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ANTI-DIABETIC AND ANTI-HYPERTENSIVE ACTIVITIES OF CITRUS FRUIT PEELS

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Keywords:

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ABSTRACT: Orange (*Citrus sinensis*), Kinnow (*Citrus reticuleta*), and Mosambi (*Citrus limetta)* methanolic, the aqueous extract showed the inhibitory activity on α-amylase and α-glucosidase assay where methanolic, acetone and aqueous extract of these fruit peels exhibited the anti-hypertensive activities. The results showed that the methanol and aqueous extract of Orange, Kinnow, and Mosambi peels inhibited α-amylase and α-glucosidase activities. However, Orange peels (IC_{50} = 18.4 and 9.43 µg/mL) and Kinnow peels (IC_{50} = 12.6 and 6.09 µg/mL) exhibited higher capacity to inhibit α-amylase activity compared to Mosambi peels (IC_{50} = 11.6 and 6.54 µg/mL) and Orange peels (IC_{50}=12.5 and 8.67 µg/mL) methanol and aqueous extract exhibited higher inhibitory effects on α-glucosidase activity compared to Kin now (IC50= 9.78 and 7.65 µg/mL) and Mosambi peel (IC_{50}=4.56 and 10.6 µg/mL).respectively. Similarly, methanol, acetone, and aqueous extract of Orange, Kin now and Mosambi inhibit the angiotensin-1-converting enzyme (ACE) activity. Moreover, methanol and acetone extract of Orange (IC_{50} =0.38 and 0.40 ug /mL) and Mosambi (IC_{50} = 0.44 and 0.46ug /mL) showed significant inhibitory capacity on ACE and aqueous extract of Orange (IC_{50} = 0.42 ug /mL), Kinnow (IC_{50}= 0.45 ug /mL) and Mosambi (IC_{50} = 0.48 ug /mL) showed significant inhibitory capacity on ACE. The study found that methanol and aqueous extract of Orange, Kinnow, and Mosambi peels showed great potential for anti-diabetic and methanol, acetone, and aqueous peels extract anti-hypertensive activities. Moreover, methanol and aqueous extract of Orange peels were more potent than Kinnow and Mosambi peels.

INTRODUCTION: *Citrus* fruit is an important medicinal plant that belongs to the Rutaceae family. These are the most popular fruits worldwide due to their delicious taste and pleasant flavor. It is a rich source of Vitamin C, fiber, and minerals, including many phytochemical compounds like Quercetin, Naringin, and Eriocitrin, which can be useful in various diagnostic and treatments.

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The flavonoids group showed the biological activity, including antimicrobial, antiproliferative, antilarvicidal, antiobesity, antiapoptotic, and antiviral activities [1, 2, 3]. Moreover, diabetes produces many harmful diseases in the human body, such as heart or cardiovascular disease,

hypertension, obesity, thrombosis, *etc*. It is found that diabetes mellitus type-2 patients contain abnormal serum lipid. Dyslipidemia contains low levels of HDL-cholesterol (High-Density Lipoprotein)-cholesterol, and high levels of LDL-cholesterol (Low-Density Lipoprotein and TGS (Triglycerides). This study suggested that excessive calorie intake produces many chronic diseases, including diabetes type- 2 and cardiovascular or heart disease [8, 9]. This is all related to oxidative stress and causes the prooxidants and antioxidants variance in cellular systems, damaging biological functions [21].

Citrus fruit peels show the α-amylase and α-glucosidase enzyme inhibitory activity and play an important role in the digestion of starch and glycogen, which is considered a strategy for treating disorders such as diabetes [3]. The peels of citrus fruits exhibited pharmacological activities such as antibacterial, anti-diabetic, antioxidant, larvicidal, anticancer, anticholinesterase, and anti-cardiovascular activity. Citrus fruits contain Flavonoids, Tannins, Alkaloids, Neringenin, Hesperidin, Pectin, and Phenolic compounds, which can be suppressed the inflammatory and hypertensive activity and prevent heart diseases in the human body [14, 15, 16]. This study exhibited anti-diabetic and anti-hypertensive activities and used citrus waste fruit peels as a traditional medicine in the community.

