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A study on anti-diabetic and anti-inflammatory properties of herbal decoction from polyherbal formulation

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Abstract
The anti-diabetic and anti-inflammatory activity of herbal decoction from equal composition of *Coccinia indica, Orthosiphon stamineus* and *Cardiospermum halicacabum* leaf was evaluated using different *in vitro*-based assays: inhibition of alpha amylase, glucosidase, hemolysis inhibition, protein denaturation inhibition, and lipoxygenase inhibition. Results revealed that the inhibition of alpha amylase, glucosidase from these herbal decoction (100 µg/mL) was within the range from 76.31% and 74.36%, showed a significantly higher ($p < 0.05$) inhibition levels. Herbal decoction inhibited protein denaturation was within the range of 78.36%. Herbal decoction showed an improved ability to inhibit lipoxygenase activity with the inhibition range of 70.23%%, The Overall result outcomes exposed that herbal decoction possess anti-diabetic and anti-inflammatory properties at different levels and this might be due to different concentration of bioactive compounds.

Keywords: anti-diabetic; anti-inflammatory activity; herbal decoction; lipoxygenase inhibition; hemolysis inhibition

Introduction
Herbal plants have been recommended for the handling of varied illnesses for thousands of years. Even with the start of modern medicine, using plants for therapeutic resolves is immobile dominant in numerous country. The international occurrence of diabetes has increased in the past two decades. Plant products possess bioactive metabolites for the use of alternative medicines to treat diabetes are in significance to their phytochemical materials. Higher plants parts are rich in flavonoids, phenolic compounds, coumarins, terpenoids and other constituents which help to control so many diseases (Kangralkar *et al*., 2010) [9]. Type 2 diabetes is more common, and its commonness is predictable to increase extra quickly in the upcoming because of growing fatness and condensed activity points. In spite of numerous novel pharmacologically active mediators have been established for the management of diabetes, the herbal remedies mostly recommended to treatment of diabetes with has also been growing amongst consultants. Olden Indian texts has agreed several herbs in the treatment of diabetes mellitus. In India numerous native medicines have been used by the practitioners of the Siddha and Ayurveda medicine for the treatment of diabetes mellitus (Arumugam *et al*., 2013) [3].
Type II diabetes is related with insulin confrontation firstly and later, as the function of the β-cell decreases, insulin deficiency. Type II diabetes is categorized both by irregularities of insulin secretion gradually foremost to secretion failure as well as insulin resistance of all major target tissues (Kebede *et al*., 2016) [10]. While insulin struggle is imperative in the early stages of type II diabetes, the failure in suitable β-cell recompense indications to the progression to the diabetic state. Compensation for insulin resistance is through increased secretion per β-cell or by an increase in β-cell mass through neogenesis or replication of the existing β-cells (Salsali and Nathan, 2006) [23]. Herbal drugs are prescribed due to their good effectiveness, fewer side effects in clinical experience and relatively low costs (Rangika *et al*., 2015) [21]. Medicinal and natural herbal plant products are traditionally used from long time in many countries for the treatment of diabetes mellitus. Type II diabetes mellitus is a different disorder due to a mixture of inherited and attained factors that unfavorably affect glucose metabolism. It is supposed that these issues chief to diabetes mostly by distressing β-cell function and tissue insulin kindliness. If the quantity of insulin produced is too little to allow for glucose to be used or stored, or if the insulin being produced does not work efficiently, glucose collects in the blood. Hyperglycemia changes when rates of glucose release into the circulation overdo rates of tissue glucose uptake. This might happen since release is augmented, because uptake is reduced, or due to a combination of factors such as increased release with a lesser increase in uptake (Anaya-Eugenio *et al*., 2014) [2].
Herbal plants have been portion of the excessive remedial civilizations around the world accepted back thousands of years. The World Health Organization (WHO) explains old-style medicine as well-being performs, attitudes, information and opinions joining plant based medicines. In Siddha medicine covered spiritual therapies, manual techniques applied singularly or in combination to treat, diagnose and prevent illness or maintain well-being. In 2020 WHO launched its first comprehensive traditional medicine strategy to assist efforts to promote affordable, effective and safe use of traditional medicine and complimentary alternative medicine. In India, traditional medicine is used by up to 60% of the population to meet primary healthcare needs and is crucial in the fight against diseases.

