Canrea Journal: Food Technology, Nutritions, and Culinary, 2022; 5 (2): 151-171 OPEN ACCESS

e-ISSN : 2621-9468

Type of the Paper (Review)

In vivo and In vitro anti-diabetic effects of cinnamon (*Cinnamomum sp.*) plant extract: A review

Alyssa MA Nazareno[1], Listya Purnamasari[2], and Joseph F dela Cruz[1*]

[1] College of Veterinary Medicine, University of the Philippines Los Baños, Laguna, Philippines
[2] Department of Animal Husbandry, Faculty of Agriculture, University of Jember, Jember, Indonesia 68121

Abstract

Research regarding the enormous potential of medicinal plants for the development of new drugs and the efficient treatment of diabetes mellitus is increasing due to the harmful effects that synthetic drugs may bring such as severe hypoglycemia, abdominal discomfort, lactic acidosis, and more. Cinnamomum sp. (cinnamon) extracts have shown to have significant anti-diabetic effects on type 2 diabetes mellitus in experimental rodent animals in a dose-dependent manner. There are different possible mechanisms of action involved in its anti-diabetic activities. The efficacy of cinnamon extract as an anti-diabetic agent in type 1 diabetes mellitus experimental rodent animal studies explored in this study.

Article History
Received June 12, 2022
Accepted November 9, 2022
Published December 2, 2022

Keyword
Cinnamon, Plant Extract, Anti-diabetic.

1. Introduction

Diabetes mellitus (DM) or diabetes is a chronic metabolic disorder characterized by high blood sugar and insulin resistance over a prolonged period strongly associated with oxidative stress. This can lead to a wide range of complications and permanent damage if left untreated. (1) investigated the breed predilection of diabetes mellitus in 180,000 insured dogs aged 5-12 years old in the United States and found that the following breeds were found to have the highest incidence: Australian Terrier, Samoyeds, Swedish Elkhounds, and Swedish Lapphunds. An animal's genetic variation could make breeds susceptible to the different types of diabetes mellitus. Meanwhile, breed, previous hyperadrenocorticism, and female sex were listed among the risk factors in the development of this disease. There are three types of DM: Type 1 DM or "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes" wherein the cause is unknown. The most common is Type 2 DM or "non-insulin-dependent diabetes mellitus'' (NIDDM) or "adult-onset diabetes" characterized by insulin resistance caused by excessive body weight and lack of exercise. Type 3 DM or "gestational diabetes" is acquired during pregnancy having hyperglycemia without a history of diabetes. Types 1 and 2 are the most common among animals (2). Treatment for DM includes medication, diet, and exercise. Hypoglycemic drugs such as insulin, biguanides, sulfonylureas, and alpha-glucosidase inhibitors can cause unpleasant side effects like severe hypoglycemia, abdominal discomfort, lactic acidosis, and more (3).

Alternative medications such as herbal plants can provide a rich source of bioactive chemicals that have antidiabetic activity, have fewer side effects, are low cost, and are more accessible, especially in rural areas. (4,5) regarded the bioactive compounds derived from natural resources as safe and cost-effective. *Cinnamomum* sp. (cinnamon) is a genus from the

* Correspondence : **Joseph Flores dela Cruz** jfdelacruz@up.edu.ph

ISSN 2621-9468 online, DOI 10.20956/canrea.v5i2.673

family *Lauraceae* first described in 1760 in which around 250 species can be found in tropical and subtropical regions, most of which are in Asia but also in South and Central America and Australia (6). It is known worldwide for its use as a spice and medicinal herb for various diseases. (7) stated that cinnamon is one of the most potent antidiabetic plants. There are 25 known species of *Cinnamomum* in the Philippines where 18 are endemic in the country. There are three commonly known species of cinnamon with economic importance: *Cinnamomum cebuense*, *C. mercado*, and *C. burmannii* (*C. mindanaense* Elmer) located mostly in Visayas and Mindanao. However, it is less explored, utilized, and distributed in the country. The Philippine Cinnamon has a promising prospect for it to become a sustainable forest-based livelihood through the utilization and processing of it into its different by-products where its bark, leaves, and fruits are commonly used (8). The review article aims to determine the in vitro and in vivo antidiabetic effects of *Cinnamomum* sp. plant extract in experimental rodent models. This review article will focus on type 2 diabetes mellitus experimental studies. This can open more opportunities for the conservation of Cinnamon in the country, additional therapy or medication for type 2 diabetes mellitus, and advancement in veterinary medicine soon.

2. Methods

This literature review is from different academic research papers. After collecting the articles, analyze each one by breaking it down and identifying the important information and then synthesize and identify the conclusions that can be drawn.

3. Results and Discussion

3.1. Background of Cinnamon

Cinnamomum (Cinnamon) is a genus from the family Lauraceae first described in 1760 together with the genus Laurus, and Persea. There are around 250 species (trees and shrubs) that can be found in the tropical and subtropical regions which are commonly found in Asia, and some in South and Central America and Australia. Genus *Cinnamomum* is said to be the most economically valuable among its family (6). It grows at various heights from highland slopes to lowland woods in tropical rain forests including swampy areas, and well-drained soils. They are extremely rare in latitudes with seasonal climatic conditions. This genus consists of small, evergreen trees and shrubs growing to a height of 10 to 15 meters. Different parts such as bark, leaves, fruits, and flowers can be utilized but the bark is frequently used as a spice (9).

Cinnamomum zeylanicum (Ceylon or true cinnamon) and *Cinnamomum aromaticum* (cassia) are the two main varieties of cinnamon that are extensively studied. *C. zeylanicum* is endemic in Sri Lanka and tropical Asia, and exotic in several African countries like Ghana, Madagascar, Mauritius, and Nigeria while *C. cassia* Blume is native to China, Indonesia, Vietnam, and African countries including Nigeria and Madagascar (10). Meanwhile, *C. verum*, also known for its medicinal and culinary properties, originated in Sri Lanka and southern India (11).

Cinnamon has been used in different culinary practices for thousands of years. It is a well-known ingredient in beverages, chocolates, and liquors. In some countries, the timber cinnamon is used for decoration, furniture, and construction (12). It is not only among the most used Chinese medicine in clinical practice but also a significant condiment and landscape plant (6). Various scientific literature suggested that it has been extensively used as a local

and traditional medicine for its anti-diabetic (7), antitumor (13), anti-inflammatory (14), antimicrobial (15), and other effects. (11) concluded that *Cinnamomum* sp. is extensively studied for its anti-diabetic potential followed by antimicrobial, antioxidant, anti-inflammatory, anti-cancer, and others. (7) also cited that it is one of the most potent antidiabetic plants.

3.2. Occurrence of Cinnamon in the Philippines

In the Philippines, there are 25 species of *Cinnamomum* sp. and 18 of them are endemic. There are three commonly known species of cinnamon with economic importance: *Cinnamomum cebuense, C. mercado*, and *C. burmannii* (*C. mindanaense* Elmer) located mostly in Visayas and Mindanao (8). (16) documented the in vitro antidiabetic activity of the aqueous bark extract of *C. burmannii*. Meanwhile, the bark of *C. cebuense Kosterm* found in Cebu, Philippines has been locally known for its use in stomach aches, and body pains and for its leaves for other diseases (17). There is still the need for additional research for the isolation of the specific compounds of *C. cebuense* and to be tested on higher animal models for a safer medication and approval of its other clinical applications. However, *C. cebuense* is endangered due to urbanization and agricultural encroachment. Its conservation and protection could result in a possible ecotourism destination in coordination with the local government unit and its communities (18). *C. burmannii* (*C. mindanaense* Elmer) or locally known as laurel leaves grows abundantly in Cebu, Philippines where 41% of its trees are harvested once or every other year. Further studies regarding this plant can potentially lead to its development in the country's market and possibly act as alternative medicine (19). With the increase of type-2 diabetes mellitus cases in animals, alternative medicines like *Cinnamomum* sp. as a supplement can help elevate its treatment plan.

3.3. In Vitro Anti-diabetic effects in Experimental Rodent Models

3.3.1. Effect of Cinnamon Extract on Glucose Uptake in Adipocytes, Myocytes, and Hepatocytes

Insulin is the main hormone that controls glucose absorption, especially in muscle and fat cells (20). Glucose transporter 4 (GLUT-4) is primarily expressed in skeletal muscle facilitating insulin-stimulated glucose uptake while adipose tissue is responsible for postprandial glucose. Insulin and muscle contraction can stimulate peripheral glucose uptake into muscle and fat cells via eliciting GLUT-4 translocation. Since patients with type 2 diabetes mellitus have impaired insulin response, GLUT-4 expression is dysregulated, and GLUT-4 translocation is significantly affected, resulting in insulin insensitivity in tissues that may lead to serious complications such as wound healing impairment, neuropathy, and nephropathy (21).

