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Determination of some components in *Valencia albedo* and monitoring its bioeffects in experimental mice

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ABSTRACT

This study aims to identify the most important components in the albedo layer of Valencia (*Citrus sinensis*) fruit peel, and to evaluate the effect of albedo on weight and blood glucose levels in experimental rats. The percentage of moisture, ash, fat, protein, carbohydrate and dietary fibers in albedo were (61.94, 3.57, 1.51, 3.19, 78.2, 13.45), respectively, and the content of phenolic compounds in albedo was 19.9 g GAE/kg. The albedo powder in the mice diet led to a decrease in weight or to preventing its gain compared to the diet without albedo powder in a statistically significant way ($p<0.05$), the addition of albedo powder to the diet also led to a decrease in blood glucose levels in the mice of the second group compared to the first group, but with a statistically insignificant difference ($p>0.05$).

Keywords: Valencia fruit, albedo, weight, blood glucose, diet, experimental rats

INTRODUCTION

Citrus species are known as one of the most widely grown products in the world, as it is cultivated in more than 100 countries. The global production of citrus is estimated at about 88-115 million tons annually[1]. Brazil is considered the most productive country of citrus in the world[2], while Syria ranks third in the Arab world in citrus production and twentieth in the world as its production of about one million tons represents about 1% of global production[3].

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Citrus is the largest genus in the Rutaceae family, which consists of 150 genera and about 1,600 species, but the exact number of species is still unclear[4]. Among the types of citrus fruits, orange production constitutes the largest portion of the total world production, followed by mandarins, then lemons, and finally grifons. The most common sweet orange is the 'Valencia' as it is among the most widely cultivated varieties worldwide, due largely to their high productivity[5,6].

The orange fruit consists of an outer layer (peel) and an inner substance (pulp). The outer shell is divided into two parts: an outer part is the colored part (epicarp or exocarp) and is called flavedo, and an inner part is the white part (mesocarp) and is called albedo. The inner substance (pulp) is called endocarp and contains vesicles with juice[7].

Citrus fruits are consumed fresh, or the different parts of the fruits are used in many fields (foods and pharmaceutical industries)[4]. Citrus fruits are also consumed after they have been processed and converted into many forms of products where the most common product of citrus fruits is fresh or concentrated juice. It is estimated that the industrial processing of citrus fruits uses 33% of citrus fruits to produce juice[8]. The process of converting citrus fruits to obtain juices generates a large amount of by-products (residues) that reach about 50-70% of the weight of the fruit, most of it are peels (60-65%)[9].

Citrus waste is often thrown into landfills or rivers, which causes environmental and water pollution[10]. As another option, citrus waste is also disposed of by burning[11].

Although citrus by-products are sometimes called citrus waste, they still contain large amounts of valuable compounds[12]. So, the concept of recycling and reuse is necessary in order to reduce the waste generated and the associated damages. In addition, this may reduce the excessive consumption of raw materials and increase economic profits and allow the use of the biological value of citrus waste[13], especially that citrus by-products are rich in contents of high health and economic value, such as proteins, fats, sugars, essential oils and vitamins, in addition to containing polyphenols and dietary fibers[8].

Phenolic compounds are plant secondary metabolites; have lots of beneficial effects on human health. There are currently about 8,000 polyphenols, generally classified into flavonoids and non-flavonoids (phenolic acids, coumarins, stilbenes and lignans)[14]. Flavonoids are classified into subclasses including flavones, flavanones, isoflavanones, flavonols, isoflavanoids, anthocyanidins, and catechins[15]. The flavanones are the most present in citrus fruits among the flavonoid groups, and the flavanones are more concentrated in the albedo and membranes than in juice bags[4]. The most important flavonoids found in

sweet oranges are hesperidin, hesperitin, diosmin, and diosmetin, in addition to narirutin[16]. Phenolic compounds structure is rich in hydroxyl groups which enable these compounds to be antioxidants and scavenge free radicals[17,18]. Antioxidants are important for health and disease prevention by reducing the damage caused by free radicals[18-20], like its anti-inflammatory[14,21], antibacterial and antifungal activity, beside its anti-hyperglycemic[22,23], and anticoagulant effects[24]. In addition, several in vitro studies have been conducted to evaluate the effects of citrus flavonoids on obesity. It has been found to have an effect on obesity by multiple mechanisms[25,26]. It was also found that effects on total body weight were more pronounced in studies using citrus peel extracts instead of standardized flavonoids, which indicates the possibility of synergy between the different phenols present in the peels[27].

