

# Pancreatic Lipase inhibition assay of various extracts of leaves of *Murraya Koenigii* in southern areas of Goa

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**Abstract.** The objective of the study was to assess the lipase inhibitory activities of chloroform, methanolic and aqueous extracts from the commonly available *Murraya koenigii* (L.) Spreng leaves (Rutaceae) in southern villages of Goa, for potential use in the treatment of obesity. Extracts of the leaves of this plant were evaluated for lipase inhibitory activity using porcine pancreatic lipase (PPL: triacylglycerol lipase) - *ortho*-phenyl butyrate in an in vitro assay. Among the three extracts screened, chloroformic extract exhibited the highest pancreatic lipase inhibitory activity of 53.42%, followed by methanolic extract (51.88%) and aqueous extract (36.42%), respectively. Chloroformic extract has not been screened for its pancreatic lipase inhibition assay. All the Crude extracts of leaves of *Murraya koenigii* (L.) Spreng leaves (Rutaceae) have potential as pancreatic lipase inhibitory agents. Chloroformic extract was found to be most effective and hence can be used as a potent anti-obesity agent to combat hyperlipidemia.

**Keywords:** *Murraya koenigii* pancreatic lipase inhibitory activity, Soxhlet extraction, *ortho*-nitrophenyl butyrate anti-obesity agent

## 1 Introduction

Obesity is one of the leading causes for metabolic disorders that is an outcome of imbalance between food intake, physical activity, metabolic rate or could be drug induced. Several approaches have been implied for the treatment of obesity targeting at specific mechanisms, which include lipase inhibition, suppressive effect on food intake, stimulatory effects on energy expenditure, inhibition of adipocyte differentiation and the regulatory effect on lipid metabolism. The irregularities seen with respect to lipid levels such as increases in total and low density lipoprotein (LDL) cholesterol, low concentrations of high density lipoprotein (HDL) cholesterol, and high triglyceride levels is termed as Dyslipidemia. Drug induced dyslipidemia in particular increases the risk of cardiovascular disease and metabolic dysfunction. Research shows that improving antioxidant status and arresting the accumulation of lipids in the hepatocytes improves blood lipid profile. [3] - [5] This is possibly the most effective way for combating Cardiovascular disorders and liver disorders. Currently there are plenty of therapeutic drugs but with limited efficacy and undesirable side effects. One of the most widely studied approach is the inhibition of pancreatic lipase. Natural plant sources can interrupt the lipase as well as adipocyte activity, thus, bring about inhibition of fat absorption and/or fat accumulation in the body. The pancreatic lipase enzyme is a crucial enzyme in the human digestive system for breaking down dietary fat. Interference with fat absorption along the gastrointestinal tract is one of the potential ways for treating obesity. Pancreatic lipase has a major role in digestion of triglycerides. Pancreatic lipase inhibitors are substances that reduce the activity of this enzyme in the small intestine, primarily by decreasing fat absorption. Inhibition of pancreatic lipase activity is the most widely studied approach to find potential anti-obesity agent [9].

In recent years, greater attention has been paid to the use of *Murraya koenigii* in traditional medicines and home remedies. This plant tolerates any soil, preferably bit loose and sandy type. Villages in south goa have Red sandy soil with good drainage which is best for a good yield. The optimum temperature of Goa is between 26 to 37 degrees which is quite favorable for the growth of this plant. The leaves have characteristic flavor and aroma. Phytochemicals like tannins, flavonoids and saponins have been progressively considered due to their obesity and antihyperlipidemic properties [11], eventually found to be inhibitors of pancreatic lipase [12]. It has been postulated that pancreatic lipase in the process of assimilation of Triacylglycerol in the small intestine in turn leads to a glucose surge post a meal. Subsequently, it has been observed this hyperglycemia mediates in insulin and glucose resistance [13].

In a study of comparison of *Murraya koenigii* with other medicinal plants for their inhibitory effect of enzymes linked in JOXFRVH DQG OLSLG PHWDEROLVP K\GURDOFRKROL- Amylase, Vihidifid W RI . Interestingly, pancreatic lipase inhibition assay with hydroalcoholic extract of *Murraya koenigii* gave the best results too [14].

A study in 2007 by Vinuthan et al, who used Aqueous and methanol leaf extract of *Murraya koenigii* to evaluate the hypolipidemic effects on male Sprague Dawley rats. There was a significant decrease in plasma cholesterol, triglycerides and phospholipids in the treatment group. The decrease in the lipid profile was attributed to the constituents present in leaf which were found to stimulate insulin secretion [17].