Cell culture is a powerful tool for addressing fundamental scientific and translational research problems which can be advantageous due to the homogeneity and related reproducibility of data generated from cell lines (22). 3T3-L1 adipocytes were used as one of the cell cultures for the assessment of the in vitro anti-diabetic studies effects of an herbal extract (6). C12C12 myocytes, a C3H mouse myoblast mouse cell line (23) were also one of the cell cultures used due to their expression of glucose transporter 4 (GLUT-4), an exhibition of glucose metabolism, insulin signaling mechanism, insulin resistance, glucose transporters at the cellular and molecular levels, and more (21). In addition, skeletal muscle is considered

an important therapeutic target for type 2 diabetes mellitus as it is a primary tissue for insulin-stimulated glucose uptake and disposal and has a huge role in energy balance (24).

The following in vitro studies showed the potential of the anti-diabetic effect of cinnamon extract in glucose uptake in cell cultures. (25)reported that AMP-activated protein kinase or AMPK plays a key role in energy metabolism regulation in metabolic diseases like diabetes mellitus. The activation of AMPK up-regulates glucose uptake by inducing GLUT-4 translocation to the plasma membrane (26). *Cinnamomum* sp. acts on diabetes through the modulation of PPAR- γ and AMPK, and via the regulation of endogenous ghrelin release. (27) showed that cinnamon extract treatment increased the phosphorylation of ACC (Ser79), an enzyme located downstream, and LKB1 which acts upstream of AMPK in 3T3-L1 adipocytes. The findings imply that the activation of the LKB1-AMPK-ACC signaling cascade by CE resulted in increased glucose uptake in cells. Hence, cinnamon extract alleviates type 2 diabetes mellitus by inducing GLUT4 translocation via the AMPK signaling pathway. (28) also reported a significant glucose uptake of cinnamon water extract in 3T3-L1 adipose cells. Adiponectin secretion of adipocytes was further examined. Adiponectin is an anti-diabetic hormone and adipocytokine is only secreted by adipose tissues. In a normal insulin treatment, adiponectin secretion was supposed to be stimulated. However, the cinnamon extract treatment from this study showed inhibition of all detectable adiponectin secretion. Hence, it was suggested that this specific form of CE treatment was not considered to have a complete insulin-mimetic activity. A possible cause may be due to the altered, inactivated, or unabsorbed components of CE durihe digestion. These findings regarding the effect of cinnamon extract on the secretion of adiponectin will require more investigation. It was then suggested that CE may limit adiponectin secretion through the same route that insulin utilizes to control adiponectin compartmental release or by acting on the peroxisome proliferator-activated receptor (PPAR)-γ. The findings from the study of (28) agree with (27) about the significant increase of glucose uptake in 3T3-L1 adipocytes induced by the cinnamon extract.

LKB1 is also known as a tumor suppressor that was found to have a significant role in the activation of an AMPK signaling pathway (29). C2C12 muscle cells were transiently transfected with LKB1 siRNA. The level of LKB1 mRNA and the CE-induced phosphorylation of LKB1 at its Ser428 were both reduced by around 60% and 40%, respectively. The findings from this study implied that the effect of CE on the signaling pathway was mediated by AMPK in LKB1-AMPK-dependent manner in C2C12 myotubes. Based on the findings above, it can be suggested that the stimulation of AMPK activity in adipocytes and myocytes, induces more GLUT4 translocation to the plasma membrane and eventually leads to more increased glucose uptake by natural compounds such as cinnamon. This can have a significant clinical impact on the management of type 2 diabetes mellitus.

Activation of PPAR-γ and AMPK are among the most important mechanisms of cinnamon in reducing metabolic syndrome complications like diabetes mellitus (30). PPARs (Peroxisome proliferator-activated receptors) are transcriptional factors that regulate insulin resistance and adipogenesis. The in vitro studies reported by (31) demonstrated that cinnamon extract acts as an activator to PPAR-γ based on three significant findings. First, the cinnamon extract was used to evaluate if this treatment can promote preadipocyte differentiation in a differentiation medium. Oil red O staining was used for its evaluation wherein results showed that the number and volume of adipocytes were increased indicating that cinnamon extract promoted 3T3-L1 preadipocyte differentiation. A pre-adipose to adipose-like conversion must be established as they progress from a rapidly increasing to a

confluent and contact-inhibited stage (32). Next is the increased mRNA levels of PPAR-γ observed as well as the increased expression of key genes up to a thousand folds including the glucose transporting protein 4 (GLUT4) during 3T3-L1 differentiation compared to untreated cells. Lastly, the cinnamon extract increased the transactivates of both full-length and ligand-binding domains (LBD) of PPAR-γ through reporter gene assays in a dose-dependent manner. The in vitro study by (31) supports the claim of (30) that one of the mechanisms of cinnamon in reducing metabolic complications was through activation of PPAR-γ which eventually resulted in improved resistance and reduced fasted glucose. With this, the cinnamon water extract can potentially act as an alternative activator of PPAR-γ in managing metabolic complications.

The first chalcone reported in cinnamon is methyl hydroxy chalcone polymer or MHCP. It is a type of polyphenol or flavonoid, and a water-soluble compound that cannot be found in spice oils sold as food additives (33). (34) reported that methyl hydroxy chalcone polymer, found in cinnamon, acts as an insulin-mimetic in 3T3-L1 adipocytes. The absorption of 2-deoxy D-[1,2-3 H] glucose was evaluated for uptake after the 60-minute time point. The authors indicated a possible lag phase in cellular response, as MHCP did not incorporate glucose above controls during its first 10 minutes in contrast to what was expected. (35) obtained the same findings regarding the insulin-mimetic activity of cinnamon. It was found that cinnamon possesses insulin-potentiating activity and glucose oxidation in rat epididymal fat cell assay.

An isolated compound from the hydro-alcoholic cinnamon extract of *Cinnamomum cassia*, cinnamic acid, was investigated by (36). The butanol fraction increased the glucose uptake by two-fold. Based on the dose-response curves presented in the study, cinnamic acid increased glucose absorption by L6 myotubes in a dose-dependent manner, with the highest glucose uptake occurring when cells were incubated with 1 ng/mL cinnamic acid. As stated by (37), rosiglitazone is a PPAR-γ agonist that has been found in mice to prevent TLSP-induced dendritic cell maturation and lessens the severity of skin lesions and scratching behaviour. It can be observed that rosiglitazone and cinnamic acid treatments in this study were nearly as effective as each other regarding the increased glucose uptake in L6 myotubes. However, further research is still needed in evaluating the mechanisms of action of both treatments. This can potentially open more opportunities with integrative medicine which combines conventional treatment with evidence-based complementary therapy.

Phosphoenolpyruvate carboxykinase or PEPCK is a crucial enzyme in gluconeogenesis as it converts oxaloacetate to phosphoenolpyruvate which is the initial step of gluconeogenesis. (38) stated that glucose-6-phosphatase or G6Pase plays a crucial role in glucose homeostasis by catalyzing the conversion of glucose-6-phosphate to glucose. Insulin is responsible for regulating PEPCK and G6Pase enzymes. However, one of the characterizations of type II diabetes mellitus is insulin resistance leading to a dysregulation of hepatic gluconeogenesis and an abnormal increase in blood glucose. The reduction of the enzymes was attributed to improved insulin resistance. (35) discovered that the aqueous extract of *Cinnamomum burmannii* and a cinnamon polyphenol-enriched defatted soy flour possess hypoglycemic and insulin-like effects by the suppression of the two major regulators of hepatic gluconeogenesis, PEPCK, and G6Pase resulting to the inhibition of hepatic glucose production. The H4IIE rat hepatoma cells (CRL-1548) were used in demonstrating the inhibition of hepatic glucose production and were treated with the aqueous extract of *Cinnamomum burmannii* (CE) bark and a cinnamon polyphenol-enriched defatted soy flour (CDSF). Eluates of CE and CDSF at a range of 1-25 µg/mL was added to the cell line. The dose of 25 µg /mL exhibited significant

levels of dose-dependent inhibition of hepatic glucose production from the eluates of CE and CDSF. H4IIE rat hepatoma cells were treated with Dex-cAMP to stimulate gluconeogenesis and expression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) genes. The suppression of the two major regulators of hepatic gluconeogenesis, PEPCK, and G6Pase led to the inhibition of hepatic glucose production significantly at 25 µg/mL and in a dose-dependent pattern at 10 and 25 µg /mL, respectively. Hence, resulted in decreased fasting blood glucose. To summarize, cinnamon was said to exhibit anti-diabetic effects in vitro such as hypoglycemic activity through the inhibition of PEPCK and G6pase leading to reduced hepatic glucose production.

Table 1. Anti-diabetic studies of Cinnamomum sp. in Experimental Rodent Animals.

