

# Studies on Bitter Orange Peel Extract as an Anti-Obesity Agent.

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## ABSTRACT

In this work, the anti-obesity properties of the ethanolic extract from locally sourced bitter orange peels (*Citrus aurantium* L. fam. *Rutaceae*) were tested as a possible substitute for phenyl-propanolamine, a synthetic sympathomimetic agent commonly used in cold and catarrh remedy and an important ingredient in over-the-counter (OTC) weight loss products which was implicated for a vital non-reversible hemorrhagic stroke. Three albino rabbits were fed with meals mixed with the extract for six weeks, while three others that served as a control group were fed with meals free of the extracts. It was found that the rabbits in the test group lost considerable weight after the test period when compared with the controlled group. Encapsulation was done with each capsule containing extracts equivalent to 200 mg synephrine - the main active ingredient.

(Keywords: anti-obesity, bitter orange, phenyl-propanolamine, PPA, rabbits, encapsulation)

## INTRODUCTION

Phenyl-propanolamine (PPA) is a synthetic sympathomimetic drug. It is used in many over-the-counter (OTC) and prescription cough and cold medications as a decongestant and OTC weight loss products. Generally, the effect of sympathomimetic agents resembles the responses to stimulation of adrenergic nerves, but there are often differences in the details and the intensity of action of the drugs (Goodman and Gilman, 1990). Most actions of sympathomimetic agents include a peripheral excitatory action and peripheral inhibitory action on certain types of smooth muscles, such as blood vessels supplying the skin and skeletal muscle. Other actions like cardiac excitatory action, metabolic actions, CNS excitatory actions and endocrine actions.

Phenyl-propanolamine exhibits some side effects that include psychiatric, hypertensive, hemorrhagic palpitations, paresthesias, tremor, tachycardia, myalgias, reversible renal failure, and increased intra-cerebral pressure. Pseudoephedrine is safer than PPA when the patient does not have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination caused by an enlarged prostate gland. In the United States, none of the non-prescription products currently marketed has been proven to achieve a reasonable level of weight loss. The two compounds that have promising weight loss properties, PPA and Benzocaine, were the only two included in the Food and Drug Administrations' (FDA) list (Pray, 1999).

Benzocaine is not marketed for this purpose at present and PPA has finally met a well deserved end. In an attempt to obtain an alternative to PPA as an anti-obesity agent, bitter orange peel, which is the dried outer part of the pericarp of the unripe or nearly ripe fruit known as bitter, Seville, or bigerade orange has been tested using three albino rabbits which are fed with the extract for six weeks, while three albino rabbits served as a control group and were fed with meals not mixed with the extract and the weights of each group were compared after the test period. The bitter orange was obtained from a farm in Ifo, Ogun state, Nigeria.

## MATERIALS AND METHODS

### Materials

The following materials were used: fresh bitter orange peels, obtained from a farm in Ifo, Ogun State, Nigeria; and reagent grade chemicals such as absolute alcohol, aqueous hydrochloric acid, Mayer's reagent, Dragendorff's reagent, Benedict's solutions, ferric chloride, benzene, 10% ammonia solution, sodium pictrate paper,

pyridine, 2% sodium nitro-prusside, 20% sodium hydroxide, methanol, 2% solution of 3,5-dinitrobenzoic acid, aqueous sodium hydroxide, acetic anhydride, sulphuric acid, chloroform, glacial acetic acid, and concentrated sulphuric acid.

## **Methods**

**Preparation of Bitter Orange Peel Extract:** 350 g of dry powdered peels was packed into the soxhlet extractor and absolute alcohol was used to extract the constituents until extraction was completed. After extraction, the solvents were evaporated using rotary evaporator and the weight of the extract was determined and the percentage yield calculated. The extract was phyto-chemically screened.

**Determination of Percentage Synephrine in the Extract:** The total synephrine in the extract was determined by using the assay method described for ephedrine sulphate in the United States Pharmacopoeia (USP) (1980) modified by substitution of bromocresol green for methyl red. 2.4 g of extract was weighed, transferred to a separating funnel and dissolved in about 200 ml of water. The solution was saturated with sodium chloride (about 2 g) and 5 ml of 1N sodium hydroxide was added, and extracted with four 25 ml portions of chloroform. The combined chloroform extracts were washed by shaking with 10 ml of a saturated solution of sodium chloride and filtered through chloroform-saturated purified cotton into a beaker. The washed solution was extracted with 10 ml of chloroform, and added to the main chloroform extract. Bromocresol green was added and titrated with 0.1N perchloric acid. The titration was repeated twice and the average titre value was determined.