Dietary fibers have been defined by The National Academy of Sciences as indigestible carbohydrates and lignin present in plants[28]. Dietary fibers are often classified based on their water solubility into water-soluble fibers (SDF) such as pectin and gum arabic, and insoluble fibers (IDF) such as cellulose, hemicellulose, and lignin. Citrus waste is a good source of dietary fiber where the main part of citrus waste in terms of dietary fiber content is albedo[16]. Albedo is a rich source of dietary fiber, especially pectin[9], as the proportion of pectin in orange albedo reaches 12-28%[29]. Studies indicate that increasing dietary fiber in the daily diet is very important for maintaining good health[16]. Frequent consumption of dietary fiber is associated with a lower risk of chronic diseases such as cardiovascular disease, diabetes, and obesity[30]. Considerable research has been conducted to evaluate the effect of dietary fiber on body weight, and it has shown an inverse relationship between fiber intake and body weight gain[31].

Albedo has better qualities than other sources of dietary fiber due to the presence of associated bioactive compounds such as flavonoids (mainly flavanones) and vitamins, which may lead to more health-promoting effects in addition to those found in dietary fiber[32].

Due to the spread of Obesity and Diabetes in addition to diseases and discarders related to them; and the possibility of reducing the risk of these diseases by regular and frequent consumption of vegetables and fruits (especially since there has been increased interest in using natural products instead of artificial ones in treating diseases). The importance of this research is the possibility of usage of the large amount of citrus waste and its ingredients in the treatment or prevention of diseases.

Therefore, the aim of this research is to study the biological effects of Valencia orange waste on body weight and blood glucose in experimental rats.

METHODOLOGY

Instruments

Analytical balance (RADWAG, AS 220/C/2), Air oven (Janat instruments), Electric grinder, Glucometer (O2 BG-202), Spectrophotometer (Jasco V-530 UV), Water bath Ultrasonic (K & H Industries).

Orange sample collection and preparation for the study

The fruits of Valencia (*Citrus sinensis*) were collected from the local market in Lattakia in the season of 2022, the fruits were washed and peeled manually, then the albedo was separated and cut into small pieces and dried in the air oven. Afterward, it was ground into a fine powder and kept in the refrigerator (-4°C) until use[33].

Chemical analysis

Moisture content, total ash, protein and fiber content were calculated by using AOAC Standard Method. Moisture content was determined by an oven method (drying until constant weight)[34]. Ash content was determined by using a muffle furnace maintained at 550°C for five hours[35]. Protein was determined by the Kjeldahl method, fiber was obtained by digesting sample with H_2SO_4 and NaOH followed by incinerating in muffle furnace at 550°C[34,36]. Fat was determined using hexane as a solvent, where about 0.5 g of the sample was weighed and soaked in 10 ml of hexane for a week (the tube was covered well), then hexane was taken with the fat substance in a clean and weighed plastic can, and left at room temperature until the hexane evaporated completely and the fat substance remained in the can (until weight stability), and the weight of the can with the oil substance was recorded. The percentage of fat in the sample was calculated according to the law:

Fat (%) = weight of the fat substance x 100 / weight of the sample

= (weight of the can with the fat substance - weight of the empty can) x 100 / weight of the sample

Carbohydrate content was calculated from the difference of 100 – [% moisture + % ash + % protein + % fibre + % fat][37].

Determination of pectin

The amount of pectin was determined in the dried, unground pieces of albedo using acid hydrolysis[38].

Extraction and determination of phenolic compounds

Phenolic compounds were extracted using the Ultrasound water bath[39]. About 5g of the sample was weighed and placed in a beaker with 50ml of ethanol 80%, then the beaker was placed in the water bath at a temperature of 35-40°C for half an hour, after that, the mixture was left to cool at room temperature, then filtered, and the extract was kept in the refrigerator until the levels of phenolic compounds were determined. For the determination of phenolic compounds levels, the Folin-Ciocalteu method was used[40].

Experimental animals

The study included normal adult female mice of the Balb-C species, ages (2-4) months and weighing (15-35) grams. They were placed in special cages that allow them to eat food and drink water easily, at room temperature (24 ± 2)°C in 12/12-hour light/dark cycles. The experiment was conducted in the laboratory of the experimental animal incubator at the Faculty of Pharmacy, Tishreen University, Syria. Ethical approval number: 524.

