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How does coumarin work in insulin resistance for diabetes mellitus type 2? (A literature review)

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Abstract

Background: Coumarin is a natural compound found in various plants, including *Cinnamomum cassia* and *Cinnamomum zeylanicum*, and has been widely studied for its potential role in metabolic regulation, particularly in diabetes mellitus type 2. While coumarin has shown potential benefits in improving glycemic control, concerns regarding its hepatotoxic and carcinogenic effects remain.

Purpose: To review the literature on how coumarin works in insulin resistance in people with type 2 diabetes.

Method: A literature review was conducted using the ClinicalKey, Science Direct, and Google Scholar databases. Boolean operators (AND, OR, NOT) were used to refine the search. Inclusion criteria included research articles published between 2015 and 2024 in accredited national or internationally reputable journals, with a JBI critical appraisal tools score above 65%. The PRISMA diagram was used for article selection, resulting in five eligible articles for analysis.

Results: The findings indicate that coumarin, predominantly found in cinnamon, has glucose-lowering effects in diabetes mellitus type 2 patients by reducing blood glucose levels, controlling glucose spikes, and lowering HbA1c. Additionally, coumarin derivatives in *Opuntia ficus-indica* and *Smilax sonchifolius* (yacon) may contribute to metabolic homeostasis through antioxidant activity. However, coumarin also poses hepatotoxic and carcinogenic risks at high doses.

Conclusion: While coumarin-containing compounds show promise in improving glycemic control. Further research is needed to determine safe and effective therapeutic doses for clinical application.

Keywords: Coumarin; Diabetes Mellitus Type 2; Insulin Resistance.

INTRODUCTION

Coumarin is a natural metabolite from plants and some microorganisms. Coumarin is a frequently used ingredient in the industries of pharmaceutical and food in natural or artificial man-made forms. Many Coumarins have numerous activities of biological nature such as antitumor, antiulcer, antimicrobial, anti-inflammatory, and anticoagulant (Anywar & Muhumuza, 2024). This natural product with fragrant and aromatic characteristics called Coumarin, widely distributed throughout the plant kingdom. Coumarin is found in various plant sources such as vegetables,

spices, fruits, and medicinal plants including all parts of the plant fruits, roots, stems, and leaves (Lončar, Jakovljević, Šubarić, Pavlić, Buzjak Služek, Cindrić, & Molnar, 2020).

The use and research of Coumarin is directed against pathologies such as diabetes mellitus, obesity, and cardiovascular disease. Other diseases in which Coumarin and its derivatives have also made important contributions include neurodegenerative diseases such as epilepsy and Alzheimer's disease, Parkinson's disease, infectious diseases, and liver

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diseases (Flores-Morales, Villasana-Ruiz, Garza-Veloz, González-Delgado, & Martínez-Fierro, 2023).

Coumarins along with their derivatives have demonstrated encouraging treatments for antidiabetic. Coumarins from plants such as *Artemisia capillaris*, *Hydrangea paniculata*, and *Urtica dentata* have the potential to slow the progression of diabetic nephropathy. It was observed that the overall coumarin concentration of *Urtica dentata* inhibits the high glucose-induced multiplication and hypertrophy of mesangial cell lines, which are early markers of progression to nephropathy. In addition, these substances significantly decreased albuminuria and serum creatinine levels in streptozotocin-induced diabetic rats. Furthermore, scoparone, a coumarin compound found in *Artemisia capillaries*, stopped glucose-induced multiplication in cultured mesangial cells. Furthermore, use of a skimming compound derived from *Hydrangea paniculate* led to a more significant reduction in glomerulosclerosis compared with streptozotocin-treated diabetic rats given losartan (Randelović & Bipat, 2021).

