Red Grape Skins Red uce Hyperuricemia Induced by High Fructose Intake in Rats

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Abstract:
Hyperuricaemia has grown to be an important health issue, since resulting in the manifestation of gout, renal damage, metabolic and hemodynamic abnormalities, called metabolic syndrome (MS). Also, high fructose intake, which lastly elevated dramatically as fructose-based sweetened beverages and foods and humans appear to be more sensitive for its effects, causes MS including hyperuricemia, dyslipidemia, hypertension, insulin resistance, obesity, and promotions of oxidative stress, inflammation, and endothelial dysfunction through nitric oxide (NO) generation impairment. Nowadays, growing research on grape phenolics has focused on how their biological effects may improve human health; while there is no sufficient knowledge about hypouricemic effects of red grape skin (RGS), as important and largely byproduct; and numerous investigations have been done to identify safe and effective anti-hyperuricemia products derived from natural sources. Consequently, this investigation was conducted to learn more about the possible impacts of RGS on fructose-cause MS and hyperuricemia. Main chemical composition, phenolic and anthocyanins contents, and antioxidant activity of RGS were measured. Hypouricemic effects of dried RGS (DRGS) examined in metabolic syndrome rats induced by high fructose intake as 10% of drinking water for 8 weeks in which DRGS were supplemented as 2.5 and 5 % of the diet at last 4 weeks. Also, sensory evaluation of DRGS supplemented cake was done. The results showed that RGS fraction was 21.96% of whole grape fruit and it has considerable levels of fiber, total phenols, anthocyanins, and antioxidant activity. DRGS able to block the features of fructose-induced MS and reduce uric acid by several effects as antioxidant action in each of renal tissue and serum and regulate renal NO production which reflect better endothelial

function, improve renal and serum lipid peroxidation marker (MDA) and lipid profile; as well as improve kidney function and levels of liver enzymes. Also, it is worthy observed that there were no significant differences between two experimental doses of DRGS in almost biomarkers, indicated that two doses can serve as a good choice and may be no need to higher dose with this model. Sensory evaluation of 2.5 and 5% DRGS cakes showed a good sensory property and over all acceptability as compared to control cake; with important observation during cake preparation of fast height and maturity of cake in line with the levels of DRGS supplementation, producing important economical and technological agents. Therefore, it could be concluded that low levels of fructose intake would be necessary and RGS, a largely natural byproduct with its chemical and biological properties, can be accepted as beneficial diet supplements either as colorant, flavoring, baking height supporting and/or preservatives agents of food or as novel, safe, and efficient functional food because of its hypouricemic, and renal protective actions against high fructose intake. Anywise more studies are needed to prove and detect the perfect dose, period, and type of grape toward these respects in different experimental animal models and in humans.

Keywords: Uric acid, antioxidant activity, kidney functions, lipid profile, liver enzymes, phenols, anthocyanins, fiber, byproduct, nitric oxide (NO), endothelial dysfunction, oxidative stress, functional food, supplements, Sensory evaluation, cake.

قشر العنب الأحمر يقلل ارتفاع حمض يوريك الدم في الفئران المصابة بواسطة المأخوذ العالي من الفركتوز

المستخلص :

أصبح ارتفاع حمض اليوريك بالدم من أكبر المشاكل الصحية على مستوي العالم حيث يؤدي الى النقرس وتلف الكلي واضطرابات ميتابوليزمية تعرف بالمتلازمة الميتابوليزمية. هذه المتلازمة الميتابوليزمية والتي تشمل "ارتفاع حمض اليوريك، اضطراب صورة الدهون بالدم، ارتفاع الضغط، مقاومة الأنسولين، السمنة، استثارة الشقوق الحرة والالتهابات، واضطراب وظيفة الأغشية الداخلية من خلال تلف انتاج أكسيد النيتريك" تحدث بسبب المأخوذ العالي من الفركتوز والذي تزايد بشدة في الآونة الأخيرة نظرا لاستخدامه بكثرة للتحلية في العديد من المشروبات والأطعمة، والذي يبدو أن الانسان أكثر حساسية من القوارض لتأثيراته الضارة بالنسبة لارتفاع حمض اليوريك. ولقد تزايد أيضا في الآونة الأخيرة الاهتمام بالمركبات الفينولية للعنب والمتركزة في القشور والبذور وتأثيراتها البيولوجية المرتبطة بصحة الانسان مع عدم وجود