Leaf and vegetables are the energetic and essential in balanced diet, and they are rich in polyphenols and vitamins. Leaf of *Coccinia indica, Orthosiphon stamineus* and *Cardiospermum halicacabum*, are generally used as leafy vegetables which, contained rich in polyphenols, carotenoids, and antioxidant activities. Further, *Cardiospermum halicacabum* is one of the leafy vegetables that possess anti-inflammatory properties. Though these leafy vegetables have been studied for their anti-diabetic and anti-inflammatory properties have not been reported extensively. Therefore, the present study was directed to determine the anti-diabetic and anti-inflammatory activity of herbal decoction using several *in vitro* bioassays, such as inhibition of alpha amylase, glucosidase, inhibition of albumin denaturation, and anti-lipoxygenase activity.

Materials and Methods

Plant Material

Coccinia indica, Orthosiphon stamineus and *Cardiospermum halicacabum* leaves were obtained from Herbal garden of Sri Sairam Siddha Medical College, West Tambaram, Chennai-48, Tamilnadu, India. A plant taxonomist authenticated the plant and samples were kept in the Medicinal Botany herbarium with voucher specimen numbers MB/GSMC-448/2021, Government Siddha Medical College, Arumbakkam, Chennai-106. The stems were sufficiently air-dried in 5 days at the ambient room temperature, while the stem was cut into smaller pieces and air-dried in 7 days.

Preparation of the Decoction

The decoction was prepared by boiling the powdered leaf of *C. indica, O. stamineus* and *C. halicacabum* (60 g or 12 “kalan”) under low heat with 960 mL of water (4 “patha”) until concentrated to 240 mL (1 “patha”) as according to the traditional method practiced in Siddha medicine to prepare “kasayam” (decoction). The concentrate was filtered through a thin silk cloth (500 μm) and freeze-dried or used to prepare the herbal drink.

Phytochemical Screening

The herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* were subjected to phytochemical screening to determine the presence of secondary metabolites such as alkaloids, flavonoids, terpenoids, tannins, glycosides, saponins and polyphenols using standard procedures (Aida *et al*., 2001; Hess *et al*., 1995).

Total Phenolic Content

The total phenolic content (TPC) of herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* was determined using the method by Singleton, (1965). The aqueous extract (1 mL, 1 mg/mL) was mixed thoroughly with 1 mL of 50% Folin-Ciocalteu reagent and 1 mL of 2% Na_2CO_3, and centrifuged at 13400X *g* for 5 min. The absorbance of upper phase was measured using a spectrophotometer (ELICO (SL150) UV–Vis Spectrophotometer) at 750 nm after 30 min incubation at room temperature. Total phenolic content was expressed as a catechol equivalent.

Estimation of Flavanoid

A 1ml aliquot of each herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* was mixed thoroughly with 1ml of 2% aluminium chloride and 0.5 ml 0f 33% acetic acid followed by the addition of 90% methanol and the content is thoroughly stirred and allowed to stand for 30 minutes (Elfalleh *et al*., 2019). The absorbance was measured at 414 nm using a UV-Visible Spectrophotometer. Quercetin was used as a standard.

Thin Layer Chromatography

Thin layer chromatography of herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* was performed using standard procedures (Harborne 1973). The aqueous methanol extract was placed carefully in precoated aluminum silica gel 60 F, Merck F 254 using a microcapillary tube. The spots were allowed to dry for few minutes and the TLC plate was placed in the solvent mixture, Toluene, acetone and Formic acid (6:6:1) or solvents of ethyl acetate-glacial acetic acid-formic acid-water (100:11:11:26 v/v/v/v). After drying, the TLC plates were observed under UV at 240nm and 360 nm in UV TLC viewer.

Antidiabetic Activity

Glucose Uptake in Yeast Cells

Glucose uptake assay by yeast cells was performed according to Cirillo *et al*. (1963) [5]. The yeast cell suspended in distilled water was subjected to repeated centrifugation (3000 × *g*, 5 min) until clear supernatant fluids were obtained and 10% (v/v) of the suspension was prepared in distilled water. Various concentrations of herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* (25 to 100 μg/ml) were added to 1 ml of glucose solution (20 mM) and incubated together for 10 min at 37 °C. Reaction was started by adding 100 μl of yeast suspension followed by vortexing and further incubation at 37 °C for 60 min. After 60 min, the tubes were centrifuged (2500 × *g*, 5 min) and amount of glucose was estimated in the supernatant. Glycomet was used as standard drug. The percentage increase in glucose uptake by yeast cells was calculated using the following formula:

Increase in glucose uptake%=Abs sample-Abs control/Abs sample×100

Where, Abs sample is the absorbance of test sample and Abs control is the absorbance of control reaction (containing all reagents except the test sample). All the experiments were carried out in triplicates.