Natural coumarins, including osthole, daphnetin, urolithin, esculetin, psoralen, umbelliferone, esculin, scopoletin, nodakenin, and imperatorin, hold promise in terms of treating diabetic nephropathy. These compounds exhibit strong anti-inflammatory and antioxidant properties, offering protective effects against kidney damage associated with diabetes. They help to decrease reactive oxygen species levels, attenuate lipid peroxidation, and inhibit what we know as products of advanced glycation end (AGEs). In addition, they regulate pro-inflammatory cytokines and control crucial cellular pathways such as the TGF- β /Smad, NF- κ B (p65), and NLRP3/Caspase 1 axes. Furthermore, coumarins are involved in preventing

the activation of myofibroblasts that conceals α -smooth muscle actin (α -SMA), as well as in restricting the synthesis and accumulation of extracellular matrix (ECM) elements in the kidneys (Ghosh, Ghosh, Rajanan, Suresh, Raut, Kundu, & Sahu, 2022).

RESEARCH METHOD

This study uses a literature review approach with ClinicalKey, Science Direct, and Google Scholar databases. The process of searching for articles or journals involves the use of keywords and Boolean operators (AND, OR, and NOT) to narrow or expand the search. The keywords in the search for evidence-based research in this literature review are "coumarin" AND "type 2 diabetes mellitus" AND "risk factors" AND "insulin resistance". The inclusion criteria in this literature review are academic papers published between 2015-2024, in Indonesian and English in accredited or internationally reputable national journals, and are research articles. The selected articles are articles that the author can download or open access and have a JBI critical appraisal tools value above 65%.

The search was carried out using the PRISMA diagram literature selection. The search results obtained articles from ClinicalKey as many as 86 articles, Google Scholar as many as 84 articles, and from Science Direct as many as 31 articles. Of the total 201 articles, there were 5 articles that were duplicates or the same articles. After that, 173 article titles were obtained that were not on topic. There were 12 articles that did not meet the inclusion criteria and 6 articles had inappropriate interventions and methodologies. Finally, 5 articles were obtained that were worthy of analysis.