Cinnamon / Isolated Compound used	Part of the Plant Used	Preparation	Main Anti-diabetic Results	Rodent Model/Cell culture Used)	Reference
C. zeylanicum	Bark	Hot-water extract	Glucose, insulin, and protein-bound sugars were brought back to near normal levels at a high dose	Adult male Albino rats (Wistar strain)	(39)
C. cassiae	Bark	Hot-water extract	Decreased blood glucose level in a dose-dependent manner, increased insulin level	Male C57BIKsj db/db mice	(40)
C. zeylanicum	Not reported	Aqueous extract	Insulin-mimetic action in the adipocytes (inhibition of adiponectin secretion & dose-dependent decrease in glucose uptake in the presence of 50 nM insulin)	3T3-L1 adipose cells	(28)
C. zeylanicum Blume / Cinnamaldehyde	Bark	Not reported	Decreased plasma glucose level in a dose-dependent manner, increased plasma insulin	Male Wistar strain rats	(41)
C. tamala	Leaf	Hot-water extract	Decreased fasting blood glucose level	Male Wistar Albino rats	(42)
C. burmaniii	Bark	Aqueous-ethanol extract	Dose-dependent inhibition of hepatic glucose production, decreased the gene expression of PEPCK & G6Pase	H4IIE rat hepatoma cells	(35)
Cinnamon polyphenol -enriched defatted soy flour (CDSF) from *C. burmaniii*	Bark	Derived from aqueous-ethanol extract	Dose-dependent inhibition of hepatic glucose production	H4IIE rat hepatoma cells	(35)
C. zeylanicum	Bark	Methanol extract	Lowering postprandial glucose	Male Albino Wistar rats	(43)
Cinnamon polyphenols	Not reported	Ethanolic extract	Down-regulation of blood glucose and serum insulin levels; Repaired pancreatic beta cells associated with the	Male mice	(44)

			reduction of iNOS, NF-κB expressions		
C. tamala extract & Cinnamaldehyde	Leaf	Oil	Reduced blood glucose level, increased plasma insulin level	Male Albino Wistar rats	(45)
C. verum	Bark	Aqueous extract	Reduction in the fasting blood glucose level	Male Albino rats	(46)
Commercial ground cinnamon	Not reported	Hot-water extract	Lowered the blood glucose level in a dose-dependent manner	Female and male adult Wistar rats	(47)
C. ceylanicum	Bark	Hot-water extract	Improved glucose intolerance and uptake; Increased glucose uptake on 3T3-L1 Adipocytes & C2C12 Myocytes	Male Otsuka Long-Evans Tokushima Fatty (OLETF) rat & Long-Evans Tokushima Otsuka (LETO); 3T3-L1 & C2C12 cells	(27)
Cinnamic acid (CA) & Cinnamaldehyde (CND)	Not reported	Not reported	CA: Lowered blood glucose level and improved glucose tolerance; CND: No significant effect	Wistar rats; Isolated pancreatic islets	(48)
Cinnamaldehyde derived from *C. zeylanicum*	Bark	Not reported	Enhanced insulin release	Pancreatic islets isolated from male Wistar rats	(49)
C. zeylanicum on	Bark	Powder	Decreased blood glucose level	Adult male Wistar Rats	(50)
C. zeylanicum	Bark	Aqueous-ethanol extract	Reduced blood glucose level in a dose-dependent manner	Female Albino rats	(51)

3.3.2. Effects of Cinnamon Extract on Insulin Secretion in Isolated Pancreatic Islets

In vitro studies on the effect of cinnamon extract on insulin secretion in isolated pancreatic islets were conducted to further exhibit if there is improved insulin sensitivity when there is a glucose-stimulated insulin secretion. The results from these studies showed promising potential as an anti-diabetic drug soon. Furthermore, (52) stated that having an increased insulin sensitivity will require less insulin that can have larger insulin effects in the regulation of blood glucose levels. (48) compared the effects of cinnamic acid and cinnamaldehyde isolated from *C. cassia* on the insulin secretion of isolated mice pancreatic islets. Cinnamic acid and cinnamaldehyde (50-200 µM) had little to no effect on insulin secretion at a basal glucose concentration (3 mM) whereas a stimulatory glucose concentration of 16.7 mM resulted in stimulated insulin secretion at 3.76 ± 0.35 ng/islet/hour. A higher concentration of cinnamic acid (100 µM) led to a more efficient insulin secretion at 6.06 ± 0.83 ng/islet/hour. This is comparable to tolbutamide (100 µM) resulting at 6.56 ± 0.82 ng/islet/hour. Meanwhile, no further stimulation at the concentration of 100 µM and above was observed. From these findings, it was suggested that cinnamic acid significantly enhanced glucose-stimulated insulin secretion in isolated mice islets in a concentration-dependent manner whereas cinnamaldehyde (50-200 µM) caused no significant insulin secretion. The

findings from (48) were in contrast with (49) regarding the effects of cinnamaldehyde on insulin secretion in isolated pancreatic islets.

According to (49), cinnamaldehyde (CND) isolated from *C. zeylanicum* directly acts on the pancreas and stimulates insulin release from in vitro incubation of pancreatic β islets. The pancreas was obtained from the anesthetized healthy animals. The insulinotropic effect of cinnamaldehyde was attributable to the increase in glucose uptake through glucose transporter (GLUT 4) translocation in the peripheral tissues. In summary, the high concentrations of cinnamic acid were better facilitate insulin secretion in islets and has the potential to stimulate insulin secretion in diabetic rats in a time and dose-dependent manner making it favorable for better diabetic control. It was suggested that extracts with high cinnamic acid levels are beneficial for better diabetic management. However, the findings obtained for cinnamaldehyde from the two studies were in contrast. Moreover, (48) mentioned that cinnamaldehyde was metabolized to cinnamic acid. It was found that cinnamaldehyde is partially metabolized to cinnamic acid in the stomach and small intestine almost entirely converted to cinnamic acid in the liver before being absorbed into the blood in rats. This may be one of the reasons for the different results for cinnamaldehyde and cinnamic acid, and possibly other environmental conditions during the experiment proper. Further research is still needed on the progress of this hypothesis.

3.4. In Vivo Anti-diabetic Activity in Experimental Rodent Models

3.4.1. Effects of Cinnamon Extract on Insulin Sensitivity and Serum Insulin Levels.

Insulin resistance is a crucial problem in type 2 diabetes mellitus, and insulin insufficiency may develop later (44). It is a condition in which insulin fails to respond adequately causing blood sugar levels to rise that will cause the pancreas to secrete large amounts of insulin in response to the high amount of blood glucose levels. With this. development of treatments for T2DM or treatment must be included in the objective and capability to increase insulin availability or counter insulin resistance. Insulin signaling is initiated by the binding of insulin to its insulin receptor (IR) leading to phosphorylation of numerous intracellular proteins including IRS-1. Insulin receptor substrate-1 (IRS1) is an insulin receptor tyrosine kinase substrate that plays a key role in the insulin-stimulated signaling cascade (53). This leads to the binding of IRS-1 to PI-3 kinase which is an important step for the translocation of GLUT-4 to the plasma membrane resulting in increased glucose uptake in response to insulin. (54) stated that expressions of IRS-1 were approximately reduced by about 50% in muscle and 29% in liver in ob/ob diabetic mice. Based on the findings of (55), cinnamon extract improved insulin sensitivity via upregulating the insulin receptor substrate1 (IRS1), p-85 regulatory subunit of PI3K (PI3K-P85), AKT2, and aortic nitric oxide synthase 3 (eNOS) while reduced the expression of NADPH oxidase 4 (NOX4) and optimized the elevated glucose level. (52) found out that cinnamon extract increases insulin-stimulated tyrosine phosphorylation of IR-β and IRS-1 association with PI 3-kinase.

According to (56), skeletal muscle is the primary target for insulin-stimulated glucose disposal. Also, around 70% of the insulin-stimulated glucose uptake during euglycemic clamp was said to be mainly credited to the glucose uptake in skeletal muscles. (52) reported that the oral administration of cinnamon extract can improve insulin sensitivity and responsiveness in peripheral tissues in a dose-dependent manner. Cinnamon extract was orally administered in awaked male Wistar rats using a two-step hyper-insulinemic euglycemic clamp to measure insulin sensitivity. Hyper-insulinemic euglycemic clamp

technique is the gold standard for measuring insulin sensitivity wherein it assesses the body's ability to absorb and metabolize glucose by measuring the rate of infused glucose (57). Cinnamon extract improves insulin action in skeletal muscle by increasing glucose uptake in vivo associated with the enhancement of the insulin-signaling pathway.

(58) stated that different species of cinnamon were found to have A or B-type procyanidin oligomer-rich CEx1–3 in vivo. (59) stated that trimeric and tetrameric Type A polyphenols potentially may have caused the beneficial effects of cinnamon extract such as altered body composition in relation to the improved sensitivity. The following studies support the claim that cinnamon polyphenols significantly alleviate insulin resistance in experimental rodent models. (59) used isolated polyphenols from *C. cassia*, to test its efficacy as an insulin sensitizer. Hence, the reduced infusion rates indicate the effectiveness of cinnamon in counteracting insulin resistance in the HF/HF diet-fed rats. Another study from (44) also examined the effect of cinnamon extract on insulin sensitivity using cinnamon polyphenols. Insulin resistance was triggered by feeding the diabetic mice with an HF/HF diet. Results showed that cinnamon polyphenols improved the insulin sensitivity index (ISI) by reducing insulin resistance, consequently alleviating diabetes syndrome by bringing insulin and blood glucose levels back to normal in streptozotocin-induced diabetic mice.