معرفة أو دراسات كافية عن إمكانية التأثير الخافض لحمض اليوريك بواسطة قشور العنب الأحمر والتي تمثل جزء كبير وهام من مخلفات استخدام العنب في الصناعة. كما أن هناك العديد من الدراسات للتعرف على المواد الطبيعية والفعالة المضادة لارتفاع حمض اليوريك والآمنة من الآثار الجانبية الضارة. ولذلك كان هدف هذا البحث دراسة التأثيرات المحتملة لقشور العنب الأحمر علي ارتفاع حمض اليوريك وبعض الاضطرابات الميتابوليزمية الناتجة عن المتناول العالي من الفركتوز. تم تحليل التركيب الكيميائي الأساسي، والمحتوي من الفينولات والانثوسيانينات، والنشاط المضاد للأكسدة في قشور العنب الأحمر؛ كما تم دراسة تأثير قشر العنب الأحمر الجاف الخافض لحمض اليوريك في الفئران المصابة بالمتلازمة الميتابوليزمية بواسطة ١٠% فركتوز في ماء الشرب لمدة ٨ أسابيع، حيث تم تدعيم الوجبة بقشر العنب الأحمر الجاف بنسبة ٢,٥ و٥ % في آخر ٤ أسابيع. كما تم التقييم الحسي لكيك مدعم بقشر العنب الأحمر الجاف بنفس النسب. وأوضحت النتائج أن قشر العنب الأحمر يمثل ٢١,٩٦% من اجمالي فاكهة العنب وبه كميات معتبرة من الالياف والفينولات والأنثوسيانينات والنشاط المضاد للأكسدة؛ كما استطاع أن يتحكم ويحسن ارتفاع حمض اليوريك وبعض أعراض المتلازمة الميتابوليزمية الناتجة عن المأخوذ العالي من الفركتوز بواسطة عدة تأثيرات مثل زيادة النشاط المضاد للأكسدة في كل من السيرم ونسيج الكلي، تنظيم انتاج أكسيد النيتريك والذي يعكس تحسن وظيفة الأغشية الداخلية لنسيج الكلي، وتحسين مؤشر MDA الدال علي أكسدة الدهون بكل من السيرم ونسيج الكلي وكذلك صور الدهون؛ علاوة على تحسين وظائف الكلي ومستويات انزيمات الكبد. ومن الجدير بالملاحظة أيضا أنه لا توجد اختلافات معنوية بين جرعتي قشر العنب في معظم المؤشرات مما يدل على أن كلا الجرعتين يمكن استخدامهما بتأثير بيولوجي جيد وأنه ربما لا حاجة للجرعة الأكبر مع هذا النموذج التجريبي. كما كانت الخصائص الحسية والقبول العام جيد للكيك المدعم بقشر العنب الأحمر الجاف بنسبة ٢,٥ و٥%؛ مع ملاحظة هامة اثناء الاعداد وهي سرعة ارتفاع ونضج الكيك بصورة طردية مع مستويات التدعيم بقشر العنب مما يفيد اقتصاديا وتكنولوجيا. وعلي هذا يمكن استنتاج أن تناول مستويات منخفضة من الفركتوز ضروري؛ وأن قشر العنب الأحمر كمخلفات طبيعية كبيرة بخصائصه الكيميائية والبيولوجية يمكن أن يكون مدعمات مفيدة سواء تكنولوجيا كمواد ملونة أو مكسبة للنكهة أو مدعمة لارتفاع المخبوزات أو حافظة، أو كغذاء وظيفي مبتكر وفعال وأمن بسبب تأثيره الخافض لحمض اليوريك والواقي للكلي ضد تأثير المأخوذ العالي من الفركتوز. على أي حال هناك حاجة لمزيد من الدراسات لإثبات وتحديد أفضل جرعة ومدة وكذلك نوع العنب والجزء الأمثل تجاه هذه التأثيرات في نماذج تجريبية مختلفة للحيوان وفي الانسان.

الكلمات الاسترشادية: النشاط المضاد للأكسدة، وظائف كلى، صورة الدهون، انزيمات كبد، فينولات، انثوسيانينات، الياف، ناتجات ثانوية، أكسيد نيتريك (NO)، اختلال وظيفة الاغشية الداخلية، الشقوق الحرة، الغذاء الوظيفي، المدعمات، تقييم حسي، كيك.

