Effects of Cinnamomum Zeylanicum on Hypergly-Caemia: A Qualitative Meta-Analysis

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ABSTRACT

Background & aims: This paper aims to impart a precise synopsis of the possible medicinal advantages of Cinnamomumzevlanicum (CZ) on hyperglycaemia for diabetic patients. Besides, the target is to establish statistical significance across studies that might have conflicting results.

Methods: A systematic literature search was carried out in the following databases: PubMed, Science direct, Google Scholar in range time studies from 2010 - 2020. A qualitative meta-analysis of research analysing the impact of CZ extracts on the hyperglycaemia condition in a patient.

Results: 14 studies were included in gualitative meta-analysis. The in vitro study showed that cinnamaldehyde in CZ helped the translocation of Glucose Transporter type-4 (GLUT4) to the membrane cell in diabetic rats. In vivo study showed that the treatment of CZ in diabetic rats with small dose in longer durations helped to reduce the Fasting Blood Glucose (FBG). Most of the studies from human trials showed the daily supplementation of 3 grams of CZ powder for eight weeks significantly reduced the FBG.

Conclusion: The extract of CZ is useful to reduce the blood glucose level in different forms. It shows an improvement in glycaemic control and increases the action of insulin in the β -cell of pancreas to produce more insulin.

Keywords

Cinnamomumzeylanicum (CZ), Ceylon cinnamon, Cinnamomumverum, Hyperglycaemia, Glucose transporters

INTRODUCTION

Diabetes is a metabolic disease that impedes our body's capability to process blood glucose. Type-1, type-2, and gestational diabetes are the major types of diabetes (Ann, 2018). Diabetes can lead to complications such as stroke, heart disease, kidney failure, and nerve damage when left untreated. Most diabetic patients have type-2 diabetes, caused by the damage of insulin action (Olokoba et al., 2012). On top of that, GLUT4 helps in glucose uptake of skeletal muscle. Most of the body insulin-induced glucose is inclined by the redistribution of GLUT4 to the plasma membrane. Thus, insulin signalling regulation in the skeletal muscle is important for glucose homeostasis (Ijuin et al., 2012).

Cinnamon is a spice that comes from a tropical evergreen plant with genus Cinnamonum and family Lauraceae(Salomon, S H., 2019). The plant has two main varieties; Cinnamomumzeylanicum (CZ) and Cinnamomum cassia (CC) (Leech, 2016). Globally, cinnamon is used for cooking and medicinal purposes and each part of the cinnamon tree including the bark, leaves, flowers, fruits, and roots are useful. (Sangal et al., 2011). A study conducted by Danish S et al., 2020 shows that the extract of Cinnamon cassia bark has an antibacterial property which can kill and surpass the growth of bacteria. The cinnamon oil also widely used in health and beauty industry for a chapstick formulation because of the characteristic found in the cinnamon is better than another formulation (Jiyauddin K et al., 2019).

The primary constituent includes cinnamaldehyde (bark), camphor (root), and eugenol (leaf) (Gruenwald et al., 2010). The coumarin level of CZ and CC is one of the important differences between these two cinnamons. Coumarins are secondary phytochemicals with high anticoagulant and hepato-toxic properties (Ranasinghe et al., 2013). The coumarin level in CC is much higher than CZ and if ingested in larger quantities, health risks may occur (Ranasinghe et al., 2017). Therefore, CZ is superior than CC. In vitro and in vivo studies have confirmed numerous health benefits of CZ including anti-diabetic, anti-oxidant, and lipid-lowering effects. (Ranasinge et al., 2017).

This paper aims to impart a precise synopsis of the possible medicinal advantages of CZ on hyperglycemia in diabetic patients. Besides, the target is to establish statistical significance across studies that might have conflicting results. This is important to increase the validity of observed differences and the reliability of the information.





Figure 1: flow diagram; number of articles (n), randomized control trials (RCT).

SEARCH STRATEGY

Pubmed[™], Google Scholar[™] and ScienceDirect[™] had been used to classify similar publication. The published Randomize Clinical Trial (RCT) had been used and searched from early 2010 to 2020. The studies also embodied if the RCTs study design was followed.