According to (58), the kind of cinnamon procyanidin oligomers is not the key indicator of the hypoglycemic activities of cinnamon. Another study using a high fructose diet in inducing diabetes in mice showed regulated insulin levels and improved insulin resistance but with the use of the cinnamon extract. (39) demonstrated the alleviated insulin resistance in high fructose-fed adult male albino rats using cinnamon bark extract (*C. zeylanicum*). The high levels of insulin because of fructose loading in the high fructose-fed rats were brought back to near-normal due to the high-dose cinnamon bark extract administration whereas the low-dose cinnamon extract did not incur a significant effect in the rats. Streptozotocin-induced diabetic rats were observed to have a significant decrease in plasma insulin which may be due to the administered streptozotocin in contrast to the high fructose and high-fat/ high-sugar diet-induced diabetes mellitus resulting in an increased insulin level (39,44). Induction of diabetes with streptozotocin causes a decrease in serum insulin due to the degeneration of beta cells (60). Meanwhile, a high fat or high fructose diet-induced diabetes in rodents induces insulin resistance and metabolic disturbances (61).

In studying insulin resistance, it can be suggested that a high sugar or high fructose diet-induced diabetes in experimental rodent animals may be more appropriate but will still need further research regarding this hypothesis. The following studies demonstrated the increased level of insulin as an effect of cinnamon extract in streptozotocin-induced diabetic rats. (41) administered cinnamaldehyde isolated from *C. zeylanicum* to streptozotocin-induced male diabetic Wistar rats. It was found that the oral administration of cinnamaldehyde resulted in a marked increase in plasma insulin levels simultaneous with the decrease in blood glucose level. The increase in the plasma insulin level can be associated with a decrease in blood glucose level. (45) obtained the same significant findings. The oral administration of *C. tamala* oil resulted in a significant increase in the plasma insulin levels in streptozotocin-induced diabetic mice. The essential oil was prepared using cinnamon leaves with a percentage yield of 0.45%.

3.4.2. Effects of Cinnamon Extract on Blood Glucose Level

One of the features of type 2 diabetes mellitus is the elevated blood glucose level due to the failure of the insulin receptors in working properly. The increased blood glucose concentration damages cells directly and causes liquid peroxidation (62). In vivo studies have been conducted to assess the potential hypoglycemic effects of cinnamon in diabetically induced experimental models. There are different mechanisms suggested for the hypoglycemic effects of cinnamon. One of these is the inhibition of glycogen synthase kinase 3, resulting in an increase in glucose uptake or decrease in blood glucose levels. Glycogen synthase kinase-3 (GSK-3) has two homologues that are widely expressed in mammals such as GSK-3 α and GSK-3 β. According to (63), GSK-3 has been a target for diabetes therapy due to functional partitioning of the enzyme, tissue selectivity, and acute dosage-dependency of effects of inhibition. GSK-3 is a serine protein kinase at the epicenter of the control of numerous cellular processes including glycogen metabolism, gene transcription, and more. The failure to inhibit GSK3 by insulin may contribute to the pathogenesis of type 2 diabetes mellitus because it is usually active in the basal state of cells.

According to (55) cinnamon enhances glucose uptake by inhibiting the enzyme glycogen synthase kinase-3 and increasing the expression of fatty acid metabolism UCP3 genes. Also, a reduction in the glucose concentration is caused by an increase in the amount of glucose transporter (GLUT4) and insulin receptors, as well as the activation of glycogen synthase. Polyphenols were also reported to contribute to the hypoglycemic properties of cinnamon. (64) studied the antidiabetic effects of polyphenol-rich extracts from *C. cassia* and found to effectively lower the blood glucose levels in streptozotocin-induced diabetic rats at 200 mg/kg body weight. In addition, the elimination of coumarin from the poplyphenol-rich extract was found to be safe and more effective with 3.4-fold enhancements in blood sugar reduction than the standard cinnamon extract at 200 mg/kg body weight for 30 days. *C. cassia* was found to possess significant levels of coumarin while it is negligible in *C. zeylanicum*. (65) mentioned that the high levels of coumarin content specifically in market samples were caused by the adulteration of *C. verum* with *C. cassia*. Furthermore, (64) stated that the enhanced efficacy of the de-coumarinated polyphenol-rich extract was associated with the presence of large amounts of water-soluble polyphenols with better bioavailability.

(44) also investigated the antidiabetic role of cinnamon polyphenols (CPS) and revealed a significantly reduced blood glucose level in both dimethyldiguanide and CPS in diabetic mice. (66) discussed how polyphenols can increase glucose uptake by increasing the glucose transporter 4 (GLUT 4). GLUT 4 has a key role in the uptake of glucose from the bloodstream and performs under the control of insulin. However, due to the insufficient sensitivity or absence of insulin caused by diabetes mellitus, GLUT 4 cannot be regulated resulting in an increase in glucose concentration in the blood or hyperglycemia. (25) mentioned that these polyphenols can potentially have a significant position in the anti-diabetic drug market. Furthermore, experiments and clinical trials have demonstrated that phenolic phytochemicals efficiently alleviate diabetes symptoms and can help prevent long-term consequences of diabetes.

The following studies have shown evidence in cinnamon extract significantly reducing blood glucose levels in vivo in alloxan-induced experimental diabetes. According to (64) and (67), Alloxan® is a urea derivative causing selective necrosis of the β-cells of pancreatic islets leading to the development of experimental diabetes. It has been one of the commonly used drugs for inducing experimental diabetes alongside streptozotocin in animals such as rats,

rabbits, mice, and dogs with different variations of doses for different grades of disease severity. Chemical induction with alloxan appears to be the most straightforward, reliable, and practical approach to inducing diabetes in rodents (68). (47) showed that the oral administration of cinnamon extract significantly decreased blood glucose levels. The results obtained agree with the study conducted by (50) investigated the effects of cinnamon (*C. zeylanicumon*) powder supplementation on glucose levels in alloxan-induced diabetic Wistar rats. Results showed that cinnamon was effective in preventing the increase in blood glucose levels. A single subcutaneous alloxan injection (15 mg/kg) was used to induce diabetes in the animals. (46) examined the effects of increasing doses of the aqueous extract of *C. verum* on fasting plasma glycemic profiles in alloxan-diabetic male rats. Results showed that the lowest dose of cinnamon extract i.e. 200 mg/kg was the most efficient in significantly ($P < 0.05$) reducing the fasting blood glucose in the animals. Moreover, the authors observed significant improvements in the hypoglycemic activities of the extract associated with improvements in body weight gain, food intake, and food efficiency ratio. It can be suggested that cinnamon extract regulates glycemic profiles in alloxan-induced diabetic rats. Cinnamon extract was shown to have great potential in the treatment of diabetes when used in conjunction with conventional treatment plans. However, further research is needed to ascertain the biological activity of the cinnamon extract.

Another drug used for the induction of diabetes was streptozotocin (STZ), a synthetic antineoplastic agent which is also used as an anti-tumor antibiotic. It causes a type of diabetes similar to diabetes mellitus with non-ketosis hyperglycemia in some animal species. Induction of diabetes was probably achieved by decreasing the nicotinamide-adenine dinucleotide (NAD) in pancreas islet beta cells leading to histopathological effects in beta cells (60) The following study exhibits the anti-diabetic activity of the cinnamon extract in lowering the blood glucose level in the streptozotocin-induced rodent model. (20) examined the anti-diabetic effects of the hydroalcoholic extract of green tea and cinnamon, individually and in combination, on streptozotocin-induced diabetic rats. The use of the cinnamon extract showed significant improvements in the blood glucose level. Cinnamon extract with green tea showed the most appropriate synergistic effect. The synergistic effect reported with the combination of green tea and cinnamon extract is a good indicator for more potential therapeutic treatments in the future. However, further research is still needed on the synergistic activities of the plant extracts with each other.

(11) elaborated that one of the reasons for the anti-diabetic function of cinnamon was due to cinnamaldehyde's structure. It has an aldehydic (-CHO) functional group that can donate hydrogen atoms to the free radicals preventing oxidative stress. Cinnamaldehyde consists of metal chelating power leading to activation of more signalling pathways wherein each pathway is involved in combating more than one disorder. The common signalling pathway previously explained, and its functional group is the reason for its broad spectrum of pharmacological antidiabetic activities. (41) orally administered cinnamaldehyde (20 mg/kg body weight) which was extracted using a bioassay-guided separation from *C. zeylanicum* in streptozotocin-induced male diabetic rat to determine its anti-diabetic effects in different doses (5, 10, and 20 mg/kg body weight) for 45 days. The plasma glucose concentration was significantly ($P < 0.05$) decreased using cinnamaldehyde in a dose-dependent manner compared to the control with a percentage of 63.29%. However, the results obtained above contradict the study conducted by (48). The authors examined the acute effects of cinnamaldehyde, cinnamic acid, and glibenclamide in blood glucose, and

glucose tolerance through non-obese type 2 streptozotocin-induced diabetic rats (90 mg/kg). The administration of cinnamaldehyde did not have a significant effect on blood glucose and glucose tolerance in this study. Cinnamic acid significantly decreased the blood glucose level in a time- and dose-dependent manner while glibenclamide efficiently lowered it at 5 mg/kg. Glibenclamide is an oral hypoglycemic drug used to manage type 2 diabetes mellitus (69).