Inhibition of Alpha-Amylase

Inhibition of alpha-amylase method followed by Narkhede *et al.*, (2011) [16]. In this assay, added 390 μl of 0.02 M phosphate buffer (pH 7), positive control (acarbose), different concentrations of herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* and 10 μl of α-amylase enzyme were mixed and incubated at 37°C for 10 min. Added 10 μl of starch to this mixture and again incubated 37°C for 1 h (Megha *et al*., 2013) [13]. After incubation, added 0.1 ml 1% iodine solution and 5 ml of distilled water and optical density was measured at 565 nm. Inhibition of enzyme activity was calculated as follows:

Percentage inhibition = (A−C) × 100/ (B−C)

Where, A=Absorbance of the sample, B=Absorbance of blank (without α-amylase), and C=Absorbance of control (without starch).

Inhibition of A-Glucosidase

The inhibitory activity of α-glucosidase method was followed by. The first step carried out substrate of starch solution (2% w/v maltose or sucrose, 1 mL) with Tris buffer (0.2 M, pH 8) and various concentrations of herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* for 5 min at 37°C. The reaction was initiated by adding α-glucosidase enzyme (1 mL of 1 U/mL yeast α-glucosidase) to the reaction mixture, followed by incubation for 10 min at 37°C. The reaction was terminated by heating the contents in a boiling water bath. 3, 5-dinitrosalicylic acid (1 mL) was added with the product before being incubated for 5 min and added with distilled water (9 mL). The amount of liberated glucose was measured by glucose oxidase peroxidase method.

Inhibition of Albumin Denaturation Activity

The anti-inflammatory activity of herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* was deliberate by inhibition of albumin denaturation was studied. The reaction mixture consists of test extracts and 1% aqueous solution of bovine albumin fraction, pH of the reaction mixture was adapted using few drops of 1 N HCl. The different concentration of alkaloid rich fraction were incubated at 37°C for 20 min and then heated to 51°C for 20 min, successively chilled the test sample was measured at 660 nm. The experiment was repeated in triplicate (Montefusco *et al.*, 2013) [15]. The percentage inhibition of protein denaturation was calculated as follows:

Percentage inhibition= (Abs Control−Abs Sample) 100/Abs control.

Heat-Induced Hemolysis

The reaction mixture (2 ml) consisted of 1 ml herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* of different concentrations (25-100 µg/ml) and 1 ml of 10% red blood cells (RBCs) suspension, in its place of the test sample, the only saline was added to the control test tube. Diclofenac sodium was used as a standard drug. All the centrifuge tubes containing reaction mixture were incubated in a water bath at 56°C for 30 min (Sadique *et al.*, 1989). The reaction mixture was centrifuged at 2500 rpm for 5 min and the absorbance of the supernatants was taken at 560 nm. The experiment was executed in triplicates for all the test samples. The percentage inhibition of hemolysis was calculated as follows:

Percentage inhibition = (Abs Control−Abs sample) 100/Abs control.

Inhibition of Lipoxygenase Activity

5-LOX inhibition assay was performed using the principle of 1-4 diene (linoleic acid) oxidations to 1-3-diene. Briefly, an aliquot of the stock solution (50 µL, in dimethyl sulfoxide (DMSO) and tween 20 mixture; 29:1, w/w) of different concentration of herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* was placed in a 3 mL cuvette, followed by addition of pre-warmed 0.1 M potassium phosphate buffer (2.95 mL, pH 6.3) and linoleic acid solution (48 µL). Thereafter, ice-cold buffer (potassium phosphate; 12 µL) was added with 5-LOX (100 U) and absorbance recorded at 234 nm (Baylac and Racine, 2003). The control was prepared with DMSO: tween 20 mixture (no enzyme inhibition).

Statistical Analyses

Statistical evaluation was carried out by the SPSS software (SPSS Inc, Chicago, USA, ver. 13.0). Descriptive statistics were ascertained for all the contemplated attributes. Analyses were carried out in triplicate and the means of all parameters were examined for significance ($p < 0.05$) by analysis of variance (ANOVA).

Result and Discussion

Phytochemical screening

The herbal decoctions of herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* displayed the presence of alkaloid, flavonoids, saponins, terpenoids, and tannin. No steroid and glycosides were detected. Table 1 presents the preliminary phytochemical screening of plant decoctions.

