Current Research in Diabetes & Obesity Journal
ISSN: 2476-1435

Juniper Publishers
key to the Researchers

Research Article
Volume 9 Issue 4 - January 2019
DOI: 10.19080/CRDOJ.2019.09.555768

Curre Res Diabetes & Obes J

Potential of *Barringtonia Racemosa* (L.) Dichloromethane extract on Streptozotocin (STZ) - Induced Type 2 Diabetic Rats

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Submission: September 28, 2018; **Published:** January 25, 2019

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Abstract

Objective: Type 2 diabetes mellitus is a heterogeneous group of metabolic disorders characterized by persistent hyperglycaemia. The aim of this research work is to gather scientific information about the possibility to utilize the dichloromethane leaf extract of Barringtonia racemosa as an agent of antidiabetic drug.

Material and Methods: The Crude extract was obtained through serial extract of five solvents, Hexane, dichloromethane, ethyl acetate, chloroform and methanol while the Assessment of type 2 anti-diabetes was conducted on Streptozotocin (STZ) -induced diabetic albino rats and the data were analysed through one-way ANOVA software. Histopathological studies of the pancreas and kidney were made to get evidence of the β-cell performance and the renal tissue respectively.

Results: The streptozotocin (STZ) induced diabetic rats treated with the Dichloromethane extract experienced an antidiabetic effect and the histopathologic observations showed increasing of the granulated β-cell at $p<0.0001$) and no renal tissue damage in the tested rats.

Conclusion: The result of this study revealed that the dichloromethane crude extract of *Barringtonia racemosa* could be utilized as an agent source of type 2 anti-diabetes

Keywords: *Barringtonia racemose*; Dichloromethane; Alloxan; Diabetic; Rats

Abbreviations: STZ: Streptozotocin; T2DM: Type II Diabetes Mellitus; WHO: World Health Organization

Introduction

Type II diabetes mellitus (T2DM) is a fast-growing epidemic affecting people globally. Furthermore, multiple complications and co-occurring with a primary disease are associated with T2 diabetes. Lifestyle modifications along with pharmacotherapy and patient education are the mainstay of therapy for patients afflicted with T2DM. Western medications are frequently associated with severe adverse drug reactions and high costs of treatment. However, herbal medications have long been used in the treatment and prevention of T2DM in traditional medicine which was presumed to avert this treat of health around the globe. This disorder is a chronic metabolic menace characterized by absolute or relative deficiencies in insulin secretion or insulin action associated with chronic hyperglycaemia and disturbances of carbohydrate, lipid and protein metabolism [1].

The disease is of three types recognized by the World Health Organization (WHO) such as (i) type 1 diabetes (insulin-dependent) (ii) type 2 diabetes (non-insulin-dependent) and (iii) gestational diabetes. The β-cells in the pancreas are the key players in this disorder called glycaemic homeostasis. The glucotoxicity, lipotoxicity, inflammatory mediators and incretion were reported to modulate function and survival of β-cell [2]. Besides, oxidative stress is thought to be a major risk factor on the onset and progression of diabetes [3]. Both type-1 and type-2 diabetes are associated with increased formation of free radicals and decreased antioxidant potential [4]. Thus, T2DM accounts for over 90% of cases globally [5-7]. According to the World Health Organization (WHO), in 2011, approximately 364 million people globally suffer from diabetes (DM), with projections that DM-related deaths will double from 2005 to 2030 [8].

Diabetes being a common disease in the developed and developing countries. According to a WHO report in 2011, approximately 360 million people globally suffer from diabetes. The epidemic is more pronounced in developing countries such as Malaysia, Nigeria respectively because of their feeding habits. As per reports of the WHO, 32 million people of Malaysia had diabetes. The Malaysians would have a total number of 2.48 million diabetics compared to 0.94 million in 2000 that is about 164% increase. it is expected that more people in Malaysia will be affected by diabetes in the near future [9].

In the study of this diabetes diseases there are several animal models available to test for the mechanisms of diabetic complications, most of the studies on diabetic in animal models are largely restricted to type 1 diabetic (T1D) conditions [10,11]. In this context streptozotocin (STZ) [12-14], or alloxan-induced diabetic models [15-17] are extensively used to study the diabetic among scientist and both these models mimic the T1D in humans. It was reported that oxidative stress appears to be a major factor in the development of other diseases in T1D, along with the activation of polyol pathway and non-enzymatic glycation [12,13,18].