Experimental design

Eighteen mice were divided into two groups (n=9 in each group). The experiment lasted eight weeks. In the first week, mice were left to adapt to the laboratory conditions and were given normal food without additives. In the second week until the eighth week, each group was given its own food, as follows[41]:

1. First group (Normal Diet: ND): normal food without additives

2. Second group (Normal Diet with albedo: ND+A): normal food with albedo

Table 1 shows the food components of each group with their proportions:

Table 1. Food components of each group with their proportions

Component	First group	Second group
bread	80%	60%
corn	20%	20%
albedo	-	20%

The food was prepared by weighing the dry ingredients, then kneading it with water until it becomes a dough that can be formed, then the dough was formed in the form of small pieces and air-dried.

The weight of the mice was measured once a week, and the blood sugar was measured in the last week after fasting for 16 hours by taking a drop of blood from the caudal vein and using the O2 BG-202 strip glucometer. These measurements were taken for each mouse separately.

Statistical analysis

The statistical study was conducted using the SPSS version 26 program, the Independent Samples T Test was used. P values lower than 0.05 were defined as statistically significant and corresponded to a confidence level of (95%).

RESULTS and DISCUSSION

Chemical analysis

Table 2 shows the values of the components that were determined in the albedo (Mean ± SD):

Table 2. Values of the components in the albedo (Mean ± SD)

Component (%)	
Moisture	61.94 ± 1.003
Ash	3.57 ± 0.33
Fat	1.51 ± 0.34
Protein	3.19 ± 0.33
Carbohydrate	78.2
Fiber	13.45 ± 0.71
Pectin	7.03

The result of moisture in the albedo was close to moisture levels in other studies, where it was 62.67% and 65.46%[42,43]. In a study conducted in Tunisia; researchers showed that citrus peels contain a very high level of water, up to 75%, this provides a suitable environment for mold growth, so it must be used immediately or stored under appropriate conditions until it is used[39]. The value of ash in our study converged with the result of a study conducted in 2021, where the percentage of ash was 3.21%[42]. According to a Brazilian study, the value of ash in the current study is considered a high value. The high ash value indicates that orange albedo contains a high content of minerals such as calcium, potassium, sodium, iron, copper, copper and magnesium[2,44].

The results of fat and carbohydrate in this study (1.51% and 78.2%, respectively) was higher than the fat and carbohydrate values reported by some other studies (0.27% and 57.15%, respectively)[45,46], while the value of protein (3.19%) was lower than the value reported by F. Omajasola et al. which was 4.69%[46].

The percentage of fiber in the albedo was 13.45%, which is higher than the value found by Mohammad et al. in Egypt (9.92%)[47], but lower than the value found by another study, where it was 27.67%[46]. Orange peel has a high level of fiber, and its unique physical and chemical properties make it suitable for food applications[47].

The result of pectin in this study was 7.03%, which is consistent with the result of the study conducted by Al-haj in 2022, where it found that the percentage of pectin in albedo ranges between (5.34-13.57%), depending on the time of harvesting the fruit[38].

The level of phenolic compounds was found to be equal to (19.9 ± 0.132) g GAE/kg, which is close to the value measured in one study, which was 17.16 g/kg[48], and higher than the result in a study conducted in Greece by Athanasiadis et al. where it was 9.2 g/kg[49] The levels of phenolic compounds in Valencia peel indicate a good antioxidant activity, as the higher the total content of phenolic substances, the higher the antioxidant capacity[50]. In addition, it gives an indication of the presence of antimicrobial activity according to some researchers[51].

The difference in the values of phenolic compounds between this study and some other studies may be due to the different solutions used to extract the phenolic compounds, or to the difference in the temperature at which the peels were dried, as it was found to affect the extraction yield of the phenolic compounds (drying at 80°C allows obtaining higher content of phenolic compounds compared to drying at 60°C and at 40°C for a longer period of time)[37,52].

In general, the difference in the levels of nutrient compounds in citrus cultivars or within the same cultivar can be attributed to climatic factors (type of soil, exposure to sunlight, rainfall...), genetic factors (diversity), and agricultural factors (maturity stage, fertilization, and irrigation...) and the analytical methods used[37].