Table 1: Phytochemical screening of herbal decoction

S. No.	Constituents	Herbal decoction
1.	Alkaloids - Dragendroffs reagent - Mayer's test	 + +
2.	Flavonoids - Alkali test - Lead acetate test	 + +
3.	Polyphenols -Ferrozine test	 +
4.	Terpenoids -Salkowski test	 +
5.	Tannins -$Fecl_3$ Test	 +
6.	Glycosides -Keller-Killani test	 +
7.	Saponins -Froth test	 +

-- = Negative (absent); + = Positive (present)

Total phenol and flavonoid content

The phenol and flavonoid contents of herbal decoctions of herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* was found to be 56.32 and 38.21 µg/g dry sample of quercetin equivalent/g respectively, as estimated using the standard plot of quercetin (r2 = 0.9911). The anti-diabetic effects recognized to the polyphenols of plants acting an essential role in defensive the body from oxidative stress, diabetes, cardiovascular diseases. Hence, the plant-based medicines are a possible alternate therapy to discover due to their described security and nutraceutical welfares (Hyun *et al.*, 2016) [8].

TLC Profile of Herbal Decoctions

The herbal decoctions of herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* loaded on Pre-coated TLC plates (60 F_2 54 Merck) and developed with a solvent system of petroleum ether, chloroform and methanol in the ratio of 1:0.5:0.1 were efficient to extract the antidiabetic compound it is used for further studies. The developed plate was viewed under UV 240nm and 360nm (Table-2 and Fig-1).

Table 2: TLC profile of herbal decoctions

S. No	Herbal decoction of *C. indica, O. stamineus* and *C. halicacabum*		
	UV 240 nm Rf value	UV 360 nm Rf value	Visible Rf value
1.	0.81	0.81	0.81
2.	0.74	0.74	0.74
3.	0.63	0.63	0.63
4.	0.52	-	-
5.	0.48	-	-
6.	0.34	-	-
7.	0.26	-	-