INCLUSION AND EXCLUSION CRITERIA

The criteria for inclusion for the selected studies were based on the experimental trial and Randomize clinical trial of the true Cinnamon tree (*Cinnamomumzeylanicum*) supplementation with a specified amount of dosage and duration of time. Effect of *Cinnamomumzeylanicum* on hyperglycaemia and blood glucose level will be prioritized in this research. In vitro, in vivo and human trial studies only using *Cinnamomumzeylanicum* will be included. The studies not written in English and had a redundant or duplicate will be excluded.

DATA EXTRACTION

Research teams used standardized extraction forms to ensure precision and continuity. The following primary data have been extracted by following the first author name, year, objectives, types of study, research outcome, the scale of all intervention and control groups, the health status of patients, the intervention specifics, and the composition of cinnamon supplementation (gram or mg per day), the duration of treatment and the significant results.

RESULTS AND DISCUSSIONS

Table 1: Table of Evidence for in vitro studies						
Variable	Types of Subject	Duration	Type of cinnamon	Dosage	Outcome	
Anand et al 2010	Muscle tissue of diabetic rats	60 days	Cinnamal- dehyde of CZ	20mg/kg	Translocation GLUT4 increased (42% to 73.1%)	
Shen et al 2010	BAT and muscle tissue of diabetic rats	22 days	cinnamon extract	3,30,100 mg/kg	Increase the GLUT4 level in adipose and muscle	
Nair et al 2013	The yeast alpha glucosidase and starch	5 minutes	methanolic extract of CZ	20-100 μg/ml (concentration)	CZ could produce the inhibition of α -glucosidase and α -amylase by using methanolic extract	
Cheng et al 2018	hyperglycaemia in mice	14 days	Cinnamomumosm ophloeum ct. linalool leaf extract oil (LEO), S-(+)-linalool and R-(-)-linalool	250 and 500 mg/kg of LEO, 500mg/kg of S- (+)-linalool and R- (-)-linalool	Changes in glucose level , TG ,TC , histopathological and body weight	
Rafiei et al 2019	Oleic acid-induced HepG2	2 hours	Polyphenols	10 µM	Polyphenols helped inhibit the accumulation of Oleic acid-induced lipid	

In vitro studyshowed that the cinnamaldehyde in CZ helped the translocation of GLUT4 to the membrane cell in diabetic rats, lower the level of glycosylated haemoglobin (HbA1c), and increased the serum insulin after 60 days (Anand et al., 2010). Further study by Shen et al., 2010 proved the statement from the previous study when the GLUT4 level in BAT significantly increased in the plasma membrane but decreased in the cytosolic fraction. The same study also demonstrated that GLUT4 level in muscle tissue significantly increased in both plasma membrane and the cytosolic fraction (Shen et al., 2010). Another study evaluated that CZ extract could produce the inhibition of α -glucosidase and α -amylase by using 20 to 100 μ g/ml of methanolic extract. The half-maximal inhibitory concentration (IC50) for α -amylase was 130.55± 10.5µg/ml and α -glucosidase was 140.01 ±10.08µg/ml (Nair et al., 2013). The study conducted by Cheng et al., 2018 showed no differences in glucose levels, triglyceride (TG) and total cholesterol (TC) between mice treated with 250 and 500 mg/kg of LEO and control group. TG level, TC and glucose of mice treated with 500 mg/ kg R- (-)-linalool was higher than the control group. S- (+)-linalool group not only maintained normal levels of TC and glucose but also caused decrease in TG levels. A recent study by Rafiei et al., 2019 showed that 10 µM of polyphenols helped in inhibiting the accumulation of Oleic acid-induced lipid in hepG2. Lastly, Jayawardena, B et al. 2020 explored the method of extracting antidiabetic components in Cinnamomumzeylanicumusing pressuredwater and decoction extraction. The result showed that CZ contains antidiabetic potential component and total phenolic material, proanthocyanidins, and essential oils were the main components causing the biological activities (Jayawardena, B et al., 2020). (Table 1)