It can be concluded that orange albedo has important properties and can be a promising source of nutritional compounds which play an important role in evaluating food quality such as dietary fiber and phenolic compounds and can be used as natural sources of functional ingredients or food additives[53], in addition to their good content of proteins and carbohydrates.

Effect on weight

Obesity is a chronic disease associated with an increase in the mass of adipose tissue, abnormal fat distribution and weight gain equal to or greater than 20% of normal weight[54]. Basically, obesity is a typical consequence of an imbalance

between calories in and calories out where the calories ingested are greater[55]. Obesity is a modifiable risk factor for type 2 diabetes, coronary heart disease, and hypertension[56]. The mainstay in the non-pharmacological treatment of obesity is diet and exercise. However, prescribing anti-obesity drugs can be a catalyst for obese patients who fail to achieve weight loss through diet and exercise[54]. Because of the adverse effects of these drugs; There has been a renewed interest in medicinal plants[57]. In recent years, the study of using citrus fruits in obesity and associated metabolic disorders prevention and treatment has attracted increasing attention[41].

Table 3 shows the total weights of the mice in the first week (the acclimation week), the second week, and the last week:

Table 3. Weights of the mice

	First group ND	Second group ND+A
Weight in 1st week	259	206
Weight in 2nd week	258	209
Weight in last week	277	210

Weight comparison between the Normal Diet group (ND) and the Normal Diet with Albedo group (ND+A)

For the effect of albedo on the weight of the mice; it was observed that the weight of the mice of the second group (ND+A) - where albedo was added to the diet - was significantly lower compared to the first group (ND) ($p<0.05$). That is, albedo prevented weight gain when added to the diet.

As mentioned earlier; albedo contains an important amount of fiber, especially pectin, and it also contains flavonoids. The effect of albedo on weight may be due to these two components.

These results agreed with the results of a study conducted by Osfor et al., which showed a decrease in body weight in rats fed a diet containing 20% *Citrus aurantium* albedo, which was attributed to a decrease in food consumption. This may be due to the high fiber content in albedo (about 10% relative to dry weight), specifically pectin, as the pectin present in orange peel can help reduce appetite [58].

These findings were supported by a study that investigated the effect of pectin on weight, which concluded that a high-fat diet with pectin led to weight loss

and reduced weight gain compared to a high-fat diet. This suggests that soluble fiber in diets may reduce weight gain caused by high nutrition. In general, dietary fiber may contribute to weight loss through several mechanisms including delaying gastric emptying (which give a feeling of fullness) and preventing fat absorption[59]. Thus, increasing the amounts of soluble dietary fiber in diet may be helpful method for weight reduction[60].

Studies that dealt with the effect of adding orange albedo on weight loss indicate the role of phenolic compounds as a study in Brazil determined content of phenolic compounds in albedo and the antioxidant activity of these compounds and indicated that the antioxidant activity of albedo and its beneficial metabolic effects may be linked to reducing oxidative stress associated with obesity. Therefore, this opens prospects for the development of food products based on the use of albedo for the prevention and treatment of obesity[61].

Citrus flavonoids have also effect on caloric intake[62], and inhibition of amylase function[63]. For example, some citrus flavonoids can suppress appetite by influencing hormones that control appetite (such as hesperidin and naringenin) or activating receptors that also suppress appetite (such as naringenin and naringenin), while both the flavonoids naringenin and nobiletin have been shown to increase energy expenditure in heat-producing brown adipose tissue[64].

Another anti-obesity strategy is to enhance lipolysis and reduce lipogenesis to reduce fat deposits by affecting enzymes. Some flavonoids, including naringenin, luteolin and hesperidin, have the ability to target enzymes such as fatty acid synthetase (FAS) and lipase Hormone-sensitive (HSL), which is involved in the mechanisms responsible for both the dissociation of existing fat cells or the generation of additional fat cells[62]. Additionally, hesperidin, neohesperidin, and luteolin have an inhibitory effect on the enzyme pancreatic lipase (PL) which is involved in the digestion of triglycerides leading to a strong effectiveness in the treatment of obesity as well[65]. In addition, naringenin, hesperidin, and quercetin were found to support the targeting of adipocytes (fat cells) through the process of apoptosis and thus reduce adipocyte numbers[66].

