (90%, Type 1a), or unknown cause (10%, Type 1b)	Insulin resistance and inability of ß-cells to produce enough amount of insulin	ß-cells are no able to compensate for the increased insulin resistance
Plasma insulin	Low to absent	High in the early stage, low in the disease of long duration	
Comments	Association with other autoimmune diseases.		May persist after pregnancy

agents development, it is essential the search for new antidiabetic agents with minimal or no side effects [43].

Over the past two decades, coumarins and their derivatives have been attracting much interest because of their beneficial effects on DM. The cellular and molecular mechanisms involved include protecting pancreatic ß-cells, improving abnormal insulin signalling, reducing oxidative stress/inflammation, activating AMP-activated protein kinase (AMPK), inhibiting α-glucosidases and ameliorating diabetic complications [44]. For example, the administration of cloricromene (10 mg/kg) in STZ-induced diabetic rats, suppress diabetes-related blood-retinal barrier breakdown by 45% [45-46]. Kang *et al*. [47] demonstrates that esculin ameliorates diabetes-induced renal dysfunction by reducing the activation of caspase-3 in the kidney both *in vitro* and *in vivo*. Some coumarins have hypoglycemic and antioxidant activity in animal models, by increasing the activity of catalase, glutathione peroxidase and super oxide dismutase. Some coumarin derivatives improve glucose metabolism disorder, and enhanced the glycolytic enzymes, followed by the regulation of glucose metabolism in the liver. Coumarin was also suggested to possess antidiabetic activity by stimulating insulin production in pancreas β-cells [48-49]. The decoction prepared from the roots of *Acourtia thurberi* is highly valued for treating DM in Mexico. *A. thurberi* decoction, rich in 8-β-D-glucopyranosyloxy- 4- methoxy- 5-methyl-coumarin, decreased blood glucose levels during acute hypoglycemic, the oral glucose tolerance and oral sucrose tolerance tests, in STZ–NA-induced T2DM rats [50]. Antidiabetic activities of coumarins have been reported (table 6)

Table 6. Summary of antidiabetic effects of coumarins derivatives.

Domínguez-Mendoza, 2016 [51]	
Experimental model	5 Groups/10 rats group/15 days (STZ–NA-induced T2DM) Male Wistar rats, 8 week old, (wt. 250 ± 50 g)
Experimental treatment	3',4'-Di-O-acetyl-cis-khellactone (DOAcK) (15 mg/kg) administrated orally by using a stomach probe
Source of drugs	Synthetic derivatives
Control treatment	Glibenclamide (2.5 mg/kg)
Health outcomes	DOAcK lowered blood glucose decreased in groups treated by 60.9%, and demonstrated a significant increase in weight gain. DOAcK did not modify lipid metabolism and did not cause damage at the renal level. Moreover it increased the activities of Catalase, Glutathione Peroxidase and Super Oxide Dismutase to levels near those of the healthy group
Comments	Histopathological analysis exhibited morphology similar to that of the healthy group and the group treated with DOAcK. This compound is not mutagenic and is not genotoxic LD_{50}>2,000 mg/kg; at this dose, no signs of toxicity or death were reported after 14 days of observation
García-Galicia, 2014 [52]	
Experimental model	7 Groups/10 rats group/21days (STZ–NA-induced DM) Adult male albino Wistar rats (wt. 250±50 g)
Experimental treatment	Hexane, ethyl acetate and ethanol extracts (250mg/kg)
Source of drugs	Aerial parts of *Arracacia tolucensis*
Control treatment	Glibenclamide (1mg/kg) orally in 10% DMSO
Health outcomes	Ethyl acetate extract decreased blood glucose levels (75%) and controlled the body weight loss, both effects comparable to the effect exerted by glibenclamide. The lipids level did not change. It inhibited the expression of inflammatory cytokines. Histopathology injury was not observed, however repair of the islet of Langerhans was exhibited
Comments	The extract of *Arracacia tolucensis* is rich in coumarins The LD_{50} was 2852 mg/kg
Kumar, 2009 [48]	
Experimental model	○ *Anti-hyperglycemic activity in sucrose loaded rat model (SLM)* 20 Groups/5 rats group/Blood glucose at 30, 60, 90 & 120 min Male albino Charles Foster/Wistar rats (wt. 160 ± 20 g). Compounds with best anti-hyperglycemic activity than metformin were further screened in STZ–induced DM ○ *Anti-hyperglycemic activity in STZ–induced DM* 7 Groups/5 rats group/24 h Male albino Sprague Dawley rats (wt. 160 ± 20 g) The most active compounds were screened in db/db mice ○ *Anti-hyperglycemic Activity in db/db mice* 7 Groups/5 rats group/10 days (Model of T2DM)