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RESEARCH RESULTS

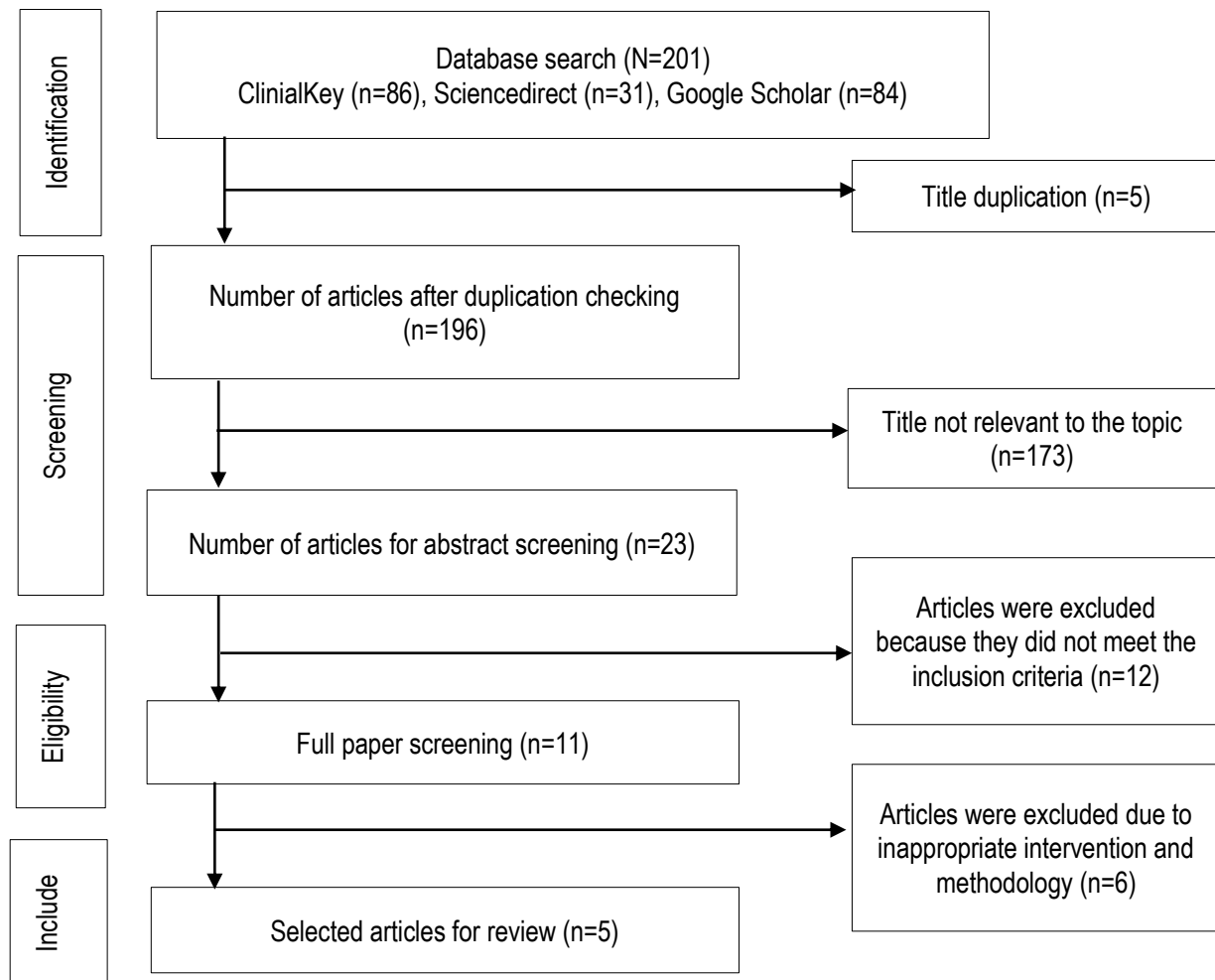


Figure PRISMA Flow Diagram

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Article Data Mapping Results Table

(Author, Years) (Country)	Purpose	Method	Coumarin Dosage	Results
(Zelicha et al., 2024) (California)	To determine the effects of daily cinnamon spice supplementation, at a level commonly used for seasoning, on blood glucose levels in individuals with obesity and prediabetes.	This study used a randomized, double-blind, controlled crossover study method. The sample size used was 18 healthy adults, aged 18 years and older who consumed a low-fiber/polyphenol diet, adults, overweight or obese participants who had a BMI between 25 and 40 kg/m ² , and were diagnosed with prediabetes. The study was conducted for 12 weeks, with a two-week washout period after which subjects switched to a second treatment for four weeks (allocation ratio 1:1). Subjects were given sixteen cinnamon capsules four times daily or were randomly assigned to receive cinnamon (16 capsules - four per day) or placebo.	Cinnamon (<i>C. burmannii</i> or in Indonesian called cinnamon) was administered in 250 mg capsules. Participants took 8 capsules at breakfast and 8 capsules at dinner (16 capsules or 4 g/day). Participants ingested an identical number of placebo capsules, each containing 250 mg of maltodextrin, rendering them unable to distinguish between them. In this study, analysis of cinnamon powder revealed a concentration of 3.64 ± 0.04 mg/g coumarin, 1.02 ± 0.01 mg/g cinnamic acid, and 29.03 ± 0.15 mg/g cinnamaldehyde. When adjusted for body weight, the intake levels were estimated at 0.17 mg/kg for coumarin, 0.054 mg/kg for cinnamic acid, and 1.55 mg/kg for cinnamaldehyde.	Incorporating cinnamon into the diet of individuals with obesity-related prediabetes may help improve glucose regulation. Compared with placebo, 24-hour glucose levels were significantly lower with cinnamon administration [mixed model; effect size (ES) = 0.96; 95% confidence interval (CI): -2.9, -1.5; $P < 0.001$]. In addition, the mean area under the curve (net AUC) for glucose was significantly reduced compared with placebo with cinnamon administration (over 24 hours; ES = -0.66; 95% CI: 2501.7, 5412.1, $P = 0.01$). Cinnamon intake led to a lower glycemic peak compared with placebo (Δp peak 9.56 ± 9.1 mg/dL vs. 11.73 ± 8.0 mg/dL; ES = -0.57; 95% CI: 0.8, 3.7, $P = 0.027$).
(Al Dhaheri et al., 2024) (United Arab Emirates)	To assess how consumption of black seed (<i>Nigella sativa</i>), cinnamon (<i>Cinnamomum</i>), and ginger	Experimental study with parallel design, randomized, double-blind, and controlled. The study was planned to last for 12 weeks to compare three treatments (ginger (<i>Zingiber officinale</i>), cinnamon (<i>Cinnamomum</i>), and black cumin (<i>Nigella</i>	Coumarin dosage was not specified in the study. However, each participant received a daily intake of three grams of spice powder or placebo. All spices were purchased in one transaction from a local spice shop in Al Ain to minimize the risk of	All $p \geq 0.05$ showed no significant changes in cardiometabolic outcomes were detected throughout the study period. Black cumin and ginger caused a significant decrease in total cholesterol (-13.055 mg/dL and -11.49 mg/dL) and LDL