(70) studied the transformation of cinnamaldehyde in rat stomach, intestine, and liver after oral administration using Ramulus cinnamomi (RC), the dry twig of *C. cassia* Presl. It was found that cinnamaldehyde is partially metabolized to cinnamic acid in the stomach and small intestine, and it is almost entirely converted to cinnamic acid in the liver before being absorbed into the blood in rats. It was also suggested that cinnamic acid may be an effective component in intragastric gavage administration. However, further research is still needed based on the progress made. (48) concluded that cinnamic acid is responsible for the hypoglycemic effect and improved glucose tolerance of cinnamon extract in a dose-dependent manner in type 2 diabetic rats. Additionally, similarities between cinnamic acid and glibenclamide in its effect on blood glucose levels were observed. It is suggested that both treatments may have the same mode of action, probably mediated through the enhancement of insulin secretion.

3.5. Chemical Composition of Cinnamon extract

The main components of Cinnamomum sp. are cinnamaldehyde, cinnamic acid, procyanidins, tannins, mucilage, cinnamate, numerous essential oils, and small amounts of coumarin (71). The following components of cinnamon will be discussed individually including some of its features. Cinnamaldehyde is a principal phytoconstituent of cinnamon which is responsible for almost all its pharmacological activities. It is primarily responsible for imparting flavor, aroma, and taste to products (88). (E)-cinnamaldehyde, the parent of the class of cinnamaldehyde functions as a hypoglycemic agent (National Center for Biotechnology Information, 2022). (41) stated that cinnamaldehyde exhibits hypoglycemic activities in streptozotocin-induced diabetic mice in a dose-dependent manner.

Cinnamic acid (3-phenyl-2-propenoic acid) is a major component of C*. cassia* found in a variety of fruits, vegetables, and drinks (72). It is also known as an antioxidant phytochemical in ameliorating effects on diabetic complications and reducing hyperglycemia (73). A high concentration of cinnamic acid found in cinnamon supplementations can potentially result in better diabetic control in experimental rat models such as decreased blood glucose level, improved glucose tolerance, and enhanced insulin secretion given in a time and dose-dependent manner (74).

Procyanidins are the most abundant type of proanthocyanidins in plants (96). Polyphenols, specifically proanthocyanidin polymers, are large groups of phytochemicals. Based on the research done by (74), C*. zeylanicum* Sri Wijaya had the highest proanthocyanidin content (PC), and total phenolic content (TPC) through decoction water extraction. A more potent anti-diabetic effect can be correlated with a higher amount of PC, and TPC. Cinnamon bark samples from C*. cassia* presl. tree was found to be rich in B-type procyanidin polymers while *C. japonicum* Sieb tree was rich in A-type trimer procyanidin oligomers through high-performance liquid chromatography (55). Procyanidin C1, a B-type proanthocyanidin epicatechin trimer (75), is a potential insulin enhancer in glucose absorption via the AKT-eNOS-NO pathway that was detected in *C. cassia* through their previous work. The major procyanidin oligomers found in the ethanolic and aqueous extracts

of *Cinnamomum burmannii* Blume, *C. cassia* Blume, and *C. loureirii* Nees were doubly linked type- A structure that enhances insulin activity (33).

Coumarin (benzo-α-pyrone) is a naturally occurring substance found in a range of plants with pleasant flavors such as tonka bean, vanilla, citrus fruits, and green tea, although cinnamon is the most common source of coumarin in the human diet. Results showed that there is a presence of high coumarin content from *C. cassia* with mean levels ranging from 2 650 to 7 017 mg · kg−1. Meanwhile, the samples received from Sri Lanka were coumarin-free (76). *C. cassia* raised concerns globally as it was reported as a hepatotoxic chemical in animal trials due to the presence of this substance. Although reported to cause these adverse effects, it was found to be rare in human clinical studies, only occurring at a high dosage, and long durations. It was stated that *C. cassia* contains up to 1% coumarin while *C. verum* only have trace amounts i.e., 0.004%. Furthermore, it was found that the high coumarin content of cinnamon in market samples was due to the adulteration of *C. verum* with *C. cassia* (65). This supports the findings of the study conducted by (76). Also, there is a higher variation in coumarin content found in the leaves of cinnamon than in barks because coumarin is produced in the leaf and then transported to the bark via the phloem (77).

(74) reported that the yield of extracts depends on the cinnamon accessions and extraction methods. Based on the authors' study, the highest yield was obtained from *C. zeylanicum* Sri Wijaya (SW) in the pressurized water extraction method. Meanwhile, microwave digestion received the lowest yield. Pressured water and decoction were seen to be viable extraction methods for the antidiabetic constituents of cinnamon. (77) stated that pressurized water extraction can extract polar compounds making it more advantageous as it results in better biological activity. (74) added that the use of pressurized water is a more environmentally friendly and non-toxic method because of the absence of organic solvents. However, steam distillation or hydro-distillation is the most often used method for extracting cinnamon. Steam distillation has several disadvantages, including the loss of volatile chemicals and extended extraction periods. (78) also stated that the concentration level of these compounds depends according to a variety of factors consequently influencing the functional properties of cinnamon, including species, tree section, development stage, and extraction method. Additionally, the percentages of each compound are dependent on the solvents used throughout the extraction procedure. It was also observed that cinnamon bark is a commonly used component not just in food flavorings, but also in the anti-diabetic experimental trials of cinnamon. Table 1 shows some of the summarized anti-diabetic studies for the comparison of the cinnamon anti-diabetic studies in rodent models. Cinnamon is usually distinguished by its brown bark from its tree, which is known as quill when rolled into a tubular shape (79). Its bark contains 90% cinnamaldehyde in its essential oil (78). Cinnamaldehyde and cinnamyl acetate are among the oils found in the bark of the cinnamon trunk, which range from 5% to 75% (80). These are the major compounds known for cinnamon's antidiabetic properties (81). According to (82) the following factors positively correlate with the yield of cinnamon essential oils namely, cinnamon species, climate, growth condition, cultivation site, age of the bark, thickness of the bark, and the density of the oil cells. However, (74) emphasized the importance of further investigation to evaluate the properties of the cinnamon bark accessions that will help in assessing the yield of cinnamon and biological activity, including the development of new methods of extraction methods.

The following studies show the different chemical components of the common species of cinnamon that may be attributed to its anti-diabetic activity. *Cinnamomum verum* contains

different classes of compounds in its essential oils such as monoterpenes, diterpenes, sesquiterpenes, oxygenated hydrocarbons, polyphenols, and more (83). With the use of Gas Chromatography-Mass Spectrometry (GC–MS), it revealed that (E)-cinnamaldehyde was the predominant compound, other components include eugenol, (E)-caryophyllene, (E)-cinnamyl acetate, and αhumulene as the five major compounds (84). The cinnamon bark from *C. verum* essential oil was also analyzed using GC/MS analysis. The gas Chromatography-Mass Spectrometry (GC-MS) technique is known for its high separation efficiency and sensitive detection of volatile compounds (82). The same findings were observed as cinnamaldehyde was also its major constituent (92.06 %) while the minor constituents were 4-Methoxycinnamaldehyde (3.26%), δCadinene (1.61%), α-Copaene (0.86%), and α-Muurolene (0.68%) (55). According to (42), the primary compound of *C. verum* leaf essential oil is eugenol. (20) measured the total flavonoid content in the extract of *C. verum* bark having 8.27 µg of quercetin in each mg extract.

(50) conducted a qualitative phytochemical screening of dried barks of cinnamon (*C. zeylanicumon*) bought from the Tunisian local market, then botanically identified. The screening was carried out based on standard methods from previous studies (85–87). This examination showed the presence of alkaloids, coumarins, flavonoids, saponins, carbohydrates, steroids, tannins, and phenols. There were no proteins, and glycosides detected. Various extraction methods were conducted by (74) for the identification of the chemical constituents of novel varieties of aqueous extracts of two new Cinnamomum zeylanicum accessions namely, *C. zeylanicum* Sri Wijaya (SW), *C. zeylanicum* Sri Gemunu (SG) and commercially available *C. zeylanicum* (CC). This method includes Microwave Digestion (MD), Pressurized Water Extraction (PWE), Steam Distillation (SD), Solvent Extraction (SE), Decoction Water Extraction (DWE), and Infusion Water Extraction (IWE). GC-MS technique was used for the phytochemical screening. The major compounds identified in SW and SG extracts were benzoic acid, cinnamyl alcohol, benzyl alcohol, trans-cinnamic acid, and 4-Allyl-2,6-dimethoxyphenol which were believed to be responsible for the strong enzyme inhibitory activity of the extracts. Also, this study reported the detection of twenty-seven chemical components for the first-time using the SW method including 4-Allyl-2,6-dimethoxyphenol in any cinnamon accessions.