	C57BL/KsBom-db mice 12 – 18 weeks, (wt. 40 – 50 g)
Experimental treatment	Compounds (100 mg/kg) administrated orally (in 1.0% acacia gum)
Source of drugs	New synthetic derivatives
Control treatment	STZ–induced DM: Metformin (100 mg/kg) STZ–induced DM: Metformin (100 mg/kg) db/db mouse model: Rosiglitazone (100 mg/kg)
Health outcomes	Two compounds were showing 38.0% and 42.0% blood glucose lowering activity in db/db mice model, while Rosiglitazone showed 48.1%
Comments	Both compounds inhibit PTP-1B (IC_{50} = 24.5 μM and 36.2 μM), revealing their possible mechanism
Lee, 2004 [53]	
Experimental model	Oral glucose tolerance test in ICR mice (n=8 for each group) Blood glucose at 30, 60 & 120 min
Experimental treatment	Oral administrations of 80% EtOH extracts from *Peucedanum japonicum* (*Umbelliferae*), subfractions or pure compounds
Source of drugs	Korean Peucedani Radix (*Peucedanum japonicum*)
Control treatment	—
Health outcomes	Peucedanol 7-*O*-*D*-glucopyranoside (coumarin) and myo-inositol (cyclitol) are the active principles. They inhibit the postprandial hyperglycemia at 39 and 34% respectively (5.8 mg/kg dose)
Comments	The hypoglycemic mechanism is no reported
Murali, 2013 [54]	
Experimental model	6 Groups/6 rats group/30 days (STZ-induced DM) Male albino Wistar rats (wt. 180-220 g)
Experimental treatment	Fraxetin (20, 40 and 80 mg/kg) in 1% DMSO
Source of drugs	Commercial available Fraxetin
Control treatment	—
Health outcomes	At 80 mg/kg b.w, fraxetin significantly reduced the levels of blood glucose and HbA_{1c}; it increased plasma insulin level. The altered activities in carbohydrate metabolizing enzymes were significantly reverted to near normal levels
Comments	Fraxetin improved b.w. and hepatic glycogen content
Pari, 2009 [49]	
Experimental model	6 Groups/6 rats group/45 days (STZ–NA-induced T2DM) Male albino Wistar rats (wt. 200–220 g)
Experimental treatment	Coumarin, 100 mg/ kg b.w./day
Source of drugs	Commercial available
Control treatment	—
Health outcomes	Significant reduction in the levels of plasma glucose and HbA_{1c}. Increase in the levels of insulin and Hb. Significant increase in the levels of glycolytic enzyme (hexokinase) and hepatic shunt enzyme (glucose-6-phophate dehydrogenase). Significant decrease in the levels of gluconeogenic enzymes