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	(Zingiber officinale) affects body composition, lipid profiles, and blood glucose.	sativa)) with a control group (placebo). A total of 120 samples were randomly divided into four groups, who were instructed to consume three grams of the specified spice powder or cornstarch per day, at different times over a 12-week period. Participants consumed one gram in the morning, one gram in the afternoon, and one gram in the evening, each with hot water. The sample criteria were aged between 18 and 50 years and met at least two of the following diagnostic indicators for metabolic syndrome (MetS): enlarged waist circumference (>80 cm for women and >94 cm for men), high blood pressure ($\geq 130/85$ mm Hg or taking antihypertensive medication), high fasting blood glucose levels (≥ 100 mg/dL [5.6 mmol/L] or using medication for hyperglycemia), low HDL cholesterol (less than 40 mg/dL [1.03 mmol/L] for men and less than 50 mg/dL [1.29 mmol/L] for women), and high triglyceride levels (≥ 150 mg/dL [1.7 mmol/L]).	error. The spices were freshly ground into a fine powder. In a clean and disinfected area, one-gram doses of spice powder and starch powder were collected, then hermetically packed in zip-lock plastic bags for easy use by the participants.	cholesterol (-2.142 mg/dL and -5.314 mg/dL), respectively, with $p = 0.031$. In contrast, the cinnamon and placebo groups did not show any measurable effect. All three spices caused slight decreases ($p \leq 0.001$) in fasting glucose, with the greatest impact due to black cumin (-7.426 mg/dL), followed by ginger (-3.404 mg/dL) and finally cinnamon (-1.27 mg/dL). In contrast, cinnamon had the most significant impact on HbA1c, decreasing it by 0.596%, followed by more modest changes for ginger (-0.291%) and black cumin (-0.008%), compared with a slight increase in the control group (+0.04%, $p \leq 0.001$). The 12-week spice intervention did not result in any statistically significant changes in anthropometric measurements (all $p > 0.05$). However, the black seed group showed a tendency toward a reduction in waist circumference ($p = 0.051$), with an average decrease of 10.56 cm over the intervention period.