Thus streptozotocin (STZ) induced rat model is one of the most frequently used for T2D-like models which mimics human diabetes [19-22]. Previous studies on this model were found to have characteristics of pancreatic beta-cell destruction followed by beta-cell regeneration and glucose intolerance [23,24]. Subsequently, other authors confirmed these findings and showed that STZ treated rats in adulthood display the typical characteristics of T2D [25,26]. This animal model is mainly used to screen hypoglycaemic or antidiabetic agents [16,17,27], and also for hypolipidemic and oxidative stress related studies [17]. However, no studies attempted to use this model for investigating the Assessment of Type 2 Anti-Diabetes of *Barringtonia racemosa* (L.) Dichloromethane extract in streptozotocin (STZ) - Induced Diabetic Rats. Therefore, in the present study we evaluated STZ model for development of an agent for T2D.

Table 1: Ethno Pharmacological uses and activity of *Barringtonia racemose*.

Part of Plant Use	Treatment	Reference
Leaves Stem-bark Roots Seeds Fruits	High blood pressure, itching, chicken pox itch, rheumatism febrifuge. Fish poison, insecticide, skin disease, Deobstruent, Relief in stomach ache Tumors, fish poison, colic, febrifuge, vermufuge Poison wild pig, cough, asthma, diarrhea, eczema. Hemicrania, ophthalmia, cough, asthma, diarrhea	Kabir et al. [34], Osman et al. [35] 2015 Lim [36]. Isaac et al. [37], Giesen et al. [38], Manjunah [39]. Jayaweera et al. [40]. Thomas et al. [41], Manjunah et al. [39], Jayaweera et al. [40], Giesen et al. [38], Nadkami [42]
Part of plant (Antioxidant) Leaves Leaves, stem-bark Fruits	Secondary Metabolites Terpenoid, Flavonoid, Phenolic and phenolic acid Phenolic acid	Behbahani et al. [43], Kong et al. [44] Sulaiman & Ooni, [45].
(Antibacterial)Leaves Stem-bark Roots	Mycobacterium smegmatic Staphylococcus aureus, Staphylococcus epidermidis, Eschericia coli, Shigella dysentriae, Vibrio cholerae, Proteus sp. Bacillus cereus, Salmonella typhy	Mmushi et al. [46] Saha et al. [47] Khan et al. [33].
(Antifungal) Leaves Leaves, stem-bark	Antimycobacterial Mycobacterium smegmatic Antifungus Fusarium sp., Tricoderma koningii, Penicillium sp., Ganoderma tropicum, Ganoderma lucidum, Aspergillus sp., Rhizopus sp. Saprolegnia sp.	Mmushi et al. [45]. Hussin et al. [48].
(Anti-inflammatory) Fruits	Carrageenan-induced paw oedema, Formalin-induced paw oedema in albino rats. Carrageenan-induced acute inflammation in rats	Sikha et al. [49]. Patil et al. [50].
(α-glucosidase inhibitor) Seed Fruits	Yeast and intestinal Glucosidase inhibition Glucosidase inhibition Saccharomyces cerevisiae	Gowri et al. [51]. Sulaiman & Ooi [45]. Ponnapalli et al. [52].
(Analgesic) Stem-bark Fruits	Albino male rats, steroid. Acetic acid-induced writhing response	Deraniyagala et al. [53] Sikha et al. [50].
(Cytotoxicity) Leaves, Stem-bark, Roots	Preliminary bioactive substances for Cancer cells proliferation.	Isaac et al. [54]

Therefore, the choice of *Barringtonia racemosa* an evergreen mangrove plant, belonging to the family Lecythidaceae to cutely the menace of Diabetic disease is an option. The stem-bark and leaves have been traditionally used for anticancer, analgesic, antibacterial, anticolic and antifungal activities this motivated us to study the antidiabetic potential of this plant extract (Table 1) [28-33].