Xie et al, 2006 observed the tendency of body weight reduction after curry leaf treatment [18]. Other than leaves, stem bark extract of *Murraya koenigii* [kant upadhyay] has shown to exert hypolipidemic effect which is similar to that effect of leaves. The results are pertaining to lipid profiles [20]. Similar lipid lowering effect has been effectively shown in spite of different solvents used for extraction like chloroform [19], dichloromethane, ethyl acetate [21] and ethanol [22] apart from aqueous and methanol extracts.

Given the abundance of evidence on *Murraya koenigii*, it is imperative to explore its phytochemicals in combating obesity. According to the literature survey, chloroform extract has not been screened for its pancreatic lipase inhibition assay. In this study, the organic and aqueous extracts of *Murraya koenigii* plant, collected from southern parts of Goa were tested for its efficacious lipase inhibition.

## 2 Materials and methods

### 2.1 Plant material

Leaves of *Murraya koenigii* were collected from different regions of South Goa. A herbarium was prepared and specimen was identified by Botany department of Goa University, Dona Paula, Goa, India. Leaves were washed and shade dried for 2 weeks. After drying, the leaf material was ground into a fine powder using a blender and stored in airtight container for further use.

### 2.2 Chemicals

Para nitrophenyl butyrate (Pnbut), Porcine pancreatic lipase (PPL, Type II) was purchased from Sigma Aldrich (USA). All other chemicals and solvents were of analytical grade and purchased from local dealers in Goa.

### 2.3 Instrumentation

EVOLUTION 300 UV-Vis spectrophotometer, Semi auto biochemistry analyser, Shaker device, filter paper, digital weighing scale, Soxhlet extractor, Rotary evaporator

### 2.4 Preparation of Plant extract

About 25gms. of dried and grounded *Murraya koenigii* leaves were taken for the preparation of crude extract using Soxhlet apparatus and was allowed to run continuously for 10 reflux cycles each. Three different organic solvents (chloroform, methanol, and distilled water) were used for the solvents diffuse into the plant material and solubilize the material. The

organic solvents were concentrated to dryness under reduced pressure at 50°C to 55°C from methanol, 40°C to 45°C chloroform and 80°C to 87°C for aqueous extract with a rotary evaporator. The extracts obtained were air dried and stored in refrigerator for further use [23].

## 2.5 Phytochemical screening

The bioactive components of *Murraya koenigii* were determined for all the crude extracts derived from methanol, chloroform, and aqueous solvents after condensation in the rotary evaporator. The bioactive components like alkaloids, saponins, tannins, terpenoids, flavanoids, phenols, steroids, glycosides and anthraquinones were tested using standard methods [24][25].

### 2.5.1 Test for Alkaloids

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3 ml sample was stirred with 3 ml of 1% HCl on steam bath. Mayer reagent was then added to mixture. Turbidity of the resulting precipitate was taken as an evidence for the presence of alkaloid.

### 2.5.2 Test for Anthraquinones (*Born Trager's reaction for free Anthraquinones*).

One gram (1 g) of the powdered plant was placed in a dry test tube and 20 mL of chloroform was added. This was heated on steam bath for 5 min. The extract was filtered while hot and allowed to cool. To the filtrate was added with an equal volume of 10% ammonia solution. This was shaken and the upper aqueous layer was observed for bright orange as indicative of the presence of Anthraquinones. Control test were done by adding 10 mL of 10 % ammonia solution in 5 mL chloroform in a test tube.

### 2.5.3 Test for Flavonoids

Ferric chloride test for flavonoids: About 0.5 of each portion was boiled with distilled water and then filtered. To 2 ml of the filtrate, few drops of 10% ferric chloride solution were then added. A green or violet coloration indicated the presence of a phenolic hydroxyl group.

### 2.5.4 Test for Phenol:

Ferric chloride test:

Extracts were treated with 4 drops of ferric chloride solution. Formation of bluish black colour indicates the presence of phenols.

### 2.5.5 Test for Glycosides:

A small amount of alcoholic extract was taken in 1 mL of water in a test tube and a few drops of aqueous NaOH were added. A yellow coloration indicates the presence glycosides.

### 2.5.6 Test for Saponins

5 ml of sample was shaken vigorously with 5 ml of distilled water in a test tube and warmed. The formation of stable foam was taken as an indication of the presence of saponins.