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(Wariyapperuma et al., 2021) (Sri Lanka)	to examine the hypoglycemic and antilipidemic effects of water-soluble nutraceuticals including Cinnamomum zeylanicum (the "Sri Wijaya" accession) in Wistar rats with and without diabetes.	This study was conducted in two stages using 90 healthy and diabetic Wistar rats. The rats were randomly assigned into groups of four using a random table, (Group 1: control The rats were randomly assigned into groups of 5 (Group 1: diabetic rats without any treatment (DM-NC); Group 2: diabetic rats given pre-treated pressurized water cinnamon extract (DM-PWE); Group 3: diabetic rats given pre-treated pressurized water cinnamon extract (DM-prePWE); and Group 5: Diabetic rats given acarbose (DM-PC) with six rats per group. The first stage focused on assessing potential toxic effects on the kidney and liver of healthy rats. Several factors, such as food and water consumption, body weight, fasting serum glucose (FSG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), and serum creatinine, were monitored for one month in the control group. healthy and diabetic patients. The first stage included four groups (Groups one to four), while the second stage was expanded to five groups (Groups one to	It is not explained how much Coumarin dose was used in this study. However, the cinnamon extract was administered to the experimental rats for one month using the gastric lavage method with an oral probe needle, performed by trained and experienced researchers. The dose for Wistar rats each day was calculated based area of the body surface, with the human dose (six g) according to previous studies.	Nutraceuticals containing in cinnamon could decrease hyperglycemia in STZ-induced diabetic rats. The compound has the ability to inhibit the action of α -amylase and α -glucosidase enzymes within pancreatic tissue. This treatment strategy has the potential to aid in managing and preventing hyperglycemia in humans. The majority of research on the medicinal benefits of cinnamon has focused on Chinese cinnamon (<i>Cinnamomum cassia</i>), while studies on <i>C. zeylanicum</i> remain relatively limited. Cinnamon is rich in coumarin alkaloids, which are known to be hepatotoxic and potentially carcinogenic. However, <i>Ceylon Cinnamon</i> contains only a low percentage of coumarin, making it a promising candidate for pharmaceutical applications. Additionally, recent pathological studies have indicated that <i>Ceylon Cinnamon</i> does not exhibit toxic effects.

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		five). The first group received distilled water, which served as a control. The second, third, and fourth groups were given cinnamon nutraceuticals extracted using different methods: pressurized water extraction (PWE), boiled water extraction (DWE), and pretreated pressurized water extraction (pre-PWE). In the second stage, the fifth group was introduced and given acarbose as a positive control.		
(Di Majo et al., 2024) (Italy)	To test the extraordinary effects of consuming <i>Opuntia Ficus Indica</i> fruit on metabolic syndrome.	In the baseline phase (T0), after the acclimatization period, NPD and HFD groups were created consisting of animals divided into these groups based on their diet for 8 weeks until MetS induction. In T1, MetS induction was evaluated by criteria frequently used in the literature. T2 shows the conclusion of the 12-week experimental study conducted after the baseline phase (T0). There were 20 samples in this study, namely male Wistar rats weighing 240–260 g provided by Envigo Srl (Indianapolis, Indiana), aged 7 weeks, n = 20, weighing 240±13.04 g.	It is not explained how much Coumarin dose was in this study. However, it is explained that <i>Opuntia ficus-indica</i> fruit contains antioxidant capacity to capture free radicals, interfere with radical production and reduce oxidative stress thanks to the number and variety of anti-oxidative molecules and extraordinary redox modulation. Flavonoids are the predominant group of secondary metabolites, with isorhamnetin being the primary flavonoid aglycone found in most flavonoid conjugates. Additionally, various organic acids and phenolic compounds, including (iso)citric acid, piscidic acid, ferulic acid, and gluconic acid, are also	<i>Opuntia ficus-indica</i> fruit modulation of leptin positively correlates with brain oxidative and systemic stress, also increased behavioral markers such as impaired lipid homeostasis and anxiety. From the other side, lower leptin levels due to <i>Opuntia ficus-indica</i> fruit consumption are linked to an enhanced antioxidant defense, improved declarative memory, and increased neurotrophic signaling.