Cinnamomum zeylanicum Blume bark volatile oil's main component is cinnamaldehyde. Other major components include cinnamic acid, procyanidins, tannins, mucilage, cinnamate, numerous essential oils, and small amounts of coumarin by GC and GC-Ms analysis. Meanwhile, eugenol was the main component of leaf essential oil (88). (45) also used GC-MS analysis in screening the phytochemical components of *C. tamala* essential oil which led to the identification and quantification of 31 components that accounted for 99.99% of the total oil. Cinnamaldehyde (44.898%), Trans cinnamyl acetate (25.327%), Ascabin (15.249%), Hydro cinnamyl acetate (3.384%), and Beta-caryophyllene (2.669%) were the chemical composition of the oil. (89) investigated the chemical constituents of *Cinnamomum cebuense Kostern*. It is a narrow endemic and critically endangered tree among the 16 species found in the Philippines. The isolation and structure elucidation of dichloromethane (DCM) extract of the air-dried bark was reported to contain the following: monoterpene, sesquiterpene, 4-hydroxy-3-methoxycinnamaldehyde, 4-allyl-2-methoxy phenol, α- terpineol and humulene. Meanwhile, its leaves yielded the following: β-caryophyllene, squalene, and a mixture of α-amyrin, β-amyrin, and bauerenol.

3.6. Toxicity studies of Cinnamon extract in Experimental Rodent Models

According to (90), large doses or prolonged ingestion of cinnamon powder may result in an increased dose of oil components causing adverse effects such as inflammation and hyperkeratosis. The median lethal dose (LD50) is a measurement of a chemical's immediate or acute toxicity in a particular animal species. The primary idea behind this experiment is to force-feed healthy animals enough medication to kill about 50% of them. The LD50 test is designed to determine at what dose a drug causes side effects if any, and at what dose 50% of the animals will be killed (49). Acute toxicity and cell viability studies were published to know the safe levels and possible cytotoxicity of cinnamon medication. *C. tamala* oil (CTO) was found to be non-lethal even up to a high dose of 1000 mg/kg. (14) conducted an acute toxicity study regarding CTO in healthy adult albino Wistar rats. It was found that oral administration of a graded dose of CTO to rats was determined to be non-lethal up to a dose of 1000 mg/kg body weight while a dose of 2000 mg/kg body weight resulted in 50% motility.

(41) performed a separate experiment to determine if the compound, cinnamaldehyde extract has any harmful effects on the liver and kidney. The acute toxicity study revealed that the oral administration of oral doses of cinnamaldehyde produced a median lethal dose of 1850±37 mg/kg body weight and was deemed harmless in mammals. (48) also determined the median lethal dose of cinnamaldehyde isolated from C. *zeylanicum* in male Wistar rats. Results showed that there were no behavioral signs observed on the administration of 5, 10, and 20 times of ED of cinnamaldehyde. Food consumption was also normal with all the doses. The values of the liver and kidney function tests remained in the normal range throughout the study. However, a slight but significant increase was observed in the values of SGOT, SGPT, and ALKP values for the 20 times of ED but returned to its initial values within 120 hours. Furthermore, even at 20 times (0.4 g/kg bw) the effective dose of CND, the median lethal dose (LD50) could not be reached. With this, the findings discussed above reveal that cinnamaldehyde was considered safe for animals and can be developed as a potential therapeutic candidate for the treatment of diabetes due to its high margin of safety.

For the in vitro studies, cell viability assays were performed by (34) to make sure that the aqueous cinnamon extract at a concentration ranging from 1–25 µg/mL was not cytotoxic to H4IIE rat hepatoma cells. It was then found that there was no cytotoxicity with the use of the cinnamon extract treatment. Furthermore, (26) mentioned that there was no cytotoxicity towards 3T3-L1 adipocytes through MTT assay with the concentrations of cinnamon extract (30 µg/mL) but the data were not shown. The MTT assay or 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide is a quantitative and sensitive detection of cell proliferation by measuring cell growth rate (87). According to (88), it is the gold standard for cytotoxicity testing. It is performed to determine the viability of nanoparticle-treated cells. MTT is a yellow dye that is degraded to the blue product formazan by cellular enzymes (89). The main disadvantage of the MTT assay is that the conversion to formazan crystals in the MTT experiment is dependent on metabolic rate and mitochondrial number, resulting in many known interferences (90).

4. Conclusions

In vitro studies demonstrated an enhanced glucose uptake in adipocytes and myocytes through the stimulation of AMPK activity and upregulation of GLUT-4 translocation. Also, the cinnamon extract increased glucose uptake in hepatocytes through the inhibition of the two major regulators of hepatic gluconeogenesis, namely phosphoenolpyruvate carboxykinase

(PEPCK) and glucose-6-phosphatase (G6Pase). Insulin sensitivity was improved in vivo by upregulating the expression of insulin receptor kinases while suppressing the dephosphorylation of insulin receptors. Cinnamon extract effectively lowered blood glucose levels by increasing GLUT-4 transporters. The active compounds of cinnamon extract prove to possess anti-diabetic activities such as cinnamaldehyde, polyphenols, cinnamic acid, and many more. Additionally, the yield of the extract depends on the cinnamon accessions and extraction methods. Cinnamon has a high margin of safety based on the toxicity studies discussed. The findings from the various studies show encouraging results on the use of cinnamon extract as an alternate or supplement treatment for type 2 diabetes mellitus in rodent models. The combination of plant extracts for the better potential treatment of type 2 diabetes mellitus. The combination of synthetic drugs and cinnamon as a treatment can also be investigated in the future to know if cinnamon extract can potentiate the effects of the drug and can lessen adverse effects, especially in long-term diabetic treatment. The efficacy of cinnamon extract as an anti-diabetic agent in type 1 diabetes mellitus experimental rodent animal studies should also be explored more.

Author Contributions

A.M.A.N analyzed the data. A.M.A.N, J.F.C and L.P wrote the paper.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Data Availability Statement

Available data are presented in the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Fall T, Hamlin HH, Hedhammar Å, Kämpe O, Egenvall A. Diabetes mellitus in a population of 180,000 insured dogs: incidence, survival, and breed distribution. J Vet Intern Med. 2007;21(6):1209–16.
2. Kaoud H. Diabetes in Animals Facts and Explanations. Creat Indep Publ Platf. 2017;
3. Ghorbani A. Best herbs for managing diabetes: a review of clinical studies. Brazilian J Pharm Sci. 2013;49:413–22.
4. Salehi B, Ata A, V. Anil Kumar N, Sharopov F, Ramirez-Alarcon K, Ruiz-Ortega A, et al. Antidiabetic potential of medicinal plants and their active components. Biomolecules. 2019;9(10):551.
5. PR A, K. J. Pharmacological evaluation of herbal extracts for their in vitro hypoglycemic activity. Int J Pharma Bio Sci. 2011;2(3):408–16.
6. Wang J, Su B, Jiang H, Cui N, Yu Z, Yang Y, et al. Traditional uses, phytochemistry and pharmacological activities of the genus Cinnamomum (Lauraceae): A review.