Diabetes mellitus type-2 is a serious health problem worldwide, which affects millions of people per year. Enzymatic degradation of carbohydrates and lipids in the cell is characteristic of hyperglycaemia which affects glucose metabolism in type-2 diabetes [5]. In treatment, hyperglycaemia is reduced by inhibiting carbohydrate hydrolyzing enzymes in diabetic patients. α-amylase and α-glucosidase enzymes break down carbohydrates complex to glucose which is rapidly absorbed in the bloodstream, causing hyperglycaemia. Previous studies reported that diabetes and hypertension are associated as 80% of type-2 diabetes patients are known to be hypertensive [2-4]. Hypertension is more likely to occur in diabetic patients, which increases the risk of producing cardiac and cerebral dysfunction. Angiotensin-converting enzyme (ACE) plays an important role in developing hypertension [10, 11]. Increased activity of ACE also increases the level of Angiotensin II, a potent vasoconstrictor, and increases blood pressure. However, hypertensive patients have reduced blood pressure by Angiotensin-Converting Enzyme (ACE) inhibitors, which convert Angiotensin I to Angiotensin II.

However, we observed that citrus fruit peels exhibited several biological activities, including antibacterial, antiviral, antifungal, antioxidative, anti-inflammatory, anticancer anti-hypertensive and anti-diabetic activities 5, 13 [17].

Furthermore, solvent and aqueous extract of Orange, Kinnow, and Mosambi are extracted from the pulp, peels, leaves, stem, bark, and roots. Citrus fruit peels showed many biological and pharmacological activities compared to other peels. It is used in the pharma, food and cosmetic industries, forming jams, jellies, drinks, cakes, ice cream, and food supplements. Therefore, this study reported that methanol and aqueous extract of Orange, Kinnow, and Mosambi peels are very effective in α-amylase, α-glucosidase, and angiotensin-converting enzyme (ACE) activities.

MATERIAL AND METHODS:

Sample Collection and Preparation: *Citrus* fruits were purchased from the local market of Allahabad, India. The fruits were identified and authenticated by the Scientist of Botanical Survey of India (BSI), Prayagraj. Using a laboratory blender, the peels were sun-dried to constant weight and pulverized into powder. Then after, peels of Orange (*Citrus sinensis*), Kinnow (*Citrus reticuleta*), and Mosambi (*Citrus limetta***)** fruits were dried at temperature (60 ºC) for 7 days. 20 g of dried peel powder of citrus fruits were crushed by a laboratory blender and stored in airtight closed containers for further use.

Extraction of Citrus Fruits:

Soxhlet Method: Orange, Kinnow, and Mosambi fruits dried peels Powder (10g) was dissolved in 100 ml of Methanol solvent and separated by Soxhlet extractor for 6 hours at room temperature. The solvents of methanol were used in this study. Solvent extracts of the different peels of citrus fruits were filtered by Whatman filter paper No.1, and extracts were stored in airtight container and kept at 4°C for future use.

Aqueous Extraction: 10 g of the dried *Citrus* peels powder soaked separately in 100 ml of aqueous at room temperature for 18 hours under shaking conditions at 120 rpm. After that, the extract was filtered by Whatman filter paper No 1. The extracts were stored in an airtight container and kept at 4°C for future use.

α-Amylase Assay: 250 µL of different concentration of Orange, Kinnow, and Mosambi extract (1–10 µg/mL) and 250 µL of pancreatic α-amylase (0.5 mg/mL) was incubated at 25°C for 10 min. In total, 250 µL of starch (1%) solution prepared with 0.02 M sodium phosphate buffer (PH- 6.9) was added to the previous mixture and was incubated for 10 min at 25°C [6, 7, 12]. Dinitrosalicyclic acid (1.0 mL) was added to the mixture to stop reaction [4]. The resultant solution was incubated for 5 min at 100 °C. The solution was allowed to cool, and aqueous was added to the mixture before the absorbance was measured at 540 nm [22-26]. The α-amylase activity was calculated and expressed as percentage inhibition using the following formula:

$$\% \text{ Inhibition} = [(Abs_{Control} - Abs_{Sample}) / Abs_{Control}] \times 100$$

α– glucosidase Assay: 50 µL of different concentrations of the Orange, Kinnow, and Mosambi fruits (1–10 µg/mL) was added to 50 µL of the enzyme solution (1.0 U/mL), which was incubated at 25°C for 10 min. Moreover, 50 µL of p-nitrophenyl-α-D-glucopyranoside solution (5 mM) which was prepared in 0.02 M phosphate buffer (pH 6.9) was added [18-20].

The solution was incubated at 37 °C for 10 min[1]. After the incubation, added 2ml of sodium carbonate was added to the mixture before the absorbance was measured at 405 nm [4]. The α-glucosidase inhibitory activity was expressed as percentage inhibition using formula (1).