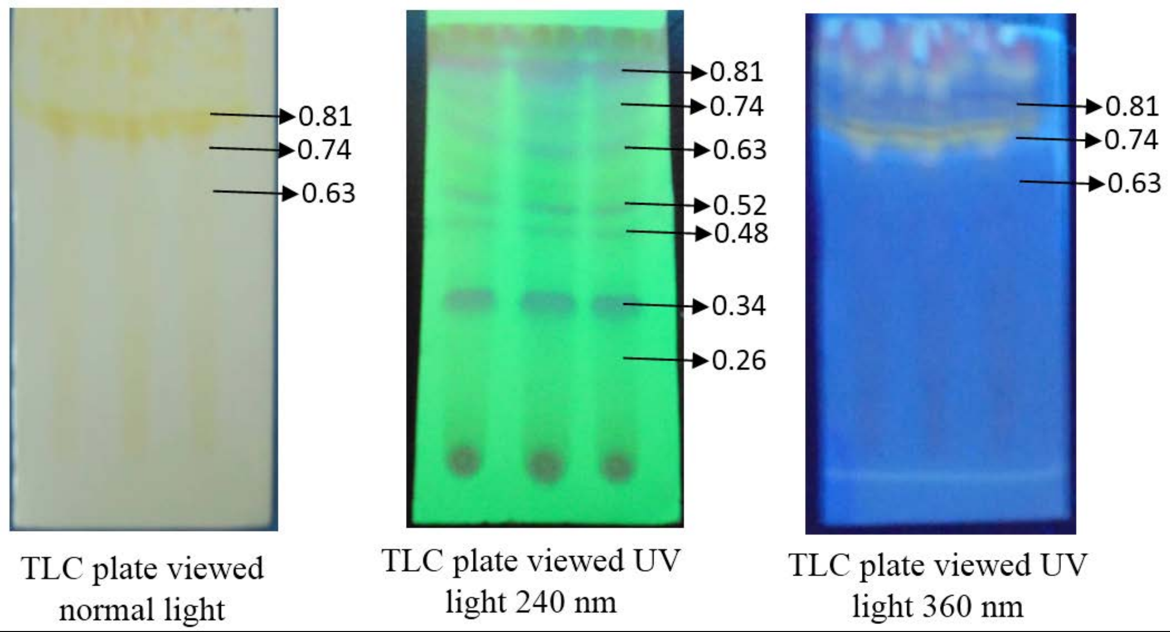

Fig 1: TLC profile of herbal decoctions

Glucose Uptake in Yeast Cells

Different concentrations of herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* were subjected to *in vitro* glucose uptake assay employing yeast as model. The percentage of glucose uptake in yeast cells by the alkaloid rich fraction was compared with standard drug diclofenac sodium (Fig-2). Herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* exhibited highest percentage of glucose uptake 72.12%, which was almost near to the standard 68.32% at 100 µg/ml concentration. Results also indicated that alkaloid rich fraction had nearly same effectiveness in increasing the glucose uptake by yeast cells as compared to standard drug acarbose. Consequently, the presence of some bioactive metabolites in the herbal decoction might help in the uptake of glucose in the present study. The over-all basis, the uptake of glucose by skeletal muscles is due to the buildup of functional glucose transporting molecules in the cell membrane. The glucose transporting molecules are regulated by leptocytes and/or myocytes in comeback to in elevation emission of insulin in blood, resulting in hypoglycemic effect (Rajeswari and Sriidevi, 2014) [20].

α-Amylase Inhibition

Inhibitory effects of α-amylase confirmed that herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* at concentrations of 25-100 µg/ml (Fig. 3). The maximum inhibition was observed at highest concentration of 100 µg/ml exhibited of 76.31% as compared to standard acarbose which showed significantly lower inhibition of 72.23% at the same concentration. Plant based nutritional polyphenols, in addition to their antioxidant effects, have been reported to exert anti-hyperglycemic effects by binding to glucose transporters and competitive inhibition of digestive enzymes (Li *et al*., 2010) [12]. The polyphenols like flavonoid, tannin and anthocyanin tend to more active on α-amylase inhibition with increase with molecular weight and degree of polymerization (Nistor *et al*., 2010) [17].

α-Glucosidase Inhibition

Additional results of antidiabetic activity using α-glucosidase inhibitory evaluate of the herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* are shown in Fig-4. The herbal decoction shown a significant inhibitory action of α-glucosidase enzyme. The percentage inhibition ranges from 16.32 to 74.36% for lowest concentration to highest concentration. Thus the inhibition of the activity of α- glucosidase by herbal decoction desired interruption the degradation of carbohydrate, this result in line with Moniruzzaman *et al*. (2012) [14] reported the hypoglycemic effect of the related species *Aloe vera* through its insulin secretagogues potential. The hypoglycemic effect of acarbose was evident due to the stimulation of insulin release from pancreatic β-cells and inhibition of glucagon secretion (Tanko *et al*., 2011) [25]. Natural compounds such as flavonoids and tannins isolated from medicinal plants are reported to stimulate insulin secretion from pancreatic β-cells (Srinivasan S and Muruganathan, 2016) [24]. Since these water soluble active constituents exist in herbal decoction, the probable mechanism of action of herbal decoction is similar to acarbose.

Albumin Denaturation Inhibition

As portion of the investigation on the mechanism of the anti-inflammatory activity, the ability to protein denaturation of herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* was documented. It was effective in inhibiting albumin denaturation in Fig. 5. Extreme inhibition was recorded in herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* 78.36% at 100 µg/ml was. Diclofenac sodium was used standard drug, which showed the maximum inhibition of 76.37% at the concentration of 100 µg/ml. The EC_{50} value of extract found to be 58.61 µg/ml which is higher than standard (Diclofenac sodium) value 61.23 µg/ml. The capacity of studied plant extracts to prevent thermal and hypotonic protein denaturation maybe responsible for their anti-inflammatory properties. Additional, several plant extracts have revealed their protein denaturation ability, as stated previous. Conversely, the authentic mechanism of this membrane stabilization is yet to be considered further. It has been planned that the extract strength inhibit the release of the lysosomal constituents of neutrophils at the site of inflammation (Govindappa *et al*., 2011) [7].

Heat-Induced Hemolysis

The herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* inhibited the heat-induced hemolysis of RBCs to varying degrees as per Fig. 5. The maximum inhibition of 81.45% at 100 µg/ml was observed herbal decoction and standard diclofenac sodium showed lower inhibition of 79.64% at the same concentration. The EC_{50} value of test extract found to be 68.23 µg/ml and 73.64 µg/ml for standard. As the red blood cell membrane is similar to that of lysosomal membrane, inhibition of red blood cell hemolysis may provide insights into the inflammatory process (Umapathy *et al*., 2010) [26]. Maintenance of these cell membranes may delay or inhibit the lysis and succeeding issue of the cytoplasmic contents which, in crack, lessen the tissue damage and, hence, the inflammatory response (Okoli *et al*., 2008) [18]. As a result, bioactive materials that contribute substantial protection of cell membrane against distressing materials are important in the event of inhibiting the progression of inflammation.