### 2.5.7 Test for Tannins

About 2ml of the sample was stirred with 2ml of distilled water and few drops of FeCl<sub>3</sub> solution were added. Formation of green precipitate was indication of presence of tannins

### 2.5.8 Test for Terpenoids (Salkowski test)

Five ml of each extract was mixed in 2 ml of chloroform, and concentrated H<sub>2</sub>SO<sub>4</sub> (3 ml) was carefully added to form a layer. A reddish brown colouration of the inter face was formed to show positive results for the presence of terpenoids.

## 2.6 Pancreatic Lipase Inhibition assay

Pancreatic lipase activity was determined by measuring the hydrolysis of phenyl butyrate (NPB) to p-nitrophenol using a method reported previously [36]. The 0.1 mg/ml of enzyme solution was prepared by reconstituting porcine pancreatic lipase using 0.1 M Tris-HCl buffer (pH 7.4) containing 0.1% Triton X-100. The substrate (NPB) was added to the mixture and the reaction was allowed to proceed for further 15 min at 37°C. After incubation, the absorbance of p-nitrophenol released was measured at 405 nm using a UV-Vis spectrophotometer [26]. Furthermore, a positive control, Orlistat, was used to ensure the reliability of results.

Relative pancreatic lipase activity (%) was calculated as  $\left[ \frac{\text{activity of the compound with the substrate}}{\text{activity of the compound without the substrate}} \times 100 \right]$ .

## Statistical analysis

All results were expressed as Mean ± Standard deviation (n=3). Significance of difference from the control was determined by TUKEY test and a p value

## 3 Results And Discussion

### 3.1 Percentage yield of extracts

Three extracts were prepared from leaves of *Murraya koenigii* taken from Cortalim village of south Goa, and tested for their anti-lipase potential at various concentrations using porcine lipase inhibition assay.

The total yield of the *Murraya* leaves was estimated using a weighing scale. The dry yield was measured by weighing sample leaves from three different areas of weight ranging from 500g, 400g and 450g. 87gms, 70gms and 75gms of dry yield was obtained respectively (Table 2). A mean ± SD of 77 ± 8.7 gm was obtained from those specimens. 17.1 % of dry yield was obtained from the *Murraya* leaf sample.

Table 2 Dry yield of *Murraya koenigii*

Wet weight(gm)	Period of drying	Dry weight(gm)	Yield percentage
500	Shade dried at RT for 3 weeks	87	17.4
400		70	17.5
450		75	16.6
Mean ±SD: 77 ± 8.7			

About 2.75, 1.5, and 7.1 gm of crude extract were obtained from dried *Murraya* leaves using methanol, chloroform, and water respectively. A mean  $\pm$  SD of  $2.67 \pm 0.09$  (10.6% yield),  $1.5 \pm 0.05$  (6.0% yield) and  $3.2 \pm 0.02$  (12.8% yield) was obtained from 25gms. (Table 3) of dried leaves of *Murraya koenigii*. Crude extracted through the aqueous solvent obtained a greater yield of 3.2 gm which was followed by the methanolic extract. Comparatively a lesser yield from the chloroform extract.

Table 3 Yield on solvent extraction of *Murraya koenigii*.

sample quantity in gm	solvents	yield in gm	Mean $\pm$ SD	yield %
25	methanol	2.75	$2.67 \pm 0.09$	10.60%
25	chloroform	1.56	$1.5 \pm 0.05$	6.00%
25	water	3.2	$7.1 \pm 0.04$	12.8%

### 3.2 Preliminary phytochemical screening

Preliminary phytochemical screening reveals the presence of Phenols, glycosides, saponins, tannins and terpenoids whereas alkaloids were tested negative in all three different extracts (Table 4)

Table 4 Phytochemical Analysis of extract of *Murraya Koenigii*

Constituents	Results		
	Methanol (Solvent)	Chloroform (solvent)	Aqueous
Alkaloids	Absent	Absent	Absent
Anthraquinones	Present	Present	Present
Coumarins	Present	Present	Present
Flavonoids	Present	Present	Present
Glycosides	Present	Present	Present
Phenol	Present	Present	Present
Saponins	Present	Present	Present
Steroids	Absent	Absent	Absent
Tannins	Present	Present	Present
Terpenoids	Present	Present	Present

### 3.3 Porcine Pancreatic Lipase Inhibition Assay(PPL )

Three extracts of *Murraya koenigii* leaves were prepared and tested for pancreatic lipase inhibition at various concentration of 200,400,600,800 and 1000 micrograms/ml. The inhibitory activities of chloroformic, methanolic and aqueous extracts towards pancreatic lipase are recorded in graph 1