Angiotensin-Converting Enzyme Inhibition Assay: The *Citrus* fruit peels inhibit the activity of ACE *In-vitro* was measured according to the spectrophotometric method of [27-30]. Briefly, 50µl of Orange, Kinnow, and Mosambi autolysate and150 µl of hippuryl-L-histidyl-L-leucine (HHL, 12.5 mM in 0.010 M sodium borate buffer containing NaCl 0.4 M, pH 8.3) were incubated at 37°C for 5 min. Then, 200 µl of ACE was added, and the mixture was incubated for an hour. The enzymatic reaction was stopped by adding 250µl of 0.5 N HCl. The hippuric acid formed by the ACE action on HHL was extracted from the acidified solution into 2 ml ethyl acetate by vortexing for 20s. The mixture was centrifuged at 3290×g for 15 min at 4°C, and 0.5ml aliquot of each ethyl acetate was transferred to clean tubes and evaporated by heating at 120°C for 20 min on a heating plate. The hippuric acid was redissolved in 3ml of 1M NaCl, and the amount formed was determined by its absorbance at 228 nm. Assay mixture without Orange, Kinnow, and Mosambi autolysate were referred to as control. The IC_{50} value was defined as the concentration of hydrolysate that inhibits 50% of the ACE activity. For calculating % ACE inhibition, the following formula was used:

$$\% \text{ inhibition} = 1 - BR_{sample} / BR_{control} \times 100$$

RESULT:

Effect of Citrus Fruit Peels on α-amylase and α-Glycosidase Activities: The anti-diabetic activity of methanol and aqueous extract of Orange, Kinnow, and Mosambi peels were estimated by different methods. The result obtained from the α-amylase and α-glycosidase enzyme assays where methanol and aqueous extract of Orange peels (IC_{50} = 18.4 and 9.43 µg/mL) and Kinnow peels (IC_{50} = 12.6 and 6.09 µg/mL) exhibited the higher capacity to inhibit α-amylase activity compared to Mosambi peels (IC_{50} = 11.6 and 6.54 µg/mL) as shown in **Table 1**.

Moreover, methanol and aqueous extract of these peels showed higher inhibitory effects on α-amylase activity than acarbose (IC_{50}=1.08 and 2.43µg/mL). Similarly, Orange peels (IC_{50} = 12.5 and 8.67 µg/mL) methanol and aqueous extract exhibited higher inhibitory effects on α-glycosidase activity compared to Kinnow (IC_{50} = 9.78 and 7.65 µg/mL) and Mosambi peel (IC_{50} = 4.56 and 10.6 µg/mL).

However, methanol and aqueous extract of Orange, Kinnow, and Mosambi peels exhibited higher inhibitory capacity on α-glycosidase activity than acarbose (IC_{50} =3.56 and 1.47µg/mL). Therefore, α-amylase and α-glycosidase enzyme assays show important therapeutic targets in treating type-2 diabetes.

TABLE 1: ANTI-DIABETIC ACTIVITY OF DIFFERENT CITRUS FRUIT PEELS

Enzyme (unit)	Orange		Kinnow		Mosambi		Acarbose(control)	
	M	DW	M	DW	M	DW	M	DW
α- amylase (µg/ml)	18.4	9.43	12.6	6.09	11.6	6.54	1.08	2.43
α- -glucosidase (µg/ml)	12.5	8.67	9.78	7.65	4.56	10.6	3.56	1.47

Methanol (M), Aqueous (DW)