In vitro studies showed that cinnamaldehyde in *CZ* had potential in controlling the GLUT4 level in muscle tissue and brown adipose tissue with an average of 20 - 30mg/kg as preferable dosage (Anand et al., 2010, Shen et al., 2010). Thus, when the GLUT4 is stimulated by the cinnamaldehyde, it will be beneficial to ameliorate diabetic hyperglycaemia. Further studies were needed to identify other substances in CZ that has potential in controlling the GLUT4 level. More studies are also needed to identify the effect of CZ on other types of glucose transporter. Another study by Nair et al., 2013 found that methanolic extract of CZ helped to produce inhibition of α -amylase and

 α -glucosidase. However, upcoming studies are needed to determine the preferable dosage that effectively control the inhibition of α -amylase and α -glucosidase. Another substance in CZ that helped in controlling diabetes is polyphenols. Polyphenols helped the inhibition of Oleic acid-induced lipid in hepG2 (Rafiei et al., 2019). More studies were needed to identify other substances in CZ that help in lipid regulation. It was found that mice treated with R- (-)-linalool gained more body weight than other groups. The body weight of mice treated with S- (+)-linalool and LEO was lower than that of the control group. The body weight of mice treated with trazodone hydrochloride also decreased. However, the mechanism behind body weight loss caused by trazodone hydrochloride was still unclear and further investigation need to be done. R- (-)-linalool increased the TG, TC and body weight of mice compared to controlled group. Cinnamon extract using the pressured water and decoction is superior compared to steam distillation because this method is safe, low cost, and consumed less time for extraction (Jayawardena, B. et al., 2020). (Table 1)

Variable		Types of	Duratio	Type of	Dosage	Outcome		
		Subject	n	cinnamon				
Shen	et	streptozotocin-	22	cinnamon	3,30,100	Significant reduction of		
al 2010		induced	days	extract	mg/kg	hyperglycaemia		
Ranasinghe		streptozotocin-	1	cinnamon	600 mg/kg	FBG in diabetic treated rats is reduced		
et al 2012		induced	month	extract		from 271 (±42) to 247 (±63)*		
El-Desoky		alloxan-	30	cinnamon	200,400,	Lowest dosage of cinnamon		
et al 2012		induced	days	extract	600,1200	(200mg/kg) exhibit the most significant		
					mg/kg	reduction in FBG of diabetic rats		
Sharma	et	alloxan-	14	cinnamon	200	Cinnamon showed a remarkable		
al 2017		induced	days	powder	mg/kg	reduction of blood glucose (337.0 \pm		
						2.86 to 229.0 ± 1.90)		
Beji	et	alloxan-	28	cinnamon	5% of <i>CZ</i>	Cinnamon administration in diabetic		
al 2018		induced	days	powder	in standard	rats caused significant drop in blood		
					feed	glucose $(337.2 \pm 29.8 \text{ to } 171 \pm 18.7)$		

Table 2. Table of Lylachee for in vivo annual statics

In vivo animalstudies showed a significant reduction of hyperglycaemia with the administration of 30 and 100 mg/kg of *CZ* extract in 22 days (Shen et al., 2010). Treatment of cinnamon (600mg/kg) for 30 days also showed a reduction in the Fasting Blood Glucose (FBG) in diabetic-induced rats (Ranasinghe et al., 2012). However, research by El-Desoky et al., 2012 using 200, 400, 600, and 1200 mg/kg respectively for 30 days and showed that the lowest dose of cinnamon (200mg/kg) exhibited the most significant reduction in FBG of diabetic rats. A similar study by Sharma et al., 2017 showed a significant reduction of blood glucose level in diabetic-induced rats fed with 200mg/kg of cinnamon for 14 days, which was also supported by Beji et al.,2018 in his 28 days animal study. (Table 2) In vivo animal study by Shen et al., 2010 showed a significant reduction of hyperglycaemia with the consumption of 30 and 100 mg/kg of CZ extract. An upcoming study by Beji et al., 2018 proved that the treatment of CZ with lower dosage in longer duration helped to reduce FBG better than higher dosage in shorter duration. However, 200mg/kg of cinnamon extract can be accepted as the most effective dosage to lower the blood glucose level in diabetic-induced rats (El-Desoky et al., 2012, Sharma et al., 2017). Further research needed to be done using this dosage to maintain a quality outcome which leads to further studies. Other than that, at least 30 days were needed to obtain a significant reduction in FBG level in diabetic-induced rats (Ranasinghe et al., 2012, El-Desoky et al., 2012, Beji et al., 2018). (Table 2)