	(glucose-6-phosphatase and fructose-1,6-bisphosphatase)
Comments	Coumarin group significantly decreased the food, water intake and urine sugar, also increased b.w.
Prabakaran, 2012 [55]	
Experimental model	6 Groups/6 rats group/45 days (STZ-induced DM) Male albino Wistar rats, 9 week-old (wt. 180-200 g)
Experimental treatment	Esculetin (10, 20 and 40 mg/kg) in aqueous solution using intragastric tube
Source of drugs	Commercial available
Control treatment	—
Health outcomes	Esculetin significantly decreased the levels of plasma glucose, HbA_{1c} and increased the levels of Hb and insulin Protection against body weight loss The dose of 40 mg/kg b.w. exerted a more pronounced effect
Comments	
Ramesh, 2006 [56]	
Experimental model	7 Groups/6 rats group/45 days (STZ-induced DM) Male albino Wistar rats, 9 week old, (wt. 180–200 g)
Experimental treatment	Intraperitoneal administration of Umbelliferone (10, 20, and 30 mg/kg) in 10% dimethyl sulfoxide
Source of drugs	Commercial available
Control treatment	Glibenclamide (0.6 mg/kg) in 10% dimethyl sulfoxide
Health outcomes	Umbelliferone (30 mg/kg b.w,) produced significantly decreased levels of blood glucose (from 244.63 mg/dL to 114.28mg/dL) and HbA_{1c}, and activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase, while elevating levels of plasma insulin, Hb, and liver glycogen and activities of glucokinase and glucose-6-phosphate dehydrogenase to near normal levels in STZ-diabetic rats when compared with normal control rats
Comments	The antihyperglycemic effect of Umbelliferone (30 mg) is comparable to that of the standard drug glibenclamide
Tchamadeu, 2010 [57]	
Experimental model	14 Groups/5 rats group (STZ-induced T1DM) Male albino Wistar rats, 3-month-old, (wt. 200–250 g) Acute (5 h) and sub-acute (21 days) effects of extract
Experimental treatment	Oral administration of dichloromethane–methanol (1:1) stem bark extract of *Mammea africana* (19, 38, 75, 150 and 300 mg/kg b.w.)
Source of drugs	*Mammea africana*
Control treatment	Glibenclamide (10 mg/kg) in 3% DMSO
Health outcomes	Acute administration reduced blood glucose in the DM rats (33.87%), while the treatment for 21 days also reduced blood glucose level (73.29%). A reduction or stabilization in total serum protein, TAG, TC and alanine amino transferase levels was also observed. No effect was detected on body weight loss but food and water intakes were significantly reduced

Comments	The maximal anti-diabetic effect was obtained with the dose of 75 mg/kg and was more important than that of glibenclamide Phytochemical screening of extracts from *Mammea Africana* stem bark reveals the presence of flavonoids and coumarins
Verma, 2013 [58]	
Experimental model	5 Groups/6 rats group/6 week (STZ-induced DM)
Experimental treatment	Scopoletin at a dose of 1mg/kg once a day (OD) and 1mg/kg twice a day (TD)
Source of drugs	Commercial available
Control treatment	Glimepiride (0.11mg/kg)
Health outcomes	Scopoletin showed significant reduction in blood glucose level at a dose of 1mg/kg OD (from 240.5mg/dl to 208.5mg/dl) and 1 mg/kg TD (from 234.3mg/dl to 166.5mg/dl). There was a significant reduction in TAG (8% and 21%) and TC (27% and 34%)
Comments	Scopoletin improved b.w. In a histopathological study of pancreas Scopoletin (TD) showed slight regeneration of β-cells when compared with diabetic control. The antihyperglycemic effect of Scopoletin (1mg/kg, TD) is comparable to that of the standard drug glimepiride

4. Conclusion

Some coumarin-based medicinal drugs have been extensively used in clinic as anticoagulant, antineurodegenerative or anticancer agents. This review summarizes the current developments of coumarin compounds, of natural or synthetic origin, as medicinal agents on the common pathogenic factors of metabolic syndrome, which includes obesity and Type II diabetes.

The present findings suggest that some coumarins such as coumarin, esculetin, umbelliferone and suksdorfin, or extract rich in coumarins such as *Peucedanum japonicum* Thunb and *Mammea africana*, may be useful in the treatment of metabolic syndrome. These derivatives present lipid lowering and antidiabetic effects, so the development of a pharmacological treatment based in these compounds could be useful to reduce the risk of side effects and interactions associated to polypharmacy. However, only animal studies were found in the medical literature. For this reason, is essential the development of clinical studies, especially with the most promising compounds. To evaluate this possibility may be warranted.

It is important to indicate that several studies in rats have shown that coumarins can be toxic to the liver, leading to concern that they can cause liver damage in humans as well. Although no relevant side effects for drugs that shown effectiveness were reported, before performing the clinical studies it is essential to establish the toxicity of each of the compounds of interest.

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