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			present. Furthermore, betaxanthin, including indicaxanthin as the main compound, coumarin accompanied by dihydroxy psoralen-O-hexoside and terpene alongside by hydroxy-megastigmen-one-hexoside complete the phytochemical profile of <i>Opuntia ficus-indica</i> fruit, which is additionally enhanced by large amounts of ascorbic acid, beta-carotene, and tocopherol.	
(Baroni et al., 2016) (Brazil)	To assess the effects of yacon hydroethanol extract on streptozotocin (STZ)-induced hyperglycemia in newborn rats.	The number of samples in this study was not mentioned. The samples used were newborn male Wistar rats (2 days old) that were injected intraperitoneally with STZ (160 mg/kg) dissolved in citrate buffer (10 mM; pH 4.5). The animals were situated at a controlled temperature ($\pm 22^{\circ}\text{C}$) and a 12-hour light-dark cycle, with a balanced diet and free access to water. The protocol for this experiment was sanctioned and allowed into practice by the Animal Experimental Ethics Committee of the State University of Maringá. The diabetic condition 7 weeks later also confirmed by determining glucose levels on urine and animals with glycosuria above 250 mg/dL were included in the study.	It is not explained how much Coumarin dose was in this study. However, it is explained that treatment with hydroalcoholic extract of yacon for 14 days (400 mg/kg/day) did not cause liver damage and death, and also did not affect animal weight gain. Non-toxic effects were also observed in previous studies in this study (de Oliveira et al., 2011) showing that polar yacon extract produced levels of toxicity only at high doses (1,000 mg/kg) after long treatment (90 days). The authors suggested that oral administration is safe if using the polar extract because it shows small levels or no sesquiterpene lactones.	<i>Smallanthus sonchifolius</i> leaves ethanol extract (hydroethanolic extract of yacon) decreased the levels of glucose in fed diabetic rats plus did not alter glucose levels in fasted diabetic rats and normal rats. Furthermore, treatment with the extract was found to lower levels of glucose in the blood of the rats with diabetic through both oral and intravenous glucose tolerance tests. The administration of yacon extract did not affect body weight, liver enzyme levels, or mortality. Phytochemical analysis identified the ferulic acid, caffeic acid, chlorogenic acid, and gallic acid presence.

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DISCUSSION

The results of the study showed that coumarin is a compound contained in cinnamon, especially in *C. burmannii*, *Cinnamomum cassia* and *Cinnamomum zeylanicum* (Al Dhaheiri, Alkhatib, Feehan, Cheikh Ismail, Apostolopoulos, & Stojanovska, 2024; Wariyapperuma, Jayawardena, Thammitiyagodage, Karunakaran, & Kumara, 2021; Zelicha, Yang, Henning, Huang, Lee, Thames, & Li, 2024). Coumarin content in *Cinnamomum cassia* is higher than *Cinnamomum zeylanicum* (Ceylon Cinnamon). Coumarin is known to have liver toxic (hepatotoxic) and carcinogenic potential (Wariyapperuma et al., 2021). Cinnamon containing coumarin has the potential to lower blood glucose levels, control glucose spikes, and lower HbA1c in type 2 diabetes patients (Al Dhaheiri et al., 2024; Zelicha et al., 2024). In *Opuntia ficus-indica* fruit, coumarin is mentioned as part of the phytochemical profile, but no specific dose or direct effect of coumarin on treatment or glucose modulation was described in the study. In addition, coumarin is found in the form of dihydroxy psoralen-O-hexoside, which is a derivative of coumarin. Coumarin, found in *Opuntia ficus-indica* fruit, may act as part of a complex of antioxidant compounds that help reduce oxidative stress and improve metabolic homeostasis (Di Majo, Ricciardi, Di Liberto, Allegra, Frinchi, Urone, & Gambino, 2024).