Material and Methods

Materials

Chemicals, drug and kit: All of the analytical grade chemicals, drug and the kit were procured commercially. The Streptozotocin (STZ) (Medical Resource SDN BHD Kuching, Sarawak) and metformin hydrochloride ($C_4H_{11}N_5$) was decided as a positive control of the antidiabetic drug. The tested-diabetic rats were

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induced by the Streptozotocin (STZ) and was operated to measure the blood glucose level of the tested rats. All other chemicals were of analytical grade and were obtained from local companies.

Experimental design

Albino rats were obtained from the National Center for Laboratory Animal Sciences, unimas, were injected intraperitoneal with 90mg/kg body weight STZ dissolved in 0.1M citrate buffer, pH 4.5 (n = 42). Control (n = 6) received normal diet. The rats were maintained on a normal diet in individual cages.

Animal care

Animal care and protocols were in accordance with and approved by the Institutional Animal Ethics Committee (IAEC). Animals were housed in individual cages in a temperature and humidity-controlled room.

Sample collection

The Leaves of *Barringtonia racemosa* was collected from Kampong Sarawak Malaysia by the river bank and Meranak at Meranak river bank in Kota-Samarahan Sarawak. Identification of the species was made by Prof Dr. Fasihuddin Bin Badruddin Ahmad and Prof Dr zaini B Assim. The samples were air-dried, cut into pieces and ground prior to analysis. It was then deposited into the polymer laboratory at Department of Chemistry, Faculty of Resource Science and Technology, UNIMAS.

Preparation of sample extracts

The collected *Barringtonia racemosa* were cut into thin slices and then air dried under shade for seven days. The dried leaves (2kg) were ground with an electric blender and sieved with 40 mm mesh sieve to get a fine powder. The powder was stored in a dark bottle at room temperature until use.

Extraction method

The leaves of *Barringtonia racemosa* was extracted by the conventional solvent extraction method as described by Fasihuddin et al. [55]. This was achieved by soaking the ground powdered leaves in non-polar, medium polar and polar solvents in the order of increasing polarity. A total of 2kg of the dried and ground Leaves of *Barringtonia racemosa* was extracted using cold soaking method with hexane (C_6H_{14}). The samples were soaked in the hexane with the ratio of 1:3 in a 5 litres Erlenmeyer flasks at room temperature for 72 hours. The resulting hexane solution was then filtered using filter paper and the residue was re-extracted with fresh hexane for another 72 hours and filtered. All the extracts were combined and concentrated using the rotary evaporator of model Heidolph Laborota 4000 efficient, under reduced pressure to obtain the hexane crude extract. The residues were then re-extracted using the same procedure with dichloromethane (CH_2CLl_2), then ethyl acetate (C_2H_5COOH), chloroform ($CHCl_3$), and methanol (MeOH) to obtain various extract of sample of dichloromethane, ethyl acetate, chloroform and methanol crude extracts, respectively.

DPPH assay

The DPPH (2,2-diphenyl-1-picrylhydrazyl, $C_{18}H_{12}N_5O_6$) as reported by [37] of the leaves extract of *Barringtonia racemosa* was applied to evaluate the antioxidant activity to be IC_{50} = 45.75 which gives a base line potential of the activity of the extract against type 2 diabetic.

In vivo experiment

The healthy albino rats (150-200 g body weight) were conditioned in a cage for a week. After a week adaptation, the rats were separated into eight groups by setting: The Normal, negative and positive group. The remain five groups are the extract (dose) group of 100, 200, 300, 400, and 500mg/kg/bwt. Individual rat in each group was collected its blood on the 7th day and marked as a pre-treatment blood. The diabetic rat was generated by giving orally one mL of 50% (w/v) Streptozotocin (STZ) to each rat in each group on the 8th and the 11th days [54]. After a week since the Streptozotocin (STZ) (90mg/kg/bwt) given, the blood was collected from individual rat to check the diabetic rat according to the value blood glucose level ≥200 mg/dL [56]. This blood was noticeable as the blood obtained before treatment. After finding out the diabetic rat, all rats were given orally: The aqueous metformin hydrochloride of 65 mg/kg/bwt in Positive control group, the aqueous tested extract of 100, 200, 300, 400 and 500mg/kg/bwt in the extract's treatment group respectively every day after 24hrs for 21 days.