Table 3: Table of Evidence for in vivo human trials						
Variable	Types of	Duration	Type of	Dosage	Outcome	
	Subject		cinnamon			
Markey et	Healthy	1-day	cinnamon powder	3 grams	No changes in postprandial	
al 2011		trial	(capsule)		glycaemic	
Wickenberg	Impaired	5 days	cinnamon powder	1.2 grams	With and without CZ, no	
et al 2012	Glucose		(400 mg in capsule		remarkable differences were	
	Tolerance		form)		observed in glucose	
					responses	

Vafa	et	T2DM	8	cinnamon powder	3 grams	
al 2012			weeks	(500mg in capsule		FBG lower in cinnamon group
				form)		$(139.28 \pm 9.11 \text{ to } 126.47 \pm 17.73)$
Azimi	et	T2DM	8	cinnamon	3 grams	FBG were significantly reduced
al 2014			weeks	powder		$(359.47 \pm 10.80 \text{ vs.} 358.25 \pm$
						10.87)
Beejmohun	L	Healthy	2	cinnamon extract	1 gram	CZ intake before a standard meal
et al 2014			hours	(500mg in capsule		helps to restrict the glucose
				form)		response in the 60 minutes after
						absorption of the meal

In vivo human trial revealed that the supplementation of 3gram cinnamon extract to patients in a 1-day trial treated with cinnamon and placebo does not show any effect in postprandial glycaemia (Markey et al., 2011). A study done by Wickenberg et al. 2012, by giving 400 mg capsule daily for 3 times a day for 5 days showed no significant effect in placebo and cinnamon treated patients. However, a further study evaluated that the levels of FBG remarkably decreased in the treated group compared to baseline by using 3gram of cinnamon over eight weeks (Vafa et al., 2012, Azimi et al., 2014). The most recent study showed the consumption of 1 gram of *CZ* before a meal could reduce the blood glucose by 21.2%, resulting in a suggestion that *CZ* intake before a standard meal helps to restrict the glucose response in 60 minutes after absorption of a meal. (Beejmohun et al., 2014). (Table 3)

In vivo human trials, studies by Markey et al., 2011, Vafa et al., 2012, and Azimi et al., 2014 clearly showed that 3gram is a preferable dosage in controlling hyperglycaemia. The duration of studies for human trials should be at least 8 weeks to obtain a significant reduction in FBG glucose level in patients (Vafa et al, 2012, Azimi et al., 2014). More investigation for human trial with different dosage, age range and longer duration is necessary to increase the knowledge of therapeutic benefits of medicines in diabetic patients. A study by Beejmohun et al., 2014 showed 1gram of CZ before a meal reduces the blood glucose level in the first 60 minutes. This proved that CZ intake should be before a meal to obtain significant effect on hyperglycaemia. However further studies were needed to confirm the result by Beejmohun et al., 2014. (Table 3)

CONCLUSION

In conclusion, meta-analysis shows an important effect on hyperglycaemia using the *Cinnamonumzeylanicum*. The extract of *CZ* is really useful to reduce the blood glucose level in different forms especially in capsule form. Besides the results of the experiments are beneficial, more tests using a larger sample are required for medical approval. This meta-analysis clearly shows that *CZ* gives a variety of positive effects in human trials, in vivo and in vitro as a preferable agent for antidiabetic. It shows an improvement in glycaemic control and increases the action of insulin in the β -cell of the pancreas to produce more insulin. Moreover, clinical studies in-vivo did not show any toxic effects using the *CZ* due to the coumarin contained is less compared to other cinnamon. However, further studies regarding the genetic aspect and apoptotic effect of CZ and are also needed. Other than that, further clinical trials for using cinnamon capsules, extracts, and powder are needed to establish the therapeutic safety precaution and efficiency consumption in human being.

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