Coumarin is mentioned as one of the compounds in the hydroalcoholic extract of yacon (*Smallanthus sonchifolius*), although the exact dosage or specific effects on blood glucose or toxicity are not described. Studies have shown that yacon extract has an abundance of phenolic compounds, such as chlorogenic acid, caffeic acid, and coumarin compounds, which contribute to the therapeutic effects of the extract. Yacon extract, which contains phenolic compounds, including coumarin, lowered levels of blood glucose in diabetic rats during intravenous and oral glucose tolerance tests. Although coumarin is not explicitly discussed in this context, phenolic compounds in yacon extract may play a role in lowering blood glucose and improving metabolic function (Baroni, da Rocha, de Melo, Comar, Caparroz-Assef, & Bersani-Amado, 2016).

According to the findings of the article search, coumarin was shown to be a bioactive compound that is widely found in medicinal plants and has various pharmacological potentials. This compound is known

for its role in lowering blood glucose levels, enhancing metabolic homeostasis, and having antioxidant activity. Other studies have shown that given the intricacies of diabetes' pathophysiology, various targets of coumarin are beneficial for usage done for antidiabetic purposes. When purposed as a medicine of integrative nature, coumarin is usable as a cure for diabetic and cardiovascular issues, it can also be used to assist other medicines in handling diabetes and other issues (Hussain, Syed, Khattak, Hafez, Reigosa, & El-Keblawy, 2019; Husain, Husain, Gawhale, Khan, Murlidhar, Siddiqui, & Kazi, 2022).

Coumarin, a compound that occurs naturally, as well as its derivatives have shown a range of pharmacological activities, including properties of antioxidant, anti-inflammatory, antimicrobial, and anticancer. These attributes position it as a promising pharmacophore for the creation and development of new molecules with potential therapeutic uses. Regarding the inhibition of α -glucosidase, coumarin compounds A-C have shown inhibitory action on this enzyme. The coumarin derivative carbohydrazone A, which has a hydroxyl group at the second position of the attached phenyl ring, exhibited 35.8 times greater potency than the standard inhibitor acarbose. Additionally, α -glucosidase inhibitor B featured a coumarin structure connected to styrene via a carboxylate linker. Notably, coumarin derivative C demonstrated an impressive 252-fold increase in potency compared to acarbose (Ganjeh, Mazlomifar, Shahvelayti, & Moghaddam, 2024).

α -Glucosidase is crucial for the final step of carbohydrate digestion in the small intestine. It breaks down α -1,4 glycosidic bonds in complex carbohydrates, such as disaccharides and polysaccharides, to release monosaccharides like glucose, which the body can absorb. This enzymatic action is vital in controlling blood glucose levels after meals. Inhibiting α -glucosidase slows down the breakdown of complex carbohydrates, reducing glucose absorption and helping to control the increase in blood sugar following eating (Sohrabi, Binaeizadeh, Iraj, Larijani, Saeedi, & Mahdavi, 2022).

Insulin receptor is a potential target for the development of anti-diabetic drugs. This receptor is a transmembrane tyrosine kinase receptor that serves to adjust glucose homeostasis through phosphorylation after insulin binding. By targeting this

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receptor, certain compounds can activate metabolic pathways that increase insulin sensitivity and improve blood glucose regulation. 3-aryl coumarin derivatives are promising as candidate molecules for antidiabetic drugs and further research. Among these compounds, those with hydroxyl groups at position 7 exhibit α -glucosidase inhibitory activity. Additionally, compounds containing 5,7-dihydroxyl and 4'-OH structures also demonstrate significant α -glucosidase inhibition. Furthermore, the 3-aryl coumarins mentioned above possess AGE inhibitory properties. Structures incorporating catechol hydroxyl groups effectively scavenge DPPH radicals, while 4-methyl-7-aminocoumarin and dicoumarin exhibit oxygen radical scavenging activity. Moreover, osthole mitigates the onset and progression of diabetic nephropathy (DNP) by inhibiting P2X3 expression in mice with diabetic. Lastly, chalcone-coumarin hybrids show significant potential in improving insulin resistance (Pan, Liu, Wang, & Sun, 2022).