Inhibition of 5-Lipoxygenase

Herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* exhibited inhibitory activity of 5-Lipoxygenase compared to the standard diclofenac sodium. Herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* recorded comparatively higher anti-inflammatory activity with regard to Lipoxygenase (EC_{50} 70.23 µg/mL) than the standard (Fig-7). Lipoxygenases are the key enzymes in the biosynthesis of leukotrienes. Leukotrienes performance a significant part in numerous inflammatory diseases, such as arthritis, asthma, cancer, and allergic diseases (Rackova *et al*., 2007) [19]. The mechanism of anti-inflammation may include a successions of measures in which the metabolism of arachidonic acid plays an important role. In this process, arachidonic acid is cleaved from the membrane phospholipids upon appropriate stimulation of neutrophils, and can be converted to leukotrienes and prostaglandins through lipoxygenase and cyclooxygenase pathways, respectively (Akinwunmi and Oyedapo, 2011) [1]. Earlier results have shown that polyphenols compounds may block or interfere with the cascade progression of arachidonic acid metabolism by inhibiting lipoxygenase activity and, also, they may serve as scavengers of various reactive free radicals which are produced during arachidonic acid metabolism (Khasawneh *et al*., 2011) [11].

Conclusions

In conclusion, results indicate that the herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* possess anti-diabetic and anti-inflammatory properties at varying levels. Herbal decoction of *C. indica, O. stamineus* and *C. halicacabum* showed higher hemolysis inhibition, protein denaturation inhibition properties and higher lipoxygenase inhibition ability. Results indicate that these anti-diabetic and anti-inflammatory activities may be due to the occurrence of bioactive compounds, such as polyphenols, flavonoids, and carotenoids in herbal decoction.

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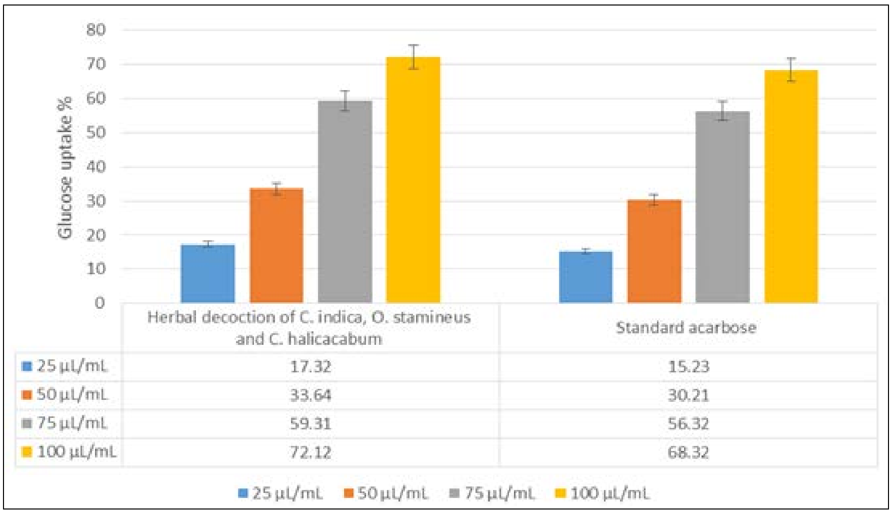

Fig 2: Effects of glucose uptake in yeast cells by herbal decoction of C. Indica, O. Stamineus and C. Halicacabum