Fitoterapia. 2020;146:104675.
7. Gulcin I, Kaya R, Goren AC, Akincioglu H, Topal M, Bingol Z, et al. Anticholinergic, antidiabetic and antioxidant activities of cinnamon (Cinnamomum verum) bark extracts: polyphenol contents analysis by LC-MS/MS. Int J Food Prop. 2019;22(1):1511–26.
8. FB S. Philippine Cinnamon: Important Lesser-Known Forest Resource. Foresh foundation philiphines. 2017.
9. Kuete V. Medicinal spices and vegetables from Africa: therapeutic potential against metabolic, inflammatory, infectious and systemic diseases. Academic Press; 2017.
10. Kuete V. Other health benefits of African medicinal spices and vegetables. In: Medicinal spices and vegetables from Africa. Elsevier; 2017. p. 329–49.
11. Singh N, Rao AS, Nandal A, Kumar S, Yadav SS, Ganaie SA, et al. Phytochemical and pharmacological review of Cinnamomum verum J. Presl-a versatile spice used in food and nutrition. Food Chem. 2021;338:127773.
12. Kumar S, Kumari R, Mishra S. Pharmacological properties and their medicinal uses of Cinnamomum: A review. J Pharm Pharmacol. 2019;71(12):1735–61.
13. Sadeghi S, Davoodvandi A, Pourhanifeh MH, Sharifi N, ArefNezhad R, Sahebnasagh R, et al. Anti-cancer effects of cinnamon: Insights into its apoptosis effects. Eur J Med Chem. 2019;178:131–40.
14. Lee S-C, Wang S-Y, Li C-C, Liu C-T. Anti-inflammatory effect of cinnamaldehyde and linalool from the leaf essential oil of Cinnamomum osmophloeum Kanehira in endotoxin-induced mice. J food drug Anal. 2018;26(1):211–20.
15. Kačániová M, Galovičová L, Valková V, Tvrdá E, Terentjeva M, Žiarovská J, et al. Antimicrobial and antioxidant activities of Cinnamomum cassia essential oil and its application in food preservation. Open Chem. 2021;19(1):214–27.
16. Ervina M, Lie HS, Diva J, Tewfik S, Tewfik I. Optimization of water extract of Cinnamomum burmannii bark to ascertain its in vitro antidiabetic and antioxidant activities. Biocatal Agric Biotechnol. 2019;19:101152.
17. Lillo E, BUOT JR IE, Malaki AB, Alcazar SMT, Rosales R, Diaz JLB, et al. Leaf architectural characteristics of Cinnamomum cebuense Kosterm.(Lauraceae) distributed in different geographical locations, taxonomic identification and conservation concerns. Biodiversitas J Biol Divers. 2020;21(1).
18. Alimpoos MR, Baguio J, Sabal S, Ursal SM, Picardal JP. Toxicity Evaluation and Anthelminthic Property of Cebu Cinnamon (Cinnamomum cebuense Kosterm.) Leaf Extracts. Recoletos Multidiscip Res J. 2019;7(1):47–61.
19. Alburo HM, Alburo RP, Gabucan MF, Albiso C. Distribution, mapping, sustainable harvesting and marketing of laurel leaves (Cinnamomum mindanaese) in Boljoon, Cebu, Philippines. Ann Trop Res. 2018;40(1):89–99.
20. Shokri G, Fathi H, Jafari Sabet M, Nasri Nasrabadi N, Ataee R. Evaluation of anti-diabetic effects of hydroalcoholic extract of green tea and cinnamon on streptozotocin-induced diabetic rats. Pharm Biomed Res. 2015;1(2):20–9.
21. Wong CY, Al-Salami H, Dass CR. C2C12 cell model: its role in understanding of insulin resistance at the molecular level and pharmaceutical development at the preclinical stage. J Pharm Pharmacol. 2020;72(12):1667–93.
22. Segeritz C-P, Vallier L. Cell culture: Growing cells as model systems in vitro. In: Basic science methods for clinical researchers. Elsevier; 2017. p. 151–72.

23. Jakovljevic NK, Pavlovic K, Zujovic T, Kravic-Stevovic T, Jotic A, Markovic I, et al. In vitro models of insulin resistance: Mitochondrial coupling is differently affected in liver and muscle cells. Mitochondrion. 2021;61:165–73.
24. Smith AG, Muscat GEO. Skeletal muscle and nuclear hormone receptors: implications for cardiovascular and metabolic disease. Int J Biochem Cell Biol. 2005;37(10):2047–63.
25. Momtaz S, Salek-Maghsoudi A, Abdolghaffari AH, Jasemi E, Rezazadeh S, Hassani S, et al. Polyphenols targeting diabetes via the AMP-activated protein kinase pathway; future approach to drug discovery. Crit Rev Clin Lab Sci. 2019;56(7):472–92.
26. Russell III RR, Bergeron R, Shulman GI, Young LH. Translocation of myocardial GLUT-4 and increased glucose uptake through activation of AMPK by AICAR. Am J Physiol Circ Physiol. 1999;277(2):H643–9.
27. Shen Y, Honma N, Kobayashi K, Jia LN, Hosono T, Shindo K, et al. Cinnamon extract enhances glucose uptake in 3T3-L1 adipocytes and C2C12 myocytes by inducing LKB1-AMP-activated protein kinase signaling. PLoS One. 2014;9(2):e87894.
28. Roffey B, Atwal A, Kubow S. Cinnamon water extracts increase glucose uptake but inhibit adiponectin secretion in 3T3-L1 adipose cells. Mol Nutr Food Res. 2006;50(8):739–45.
29. Shaw RJ, Kosmatka M, Bardeesy N, Hurley RL, Witters LA, DePinho RA, et al. The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress. Proc Natl Acad Sci. 2004;101(10):3329–35.
30. Mollazadeh H, Hosseinzadeh H. Cinnamon effects on metabolic syndrome: a review based on its mechanisms. Iran J Basic Med Sci. 2016;19(12):1258.
31. Sheng X, Zhang Y, Gong Z, Huang C, Zang YQ. Improved insulin resistance and lipid metabolism by cinnamon extract through activation of peroxisome proliferator-activated receptors. PPAR Res. 2008;2008.
32. Gual P, Gonzalez T, Gremeaux T, Le Marchand-Brustel Y, Tanti J. Osmotic regulation of cellular glucose uptake. In: Methods in enzymology. Elsevier; 2007. p. 343–54.
33. Anderson RA, Broadhurst CL, Polansky MM, Schmidt WF, Khan A, Flanagan VP, et al. Isolation and characterization of polyphenol type-A polymers from cinnamon with insulin-like biological activity. J Agric Food Chem. 2004;52(1):65–70.
34. Jarvill-Taylor KJ, Anderson RA, Graves DJ. A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. J Am Coll Nutr. 2001;20(4):327–36.
35. Cheng DM, Kuhn P, Poulev A, Rojo LE, Lila MA, Raskin I. In vivo and in vitro antidiabetic effects of aqueous cinnamon extract and cinnamon polyphenol-enhanced food matrix. Food Chem. 2012;135(4):2994–3002.
36. Lakshmi BS, Sujatha S, Anand S, Sangeetha KN, Narayanan RB, Katiyar C, et al. Cinnamic acid, from the bark of Cinnamomum cassia, regulates glucose transport via activation of GLUT4 on L6 myotubes in a phosphatidylinositol 3-kinase-independent manner. J Diabetes. 2009;1(2):99–106.
37. GR L, DE L, VY S. Emerging Targeted Treatments. Atopic Dermat Insid Out Or Outs. 2022;237–51.
38. Hutton JC, O'Brien RM. Glucose-6-phosphatase catalytic subunit gene family. J Biol Chem. 2009;284(43):29241–5.
39. Kannappan S, Jayaraman T, Rajasekar P, Ravichandran MK, Anuradha C V. Cinnamon

bark extract improves glucose metabolism and lipid profile in the fructose-fed rat. Singapore Med J. 2006;47(10):858.
40. Kim SH, Hyun SH, Choung SY. Anti-diabetic effect of cinnamon extract on blood glucose in db/db mice. J Ethnopharmacol. 2006;104(1–2):119–23.
41. SubashBabu P, Prabuseenivasan P, Ignacimuthu S. Cinnamaldehyde-A potential antidiabetic agent. Phytomed14, 15-22. 2007.
42. Chakraborty U, Das H. Antidiabetic and antioxidant activities of Cinnamomum tamala leaf extracts in STZ-treated diabetic rats. Glob J Biotechnol Biochem. 2010;5(1):12–8.
43. Mohamed Sham Shihabudeen H, D Priscilla H, Thirumurugan K. Cinnamon extract inhibits α-glucosidase activity and dampens postprandial glucose excursion in diabetic rats. Nutr Metab (Lond). 2011;8(1):1–11.
44. Li R, Liang T, Xu L, Li Y, Zhang S, Duan X. Protective effect of cinnamon polyphenols against STZ-diabetic mice fed high-sugar, high-fat diet and its underlying mechanism. Food Chem Toxicol. 2013;51:419–25.
45. Kumar S, Vasudeva N, Sharma S. GC-MS analysis and screening of antidiabetic, antioxidant and hypolipidemic potential of Cinnamomum tamala oil in streptozotocin induced diabetes mellitus in rats. Cardiovasc Diabetol. 2012;11(1):1–11.
46. El-Desoky GE, Aboul-Soud MAM, Al-Numair KS. Antidiabetic and hypolipidemic effects of Ceylon cinnamon (Cinnamomum verum) in alloxan-diabetic rats. J Med plants Res. 2012;6(9):1685–91.
47. Kumar SS, Mukkadan JK. Anti diabetic effect of oral administration of cinnamon in wistar albino rats. Bali Med J. 2013;2(3):97–9.
48. Hafizur RM, Hameed A, Shukrana M, Raza SA, Chishti S, Kabir N, et al. Cinnamic acid exerts anti-diabetic activity by improving glucose tolerance in vivo and by stimulating insulin secretion in vitro. Phytomedicine. 2015;22(2):297–300.
49. Anand P, Murali KY, Tandon V, Murthy PS, Chandra R. Insulinotropic effect of cinnamaldehyde on transcriptional regulation of pyruvate kinase, phosphoenolpyruvate carboxykinase, and GLUT4 translocation in experimental diabetic rats. Chem Biol Interact. 2010;186(1):72–81.
50. Beji RS, Khemir S, Wannes WA, Ayari K, Ksouri R. Antidiabetic, antihyperlipidemic and antioxidant influences of the spice cinnamon (Cinnamomum zeylanicumon) in experimental rats. Brazilian J Pharm Sci. 2018;54.
51. Qureshi AS, Ghaffor J, Usman M, Ehsan N, Umar Z, Sarfraz A. Effect of ethanolic preparations of cinnamon (Cinnamomum zeylanicum) extract on hematologic and histometric parameters of selected organs in Alloxan® induced diabetic female albino rats. J Diabetes Metab Disord. 2019;18(2):505–12.
52. Qin B, Nagasaki M, Ren M, Bajotto G, Oshida Y, Sato Y. Cinnamon extract (traditional herb) potentiates in vivo insulin-regulated glucose utilization via enhancing insulin signaling in rats. Diabetes Res Clin Pract. 2003;62(3):139–48.
53. Shaw LM. The insulin receptor substrate (IRS) proteins: at the intersection of metabolism and cancer. Cell cycle. 2011;10(11):1750–6.
54. Kerouz NJ, Hörsch D, Pons S, Kahn CR. Differential regulation of insulin receptor substrates-1 and-2 (IRS-1 and IRS-2) and phosphatidylinositol 3-kinase isoforms in liver and muscle of the obese diabetic (ob/ob) mouse. J Clin Invest. 1997;100(12):3164–72.
55. Zare R, Nadjarzadeh A, Zarshenas MM, Shams M, Heydari M. Efficacy of cinnamon in patients with type II diabetes mellitus: A randomized controlled clinical trial. Clin Nutr.