Effect on blood glucose levels

Diabetes mellitus is a chronic metabolic disorder characterized by higher blood sugar levels than normal values, it is caused by the inability of the pancreas to produce sufficient insulin, or it results from the ineffective use of the insulin that is produced[67].

There is a condition called “prediabetes” which is a chronic metabolic condition in which blood glucose values are higher than the upper limit that is con-

sidered normal, but less than the lower limit for diagnosing diabetes[68]. Prediabetes progresses to diabetes in up to 70% of individuals during their lifetime[69]. This condition may be reversible through lifestyle modification, by adopting a healthier diet and increasing levels of physical activity[68].

In our study the blood glucose values of the mice were measured in the last week of the experiment, after a 16-hour fasting, where a drop of blood was taken from the caudal vein, Table 4 shows the blood sugar values of the mice in each group:

Table 4. Blood sugar values of the mice

	ND	ND+A
1	**134***	61
2	**88**	74
3	**66**	61
4	**64**	78
5	**62**	58
6	**62**	**L
7	**85**	58
8	**85**	72
9	**62**	57
Mean ± SD	**71.75 ± 11.91**	64.87 ± 7.98

*Outlier excluded
**Low value not measured by instrument (L<30mg/dl)

Comparison of blood glucose levels between the Normal Diet group (ND) and the Normal Diet with Albedo group (ND+A)

Our results showed that ND+A mice had lower blood sugar values than the first group that ate a normal diet without albedo, but in no significant difference ($p>0.05$).

These results do not agree with the results of a study showed that the rats' intake of albedo in the proportions of 10% and 20% as a source of fiber in food significantly reduced blood glucose levels. This may be due to the presence of dietary fiber and polyphenols[58].

A lot of studies have examined the relationship between dietary fiber and diabetes. large number of reports indicate that soluble fiber (which includes pectin) can significantly improve glycemic control[70]. In general, dietary fiber can reduce blood glucose by increasing satiety by different mechanisms: increasing chewing, forming a gel in the stomach that delays gastric emptying, and reducing the interaction between lumenal contents and digestive enzymes, and thus reduces glucose absorption[71].

A study carried out in China on pectin extracted from orange peels has confirmed that experimental rats which consumed pectin had significant increase in hepatic glycogen content, and thus can reduce blood glucose, meaning that citrus pectin can enhances insulin sensitivity by stimulating hepatic glycogen synthesis. Pectin improved glucose tolerance, as was shown by Fasting Blood Glucose (FBG) and the Oral Glucose Tolerance Tests (OGTT), meaning that pectin reduced insulin resistance, which led to improvements in glucose metabolism[72].

In addition to pectin, phenolic compounds in albedo have beneficial effects on pancreatic cells by neutralizing oxidative stress due to their antioxidant activity, since previous studies have shown that high blood sugar leads to deterioration of pancreatic cells due to oxidative stress[73]. Some studies investigated the effect of the flavonoid's hesperidin and naringenin on blood sugar in experimental rats, where a significantly lower blood glucose was observed compared to the control group. Another study has found hypoglycemic effect of both hesperidin and naringenin, this effect was mediated by changes in hepatic glucose-regulating enzyme activities in mice, as these compounds increased hepatic glucokinase (an enzyme involved in the conversion of glucose into glycogen) and glycogen, and decreased levels of the enzyme glucose-6-phosphatase (involved in the breakdown of hepatic glycogen into glucose units), in addition to an increase in plasma insulin levels at the end of the study[73]. Other studies provide evidence that naringenin can inhibit intestinal glucose uptake as well as renal glucose reabsorption[74] in addition to significantly increasing glucose uptake into muscle and liver cells, which contributes to reduce blood glucose[58].

Obesity and diabetes are among the widespread diseases in the world, and the medications used to treat it have many side effects. Our study suggests that adding the *Valencia albedo* to the diet may help prevent or slow the development of these diseases due to beneficial health effects of active ingredients, like dietary fibers and polyphenol, which have shown weight and blood sugar lowering effects by several mechanisms.

STATEMENTS OF ETHICS

The protocols used in this study were following the guide for the care and use of experimental animals. The experiment was conducted in the laboratory of the experimental animal incubator at the Faculty of Pharmacy, Tishreen University, Syria. Ethical approval number: 524.

CONFLICT OF INTEREST STATEMENT

All authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to data collection and analysis, methodology, review, editing, and study design. All authors contributed to revision and approval of the final manuscript.

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