Coumarin derivatives already demonstrated significant potential as anti-diabetic agents by inhibiting α -glucosidase, an enzyme situated on the brush border membrane, making it a key therapeutic target for diabetes treatment. A new set of compounds, identified as N-aryl-2-(4-(((2-oxo-2H-chromen-4-yl) oxy) methyl)-1H-1,2,3-triazol-1-yl) acetamide 8a-p, was synthesized through a straightforward process. Further evaluation of their α -glucosidase inhibitory activity revealed that all the synthesized derivatives exhibited strong inhibitory effects, surpassing the efficacy of the standard antidiabetic drug, acarbose (Khouzani, Mogharabi, Faramarzi, Mojtabavi, Azizian, Mahdavi, & Hashemi, 2023).

However, on the other hand, coumarin has also been reported to have potential hepatotoxic and carcinogenic effects, so its use in medicine requires special attention regarding dosage and safety. Coumarin is generally secure and tolerable for most patients, although a small number experience mild to moderate hepatotoxicity. Because hepatotoxicity is rare, some countries limit or prohibit its use. Further study is required to identify individuals at risk for hepatotoxicity, focusing on the analysis of gene polymorphisms involved in coumarin metabolism and contributing environmental factors (Pitaro, Croce, Gallo, Arienzo, Salvatore, & Antonini, 2022).

Based on research on coumarin compounds found in avocado plants (*Persea americana* Mill.), compounds of coumarin along with their derivatives satisfy the criteria of Lipinski's Rule of Five in terms of lipophilicity, molecular weight, molar reactivity, and hydrogen bonds. This indicates that the compound is expected to be absorbed and capable of binding to target receptors. Alpha glucosidase receptors are favored by coumarin molecules and their derivatives, according to molecular docking data. With an inhibition constant of 0.29255 μ molar and a free energy value of -8.91 kcal/mol, the edgeworoside c molecule has the highest affinity. The findings collected from the research shows that all compounds used in the test were classified as class III in its toxicity levels, which means that when used in large amounts, there is no guarantee that its use would be safe. Then all compounds of coumarin used in the test along with its derivatives are not mutagenic or carcinogenic (Prahayati & Rusdi, 2023).

Based on other studies, food and food ingredient toxicity data are often insufficient for direct human toxicity evaluation, so the use of models to assess toxicity risk becomes important. Models that combine logP, MW, and coumarin chemotype have been used to predict hepatotoxicity potential. In previous research analyses, coumarin at daily doses of 2.5 and 25 mg/kg was anticipated to have a moderate risk of hepatotoxicity, while drugs that are structurally related, such as warfarin, showed a low risk, and methoxsalen had a moderate risk. The estimation results are consistent with human hepatotoxicity data, indicating that this model can provide useful information to assess the possibility of hepatotoxicity caused by coumarin. In addition, this model can also be applied to other foods, providing initial discrimination in the evaluation of human hepatotoxicity potential (Yamada, Katsutani, Maruyama, Kawamura, Yamazaki, Murayama, & Hirose, 2022).

CONCLUSION

Coumarin is a bioactive compound found in numerous medicinal plants, such as cinnamon, *Opuntia ficus-indica*, and yacon, with pharmacological potential as an antioxidant, anti-inflammatory, and blood glucose-lowering agent that is useful in managing diabetes mellitus. This compound also shows α -glucosidase inhibitory activity, which hinders

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complex carbohydrates digestion and reduces postprandial glucose spikes, and has positive effects on insulin sensitivity and metabolic homeostasis. However, despite its therapeutic benefits, coumarin also has hepatotoxic and carcinogenic potential, so its use requires special attention regarding dosage and safety. Therefore, further studies are required to explore the safety and efficacy of coumarin, especially in long-term use, in order to maximize its clinical benefits while minimizing the risk of toxicity.

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