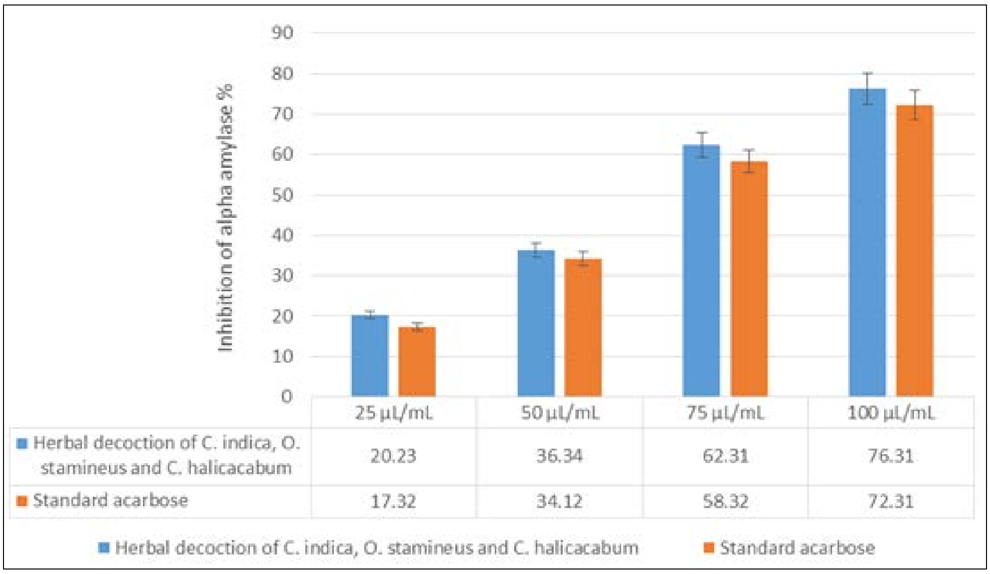

Fig 3: Inhibition of a-amylase inhibition by herbal decoction of C. Indica, O. Stamineus and C. Halicacabum

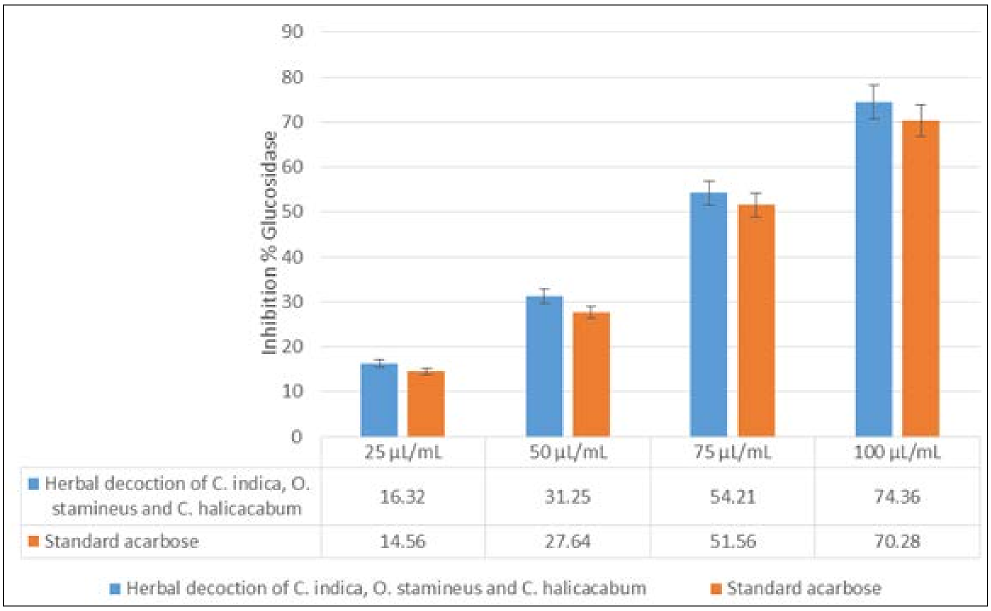

Fig 4: Inhibition of a-glucosidase by herbal decoction of C. Indica, O. Stamineus and C. Halicacabum

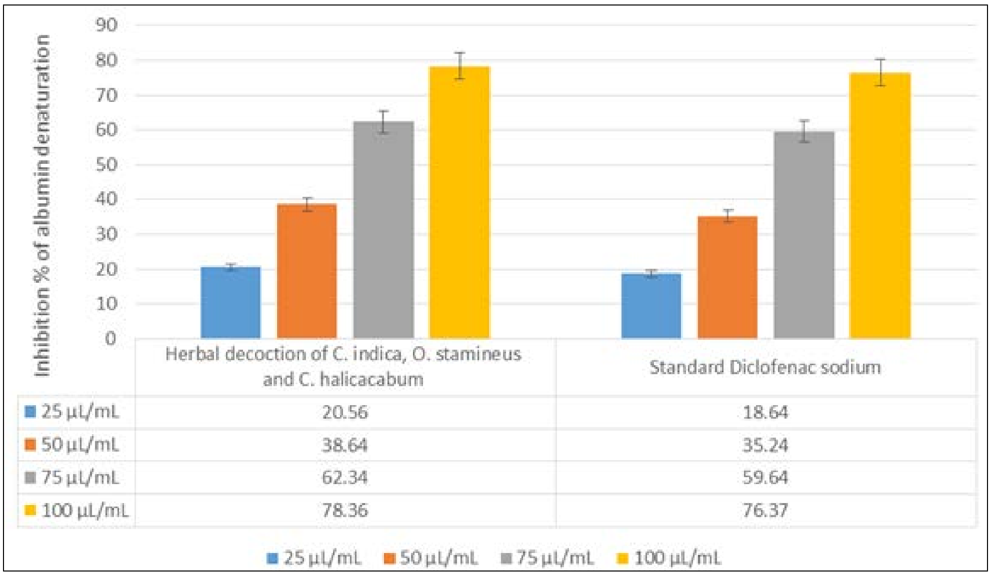

Fig 5: Inhibition of albumin denaturation by herbal decoction of C. Indica, O. Stamineus and C. Halicacabum