**Determination of Weight Reducing Properties of Bitter Orange Peel Extract:** Six albino rabbits were used for this test. They were placed into two groups of three animals each. The first group served as the control and the animals were fed with diets that do not contain the extract at a daily dose of 30 mg/kg. At the end of each week, the animals were weighed. The six albino rabbits were fed for six weeks.

**Encapsulation of Bitter Orange Peel Extract:** 45 g of the powder extract was mixed with 290 g of lactose as diluent. The two were thoroughly blended together and 5 g of talc was added and mixed together. Empty gelatin capsule shells were manually filled with the powder mix. Each of the capsule shells was filled with powder mix equivalent to 20 mg of synephrine, that is, 140 mg of powder mix synephrine, that is, 140 mg of powder mix.

## **Evaluation of Capsule Properties**

The capsules were evaluated for uniformity of weight and disintegration time.

**Uniformity of Weight:** 20 capsules were used for this test. The first capsule was weighted. It was then emptied of its content; after which the empty capsule shell was weighed. This procedure was repeated for the remaining capsules. The difference in the weights obtained yielded the weight of the content. The average weight of the content of the 20 capsules was then determined.

**Disintegration Test:** A six chamber disintegration apparatus (Comply, Germany) was used. Four tablets were placed in each of the chambers and the time taken for the first tablet and the last tablet to disintegrate was noted. The average in each chamber was taken and the values in all the chambers added together and the average determined. This gave the disintegration time.

## **RESULTS AND DISCUSSION**

The percentage yield of extract was 15.38% while the percentage of synephrine in the extract was 5.39%. This indicates that bitter orange peel has a very good potential as an anti-obesity agent due to the high synephrine level of the extract. Factors such as geographical location of the bitter orange tree, the level of maturity of the bitter orange fruits and methods of extraction could affect the percentage yield of synephrine in each extract. Also the phyto-chemical screening of the extract showed that it is non-toxic and hence suitable for human consumption. Table 1 shows the weight (g) of the albino rabbits after they were fed.

**Table 1:** Weights of the Albino Rabbits used for the Tests.

| Week | Group A Weight (g) |     |     | Group B Weight (g) |     |     |
|------|--------------------|-----|-----|--------------------|-----|-----|
|      | 1                  | 2   | 3   | 4                  | 5   | 6   |
| 0    | 584                | 611 | 602 | 593                | 575 | 580 |
| 1    | 584                | 612 | 603 | 594                | 575 | 579 |
| 2    | 585                | 612 | 603 | 592                | 573 | 579 |
| 3    | 586                | 614 | 605 | 589                | 571 | 577 |
| 4    | 586                | 614 | 605 | 589                | 569 | 575 |
| 5    | 587                | 615 | 606 | 587                | 567 | 573 |
| 6    | 597                | 616 | 608 | 586                | 566 | 572 |

Group A- Control group

Group B- Test group

The results obtained showed that rabbits 1, 2, and 3 that constituted the controlled group weighed 584 g, 611 g, and 602 g at the beginning and 597 g, 616 g, and 608 g, respectively at the end of the experiment. These results imply about 2.23%, 0.81%, and 1.00% increase in weights for controlled rabbits 1, 2, and 3, respectively, over the six weeks period.

For the test group rabbits 4, 5, and 6, the initial weights were 593 g, 575 g, and 580 g, while the final weights were determined as 586 g, 566 g, and 572 g, respectively. These results translated to weight percent decrease of about 1.18%, 1.57%, and 1.21% for test rabbits 4, 5, and 6, respectively. These results indicate that while the controlled group rabbits all gained weight, the test group members lost weight. The results thus strongly suggest that synephrine is reasonably effective as an anti-obesity agent.

The disintegration time determined for the prepared capsules was 5 minutes 57 seconds. This value obtained fall within the official range. The British pharmacopoeia (1993) specified that capsules must disintegrate within 30 minutes. The disintegration time determined is thus below the specified upper limit. The result obtained for the uniformity of weight of the filled capsule falls within the British Pharmacopoeia specification due to the fact that the highest deviation obtained was 7.14%.

## CONCLUSIONS

The present study has shown that bitter orange peel extract can be used as an alternative to phenylpropanolamine as an anti-obesity agent.

This bitter orange peel is widely distributed in tropical West Africa and can be harnessed for its anti-obesity potentials. The extract from the peel can be formulated into suitable dosage for obese patients. It has been established earlier before this study that synephrine (the main active ingredient in bitter orange peel extract) exerts its adrenergic actions through the stimulation of a different receptor ( $B_2$  receptors). Therefore series of side effects noticed with the use of other adrenergic drugs like ephedrine were not experienced when synephrine containing drug is being used.

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