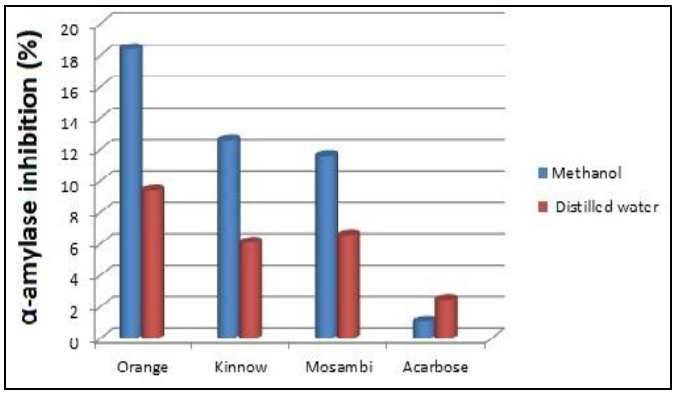

FIG. 1: A- AMYLASE (µL/ML) ACTIVITY OF DIFFERENT CITRUS FRUIT PEELS

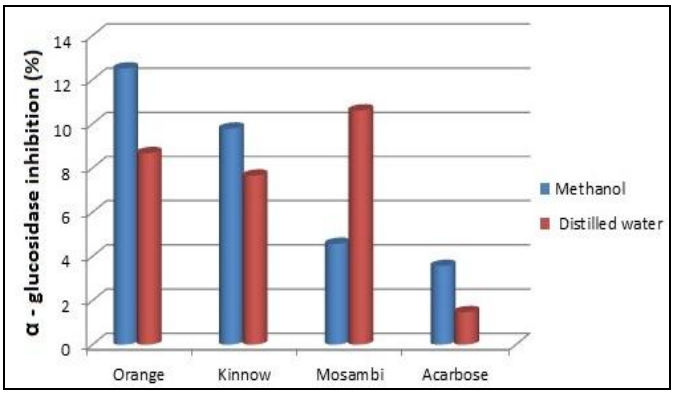

FIG. 2: A - GLUCOSIDASE ACTIVITY OF DIFFERENT CITRUS FRUIT PEELS

Converting Enzyme (ACE) Inhibition Activity of Different Citrus Fruit Peels: Orange, Kinnow, Mosambi Methanol, Acetone, and aqueous peel extract are exhibited Angiotensin Inhibitory Activity. Methanol and acetone extract of Orange (IC_{50}=0.38 and 0.40ug/ml) and Mosambi (IC_{50} = 0.44 and 0.46ug /ml) showed significant inhibitory capacity on ACE where the methanol and acetone extract of Kinnow does not show any Inhibitory activity against the ACE. Aqueous extract of Orange (IC_{50} = 0.42ug /ml), Kinnow (IC_{50}= 0.45), and Mosambi (IC_{50} = 0.48) showed significant inhibitory capacity on ACE, where methanol and acetone extract of Orange showed the highest inhibition activity on ACE when compared to methanol and acetone extract of Mosambi [27-29]. Aqueous extract of Orange and Mosambi exhibited stronger inhibition activity on ACE compared to aqueous extract of Kinnow.

Inhibition of ACE is an important therapeutic intervention in managing/treating hypertension. The decrease in ACE activity hinders the conversion of angiotensin I to angiotensin II, a vasoconstrictor implicated in elevated blood pressure. In addition, inhibition of angiotensin-II production can prevent the progression of type-2 diabetes at elevated levels. Angiotensin II may induce insulin insensitivity in the peripheral tissues, which is critical in developing this degenerative condition. This study observed that the methanolic and acetone extract of Orange, Kinnow and Mosambi peels reduced ACE activity. Moreover, the ACE inhibitor of the peels of different fruit, grapes, bananas, and apples, agrees with previous studies, inhibiting ACE activity *in-vitro*. These fruit peels exhibited stronger inhibitory capacity on ACE than other fruit peels. However, Orange and Mosambi exhibited stronger inhibitory effects than the Kinnow peels. Here we used the HHL chemical as a positive control and observed the value (IC_{50} = 0.51), which was higher than the extract.

TABLE 2: ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITION ACTIVITY OF DIFFERENT CITRUS FRUIT PEELS

Fruits name	Methanol	Acetone	Aqueous
Orange	0.38	0.40	0.42
Kinnow	-	-	0.42
Mosambi	0.44	0.46	0.42

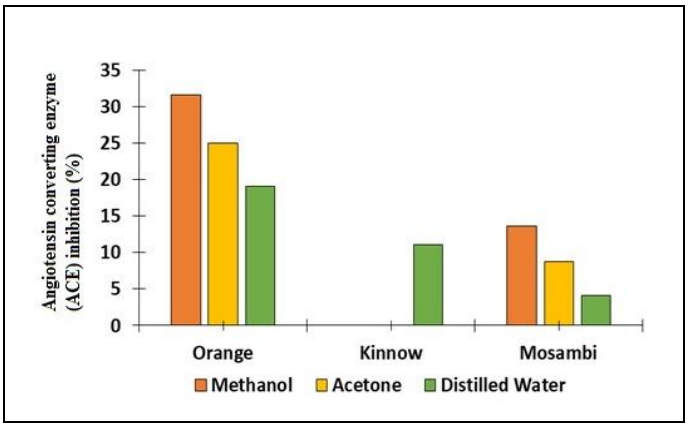

FIG. 3: ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITION ACTIVITY OF DIFFERENT CITRUS FRUIT PEELS

CONCLUSION: This study revealed that methanolic and aqueous extract of Orange, Kinnow, and Mosambi peels show *in-vitro* inhibitory effects on α-amylase and α-glucosidase enzyme assays and methanol acetone and aqueous extract show the anti-hypertensive activity (ACE). Moreover, Orange and Kinnow peels of methanol and aqueous exhibited higher anti-diabetic activities than Mosambi peels. Similarly, Orange and Mosambi extract of methanol acetone and aqueous exhibited higher anti-hypertensive activity than Kinnow peels. This study found that Orange, Kinnow, and Mosambi extract exhibited higher potential for anti-diabetic and anti-hypertensive agents.

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