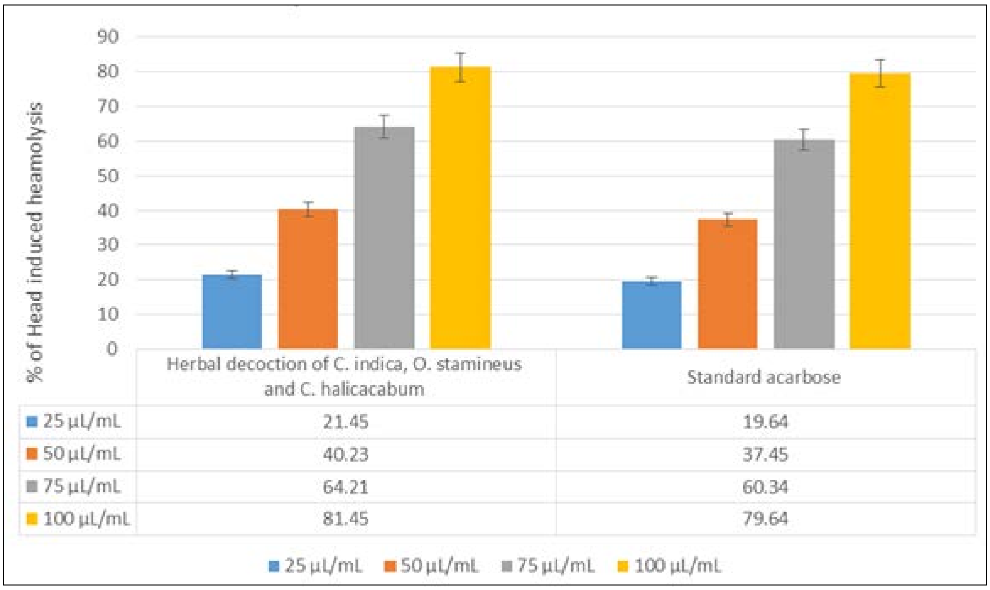

Fig 6: Heat-induced heamolysis by herbal decoction of C. Indica, O. Stamineus and C. Halicacabum

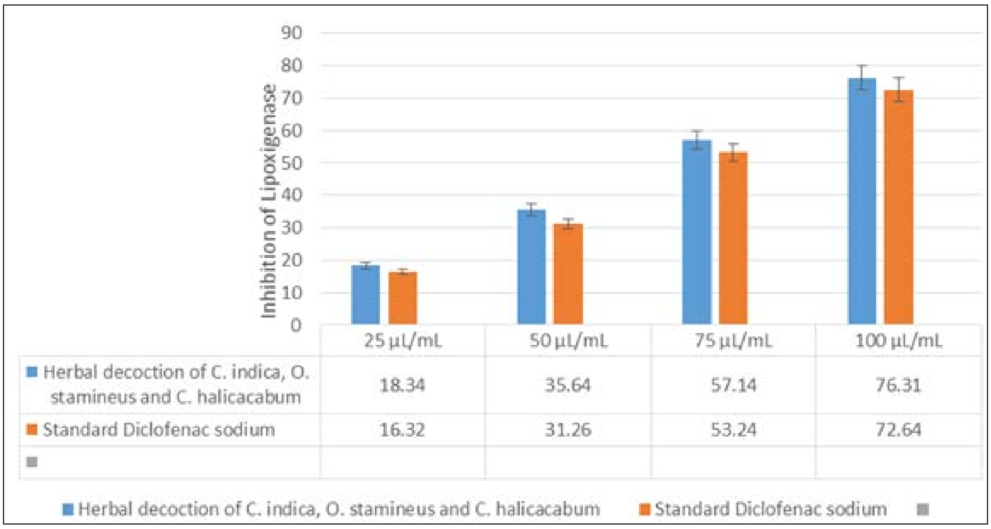

Fig 7: Inhibition of 5-lipdxygenase by herbal decoction of C. Indica, O. Stamineus and C. Halicacabum

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