2019;38(2):549–56.
56. Deshmukh AS. Insulin-stimulated glucose uptake in healthy and insulin-resistant skeletal muscle. Horm Mol Biol Clin Investig. 2016;26(1):13–24.
57. Halama A, Suleiman NN, Kulinski M, Bettahi I, Hassoun S, Alkasem M, et al. The metabolic footprint of compromised insulin sensitivity under fasting and hyperinsulinemic-euglycemic clamp conditions in an Arab population. Sci Rep. 2020;10(1):1–12.
58. Lu Z, Jia Q, Wang R, Wu X, Wu Y, Huang C, et al. Hypoglycemic activities of A-and B-type procyanidin oligomer-rich extracts from different Cinnamon barks. Phytomedicine. 2011;18(4):298–302.
59. Couturier K, Batandier C, Awada M, Hininger-Favier I, Canini F, Anderson RA, et al. Cinnamon improves insulin sensitivity and alters the body composition in an animal model of the metabolic syndrome. Arch Biochem Biophys. 2010;501(1):158–61.
60. Akbarzadeh A, Norouzian D, Mehrabi MR, Jamshidi SH, Farhangi A, Verdi AA, et al. Induction of diabetes by streptozotocin in rats. Indian J Clin Biochem. 2007;22(2):60–4.
61. Softic S, Stanhope KL, Boucher J, Divanovic S, Lanaspa MA, Johnson RJ, et al. Fructose and hepatic insulin resistance. Crit Rev Clin Lab Sci. 2020;57(5):308–22.
62. Davì G, Falco A, Patrono C. Lipid peroxidation in diabetes mellitus. Antioxid Redox Signal. 2005;7(1–2):256–68.
63. MacAulay K, Woodgett JR. Targeting glycogen synthase kinase-3 (GSK-3) in the treatment of Type 2 diabetes. Expert Opin Ther Targets. 2008;12(10):1265–74.
64. IM KK, Issac A, Ninan E, Kuttan R, Maliakel B. Enhanced anti-diabetic activity of polyphenol-rich de-coumarinated extracts of Cinnamomum cassia. J Funct Foods. 2014;10:54–64.
65. Jose AJ, Leela NK, Zachariah TJ, Rema J. Evaluation of coumarin content and essential oil constituents in Cinnamomum cassia (Nees & T. Nees) J. Presl. 2019;
66. Sharma S, Mandal A, Kant R, Jachak S, Jagzape M. Is cinnamon efficacious for glycaemic control in type-2 diabetes mellitus? Diabetes. 2020;30:32.
67. Iranloye BO, Arikawe AP, Rotimi G, Sogbade AO. Anti-diabetic and anti-oxidant effects of Zingiber officinale on alloxan-induced and insulin-resistant diabetic male rats. Niger J Physiol Sci. 2011;26(1).
68. Etuk EU. Animals models for studying diabetes mellitus. Agric Biol JN Am. 2010;1(2):130–4.
69. Gurusamy U, Shewade DG. Pharmacogenomics in India. Handb pharmacogenomics Stratif Med. 2014;1037–59.
70. Chen Y, Ma Y, Ma W. Pharmacokinetics and bioavailability of cinnamic acid after oral administration of Ramulus Cinnamomi in rats. Eur J Drug Metab Pharmacokinet. 2009;34(1):51–6.
71. Al-Samydai A, Al-Mamoori F, Shehadeh M, Hudaib M. Anti-Diabetic Activity of Cinnamon: A Review. Int Res J Pharm Med Sci. 2018;1(5):43–5.
72. Anlar HG, Bacanli M, Çal T, Aydin S, Ari N, Bucurgat ÜÜ, et al. Effects of cinnamic acid on complications of diabetes. Turkish J Med Sci. 2018;48(1):168–77.
73. Bacanli M, Dilsiz SA, Başaran N, Başaran AA. Effects of phytochemicals against diabetes. Adv Food Nutr Res. 2019;89:209–38.
74. Wariyapperuma WANM, Kannangara S, Wijayasinghe YS, Subramanium S,

Jayawardena B. In vitro anti-diabetic effects and phytochemical profiling of novel varieties of Cinnamomum zeylanicum (L.) extracts. PeerJ. 2020;8:e10070.
75. Murkovic M. Phenolic compounds: occurrence, classes, and analysis. 2016;
76. Blahová J, Svobodová Z. Assessment of coumarin levels in ground cinnamon available in the Czech retail market. Sci World J. 2012;2012.
77. Jayawardena B, Smith RM. Superheated water extraction of essential oils from Cinnamomum zeylanicum (L.). Phytochem Anal. 2010;21(5):470–2.
78. Bhavaniramya S, Vishnupriya S, Al-Aboody MS, Vijayakumar R, Baskaran D. Role of essential oils in food safety: Antimicrobial and antioxidant applications. Grain oil Sci Technol. 2019;2(2):49–55.
79. Siripatrawan U. Active food packaging from chitosan incorporated with plant polyphenols. In: Novel approaches of nanotechnology in food. Elsevier; 2016. p. 465–507.
80. Sharif MK, Ejaz R, Pasha I. Nutritional and therapeutic potential of spices. In: Therapeutic, probiotic, and unconventional foods. Elsevier; 2018. p. 181–99.
81. Gilani S, Najafpour G. Evaluation of the extraction process parameters on bioactive compounds of cinnamon bark: A comparative study. Process Biochem. 2022;114:93–101.
82. Li Y, Kong D, Wu H. Analysis and evaluation of essential oil components of cinnamon barks using GC–MS and FTIR spectroscopy. Ind Crops Prod. 2013;41:269–78.
83. Cardoso-Ugarte GA, López-Malo A, Sosa-Morales ME. Cinnamon (Cinnamomum zeylanicum) essential oils. In: Essential oils in food preservation, flavor and safety. Elsevier; 2016. p. 339–47.
84. Azeredo CMO, Santos TG, Maia BHL de NS, Soares MJ. In vitro biological evaluation of eight different essential oils against Trypanosoma cruzi, with emphasis on Cinnamomum verum essential oil. BMC Complement Altern Med. 2014;14(1):1–8.
85. Poongothai A, Sreena KP, Sreejith K, Uthiralingam M, Annapoorani S. Preliminary phytochemicals screening of Ficus racemosa Linn. Bark. Int J Pharm Bio Sci. 2011;2(2):431–4.
86. Yadav RNS, Agarwala M. Phytochemical analysis of some medicinal plants. J Phytol. 2011;3(12).
87. Saxena J, Sahu R. Evaluation of phytochemical constituent in conventional and non conventional species of curcuma. Int Res J Pharm. 2012;3(8):203–4.
88. Singh G, Maurya S, DeLampasona MP, Catalan CAN. A comparison of chemical, antioxidant and antimicrobial studies of cinnamon leaf and bark volatile oils, oleoresins and their constituents. Food Chem Toxicol. 2007;45(9):1650–61.
89. Ragasa CY, Espineli DL, Agoo EMG, Del Fierro RS. Chemical constituents of Cinnamomum cebuense. Chin J Nat Med. 2013;11(3):264–8.
90. Bickers D, Calow P, Greim H, Hanifin JM, Rogers AE, Saurat JH, et al. A toxicologic and dermatologic assessment of cinnamyl alcohol, cinnamaldehyde and cinnamic acid when used as fragrance ingredients: The RIFM expert panel. Food Chem Toxicol. 2005;43(6):799–836.