Later on, this point, the individual rat in each group was collected its blood. The blood was noticeable as the blood obtained after treatment. One day later, a rat in each group was selected to be sacrificed for histopathological observation on the kidney and pancreas organs. The difference of blood glucose level was stated as an antidiabetic effect.

Histopathological study

Table 2: Effect of *Barringtonia racemosa* Dichloromethane extracts on Mean Streptozotocin (STZ) of type 2 Diabetic Rats.

			(Mean±SD mg/dl) Blood glucose level pre-treatment (Days)		
	Treatment Groups	**Dose mg/kg**	**Before Experiment**	**3 Pre-Treatment**	**7 pre-Treatments**
1	Normal	0.25ml	131.3±11.3	132.5±6.41	132.6±6.43
2	Negative	90mg/kg/bwt	414.3±13.5	414.5±5.32	415.7±5.41
3	Positive	65mg/kg/bwt	428.4±4.5	428.5±45.5	428.5±3.62
4	Extracts	100 mg/kg/bwt	415.3±12.3	417±5.35	418.7±52.42
5	Extracts	200 mg/kg/bwt	435.6±13.5	437.7±7.7	438.5±6.71
6	Extracts	300 mg/kg/bwt	425.3±2.8	427.3±5.9	435.9±7.62

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7	Extracts	400 mg/kg/bwt	457.6±6.	457.9±1.3	458.2±4.31
8	Extracts	500 mg/kg/bwt	418.6±32.5	433.4±3.5	434.3±3.92

Value with superscripts c with a group along the row is significantly (P<0.05) higher than zero hours' blood glucose value with superscript d within the group along the row are significantly (P<0.05) lower than zero hours' blood glucose value. While value with superscript * between groups along the column is significantly (P<0.05) lower than blood glucose value in the diabetic control group.

Table 3: Effect of Barringtonia racemosa dichloromethane extracts on blood glucose level of Streptozotocin (STZ)-induced diabetic Rats.

(Mean±SD mg/dl) Blood Glucose Level Post Treatment (Days)								
	Treatment groups	**Dose mg/kg/bwt.**	**0**	**3**	**7**	**14**	**21**	**28**
1	Normal	0.25ml	132.6±6.43	123.5±6.4*	122.6±6.4*	119.4±7.3*	120.0±5.5*	121.2±4.4b*
2	Negative	90mg/kg/bwt	415.7±5.14	388.5±5.3a*	411.7±5.4a*	417.7±5.9a	427.2±8.6b*	456.7±6.4a
3	Positive	65mg/kg/bwt	428.5±3.62	243.5±45.5	222.5±3.6*	199.3±3.4c*	176.3±6.4	166.6±5.2a*
4	Extracts	100	418.7±52.42	326.4±5.3*	298.7±52.4a*	232.78±15.3	224.6±11.8	217.7±9.7
5	Extracts	200	438.5±6.71	327.7±7.7c*	311.5±6.7a*	255.5±4.4	233.3±4.5	115.2±8.5b
6	Extracts	300	435.9±7.62	287.3±5.9c*	235.9±7.6a*	218.7±7.4	205.8±3.7	176.9±6.4*
7	Extracts	400	458.2±4.31	277.9±1.3	201.8±4.3	195.3±7.3*	182.4±2.2	152.8±3.6*
8	Extracts	500	434.6±3.29	233.4±3.5	190.8±3.9	175.3±2.7*	153.4±5.5*	95.5±5.8*

Value with superscripts a with a group along the row is significantly (P<0.05) higher than zero hours' blood glucose value with superscript b within the group along the row are significantly (P<0.05) lower than zero hours' blood glucose value. While value with superscript * between groups along the column is significantly (P<0.05) lower than blood glucose value in the diabetic control group.

The kidney and pancreas organs were submerged in Neutral Buffered Formalin for a week and then histopathological investigations were performed [57]. The slices were stained with Haematoxylin Eosin (HE) and studied under Olympus binocular research microscope (Tables 2-4 & Figures 1 & 2).