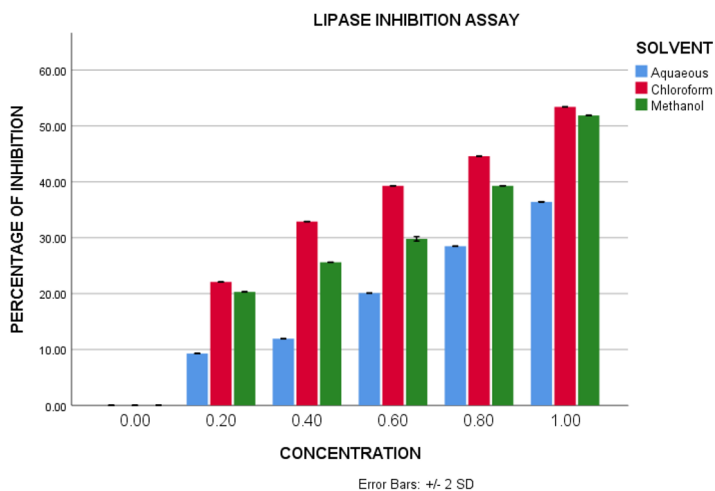


Fig. 1 Pancreatic lipase inhibition activity *Murraya koenigii* leaves

As shown in Fig. 1, The chloroformic extract of *Murraya koenigii* showed an activity of 53.42% at a concentration of 1 mg/ml, proving to be most effective in inhibiting pancreatic lipase followed by methanolic extract reported 51.88%. The aqueous extract does show inhibitory activity of 36.42% but to a lesser extent. Values obtained with reference to Fig. 1. are represented in Table 1.

Table 1. Values obtained with reference to Fig.1.

Multiple Comparisons of Lipid peroxidation using Tukey HSD						
(I) SOLVENT		Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Aqueous	Chloroform	-209.9400	11.07060	0.000	-245.3920	-174.4880
	Methanol	-278.2067	11.07060	0.000	-313.6586	-242.7547
Chloroform	Aqueous	209.9400	11.07060	0.000	174.4880	245.3920
	Methanol	-68.2667	11.07060	0.001	103.7186	-32.8147
Methanol	Aqueous	278.2067	11.07060	0.000	242.7547	313.6586
	Chloroform	68.2667	11.07060	0.001	32.8147	103.7186
Based on observed means. The error term is Mean Square(Error) = 183.837.						
*. The mean difference is significant at the 0.05 level.						

Our results are in concordance with the values obtained by Birari et al, 2009 and Rani et al and Gaur et al proving that *Murraya koenigii* can be an alternative to synthetic drugs used to combat dyslipidemia. Traditionally used edible plants are gaining global attention. The phytochemicals present in the plant extracts could be responsible for its pancreatic lipase activity [27]. In many of the previous studies, flavonoids and phenols have shown inhibition activity by binding to the enzyme substrate complex, thereby bringing down the rate of lipid absorption [28]. Phatak et al., 2019 attributed the antihyperlipidemic properties of *Murraya koenigii* to the presence of bioactive elements saponins, alkaloids, and flavonoids. Mere existence of the phytochemicals does not prove the ability to reduce lipids but it is their concentration that plays a role in contributing to anti-lipidemic property [7]. Polyphenols have been implicated in bringing about conformational changes in the structure of the lipase enzyme, the amino acids linked in binding being tyrosine and tryptophan [29].

The process of lipolysis in fat cells of adipose tissue is signaled by irregularities in cAMP levels, which in turn activates protein kinase A and substrates such as hormone-sensitive lipase and perilipin [56], out of which HSL is a key enzyme in mobilization of fats. It is known that Calcium and colipase contribute to stability of pancreatic lipase in the sense that the heterodimer stays associated, and using herbal drugs like *Murraya koenigii* causes the dissociation of the enzyme heterodimer. [11] This hypothesis is in line with this present study where the least polar solvents extracts showed slight better lipolytic effect than polar solvent extracts [10].

#### 4 Conclusion

In the present study a comparison was made for pancreatic lipase inhibition assays for three different extracts of the leaves of *Murraya koenigii*. Chloroformic extract was found to be most effective and hence can be used as an anti-obesity agent to combat hyperlipidemia. It can be postulated that tannins, saponins and flavonoids predominantly found in this plant contribute to the anti-hyperlipidemic property. The process of identification of bioactive phytochemicals responsible for the anti-obesity property of *Murraya koenigii* is under progress in order to get a clear picture of the inhibition mechanism and clinical applications of this plant.

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