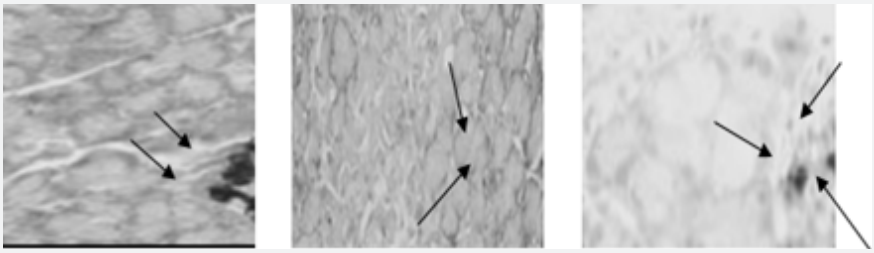

Figure 1: (b) Histopathological observation of pancreatic H-cell as indicated by the black arrow in the normal rat, while (a). Streptozotocin (STZ)induced pancreatic H-cell and (c). Diabetic rat + *Barringtonia racemosa* Dichloromethane extract with a dose of 400mg/kg/ bwt.

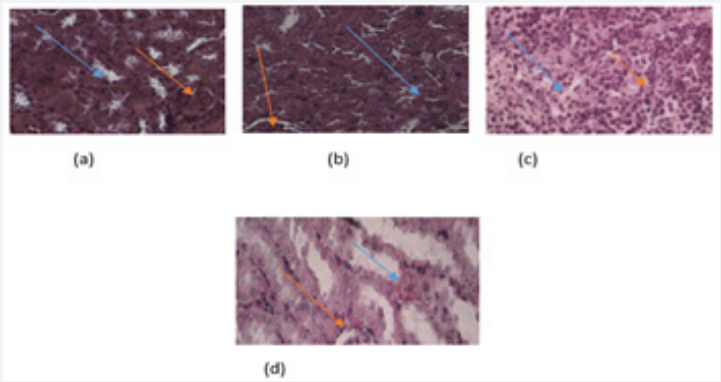

Figure 2: Histopathological performance of kidney in the normal rat (a), Metformin hydrochloride (b), diabetic rat + Dichloromethane extract with dose in 100mg kg−1 b.wt. (c), diabetic rat + bound flavonoids extract with a dose of 500 mg/kg/bwt. (d). Pink arrow: Proximal convoluted tubule, Blue arrow: Glomerulus.

Results

The *in vivo* experiment on the Streptozotocin (STZ)-induced T2-diabetic rats shown decreasing the blood glucose level along with increasing dose of the extract as shown in Table 3, The study of the proximate renal tubule cell scores in the rat's kidney at various treatment indicated renal damage within the normal range and as well as increase in the β-cell granulation Tables 4 & 5.

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Table 4: Proximate renal tubule cell score in the rats at various treatments.

Group	Dose (mg/kg/bwt)	Proximate Convolution Tubule Score (Mean ±SD)	
1	Normal	-	-
2	Negative	90mg/kg/bwt	0.23±1.05
3	Positive	65mg/kg/bwt	0.45±0.63
4	extract	100	0.35±0.60
5	extract	200	0.32±0.63
6	Extract	300	0.34±0.61
7	Extract	400	0.33±0.59
8	Extract	500	0.32±0.62

P = (0.001) in proximal renal tubule cell count among the treatments based on one-way ANOVA analysis. Significant statistical difference

Table 5: Granulation of pancreatic β-cell at various treatments.

	Group	Dose (mg/kg/bwt)	Pancreatic β-cell (Mean ±SD)
1	Normal	-	-
2	Negative	90mg/kg/bwt	463.20±10.73
3	Positive	65mg/kg/bwt	394.04±15.35
4	extract	100	382.01±10.66
5	extract	200	397.23±11.45
6	Extract	300	432.11±13.54
7	Extract	400	486.00±23.33
8	Extract	500	520.31±14.64

P< (0.001) in Pancreatic cell count among the treatment is based on one-way ANOVA analysis. Different letters indicated statistical difference

Discussion

Type 2 Diabetes is a metabolic disorder which has genetic and lifestyle etiology. A delayed treatment that is inadequate and when administered too late its pre-disposes the affected individual to the complications of diabetes. However, Streptozotocin is an agent that is frequently used to induce diabetes mellitus in albino rats [58,59]. It is generally accepted that the cytotoxicity produced by streptozotocin affects the DNA alkylation and subsequent activation of poly(ADP-ribose) synthetase. This causes rapid and dangerous depletion of NAD in pancreatic islets [60,61]. It was also reported that the free radicals may play an essential role in the mechanism of β -cell damage and effect of streptozotocin induced-diabetes [62], thus the presence of antioxidant at 36.55µg/mL [63].

The progression of T2Diabetes begins with an impairment of glucose tolerance [64,65] and is often associated with a state of insulin resistance. Renal histopathologic observational data were described in semi-quantitative descriptive and scores with a scale of 0 to 2 [66]. The mark 0 states no lesions in the organ. The mark 1 suggests hydropic degeneration, fatty degeneration, karyomegaly and pycnosis. The mark 2 states the occurrence of necrosa. Each individual score was then counted up and the mean of the group was determined for comparison with controls, then, a mild (score 0), moderate (score 1) and severe (score 2) lesions were identified.

The renal histopathologic observation was performed on proximal tubule nuclei as revealed in Table 5. The kidney is a target organ of insulin. Insulin binds to the insulin receptors via the nephron [67], which is essential for the proper function of the nephron, glomerulus and tubule [68]. In insulin resistance, the insulin signaling cascade in the glomerulus seems to be impaired [69]. In diabetic conditions, insulin stimulation in the transportation of proximal renal tubules is impaired so that glucose reabsorption decreases, and glucose is excreted through urine [68]. The administration of the *Barringtonia racemosa* extract improved the kidney and the visible cells in the proximal tubule were the same as absorbed in the normal rat (Figure 2). However, plant extract as reported by Isaac et al. [37] is said to have antioxidant potential with IC50 value of 36.55µg/mL, this fact suggested the ability of the extract to reduce free radical molecule which in this case may be contributed to the potential activity of this extract against T2D, as well as some result of some bioactive compound such are responsible for its antibacterial, antifungal, analgesic such as terpenes and flavonoid which has the ability to neutralize the DPPH molecule and also the properties as a free radical and a scavenger for other free radicals.

The result obtained from Figure 2 showed that the Dichloromethane extract of *Barringtonia racemosa* given to the diabetic rats did not cause any significant change in the histologic structure of the kidney. Thus, agreed with [70]. This suggested that administration of the *Barringtonia racemosa* dichloromethane Leave extract in diabetic rats did not show specific damage to proximal renal tubular cells either. Thus, the bioactive compound contained in the extract did not cause damage to the kidney organs in the tested rats when compared to the controlling agent for type 2 diabetes.

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However, the histopathologic images demonstrated that the pancreatic β-cell granulation was directly proportional to the given extract dose as shown in Table 5. The number of β-cells enhancement is significant with $p<0.0001$) for each treatment stated that the dichloromethane extract administered to hyperglycaemic rats could improve pancreatic β-cells and depresses necrosis or apoptosis of pancreatic β-cells compared to metformin hydrochloride as shown in Figure 2. It was assumed that the modulatory effects of *Barringtonia racemosa* crude extract constituents on the blood glucose transporter by increasing insulin secretion, decreasing apoptosis and stimulating proliferation of pancreatic β-cells Zheng et al. [70] [71].

Conclusion

The bound flavonoids extract of *B. racemosa* kernel showed the strong antioxidant power and it displayed the type 2 anti-diabetes property. Administration of the extract with doses of 100 mg/kg/bwt. and 200 mg/kg/bwt. orally for 14 days was not causing the histopathologic disturbance on the tested rat kidney organ.

Acknowledgement

The author Isaac John Umaru wish to appreciate Federal University of Wukari for Grant Fellowship and Universiti Malaysia Sarawak Natural Product Laboratory for their support.

Author's Contribution

Isaac John Umaru: Conceived, designed, performed the experiments and wrote the paper. Hauwa A. Umaru: Provided reagents, data analyses and experimental tools analyses. Kerenhappuch I. Umaru: Materials and analysed the data.

Ethics

This original article contains unpublished material. The corresponding author states that all of the other authors have read and agreed to the manuscript and no ethical issues are involved.

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