Introduction

Hyperuricaemia has grown to be an important health issue, in which it is a clue to the development of gout, kidney injury, and anomalies in metabolism and hemodynamics known as metabolic syndrome (MS), described by hypertension, obesity, dyslipidaemia, glucose intolerance, and insulin resistance as evidence by several studies as **Nakagawa et al., (2006) Zhang et al., (2012) and Essawy et al., (2012).**

Hyperuricemia, caused by faulty purine metabolism involving hyperproduction and inadequate uric acid excretion and medications that lowers the excretion of urate **(Hwa et al., 2011).** Hyperuricemia can support the development of urate crystals that cause gout in the joints, urate nephropathy (UN), and inflammatory arthritis **(Vitart et al., 2008 and Chen et al., 2013)**, as about 10% of people with hyperuricemia **(Vitart et al., 2008).** Patients with hyperuricemia or gout are usually treated with agents that inhibit uric acid biosynthesis or enhance the excretion of uric acid, as well as with anti-inflammatory components **(Hwa et al., 2011)**. Lowering uric acid is the key to prevent gout flares can achieved by limit drinking beverages with fructose-rich corn syrup that used as the most prominent sweetener and purine-rich foods (**Kedar and Simkin, 2012 and Hainer et al., 2014)**

Fructose intake has elevated dramatically over the last century as fructose-based sweetened beverages and foods, where it is greatly industrial utilize in syrups, soft drinks, juices of fruit, jams, candies, and baked products as sweetener in the world **(Fan et al., 2014 and Vieira et al., 2015)**.Several animal models, ecological studies, and select human trials of fructose overfeeding have proved that excessive fructose intake is a danger agent for MS plus produces hyperuricemia and kidney damage in peoples and rodents **(Zhang et al., 2012; Ha et al., 2013; Fan et al., 2014; Vieira et al., 2015 and Ma et al., 2015)**. Humans lack uricase and then develop hyperuricemia more sensitive to diet than mammals that do not express uricase or rodents that have an active uricase so high fructose levels are needed to cause severe metabolic alterations and kidney impairment in rats since human deficiency uricase, they seem to be considerably more vulnerable to fructose's impacts; and lower levels of fructose would be necessary in humans **(Sánchez-Lozada et al., 2007; Johnson et al., 2009 and Tapia et al., 2013)**. Fructose is an effective catalyst for ATP breakdown which results in uric acid creation **(Kedar and Simkin, 2012);** also, **Chen et al., (2013) and Fan et al., (2014)** who found that excess fructose-

caused hyperuricemia is correlated by a reduced kidney excretion of uric acid. Several studies on animals have supported that consuming a lot of fructose causes MS including hyperuricemia, dyslipidemia, hyperleptinemia, insulin resistance hyperinsulinemia, and chronic inflammation as **Vasiljević et al., (2013)**; since these correlations are explained by several biological mechanisms based on animal models, involving increased lipogenesis and hypertension mediated by uric acid **(Ha et al., 2013)**, and oxidant strain **(Taleb-Dida et al., 2011 and Wang et al., 2015)** induced by fructose. Also, UA can act to promote oxidative stress, inflammation, and endothelial dysfunction through subsequent nitric oxide (NO) generation impairment. Therefore, regarding the abovementioned explanations for the varied mechanisms, it's critical to cut down UA and oxidative strain, and control NO production to block the features of fructose-induced MS as explained and found by many studies as **Hu et al., (2009); Zhang et al., (2012) and Chen et al., (2013)**.

Free radicals are associated with chronic human diseases in which induce DNA damage, cause peroxidation of lipids and alter the cell membrane's function and structure of resulting in cellular membrane damage and can produce several inflammatory substances related to tissue damage and a general inflammatory reaction **(Nijveldt et al., 2001; Halliwell, 2002 and Philpott et al., 2009)**.

Additionally, plant polyphenols' beneficial health impacts are frequently linked to their powerful antioxidant properties **(Taleb-Dida et al., 2011 and Wang et al., 2015).** Flavonoids could enhance an additional effects of endogenous antioxidant substances which were depleted by elevated production of reactive oxygen species (ROS) during illness. Flavonoids interfere with more than three various free radical–output systems, in addition to increase the function of endogenous antioxidants **(Nijveldt et al., 2001)**. Anthocyanins are among major classes of flavonoids plus presenting antioxidants naturally, that may avoid or reverse free radicals damage, so there is a lot of interest in anthocyanin foods. Anthocyanins liable for the attractive, blue, red or purple colors found in many plants as red grapes **(Nijveldt et al., 2001 and Philpott et al., 2009)**; which mainly found in grapes skins **(Xia et al., 2010)**. Epidemiologic and scientific reports have showed that the intake of anthocyanins decreases the danger of arthritis, diabetes, cardiovascular, and cancer disease which in related to antioxidant activity **(Bobinaitė and Viškelis, 2013)**; also study by **Hwa et al., (2011)** suggested the hypouricemic impacts of sweet purple potato anthocyanin extract in hyperuricemic mice. So nowadays, increasing interests on grapes phenols have turned to their biological actions related to benefits for human health **(Batu and Kirmaci, 2007 and Xia et al., 2010)**.

Grapes, come in the most economically important and extensively grown and eaten fruits worldwide by its usage in making juices, jam, jelly, raisins, wines, and other grape-derived products, are rich in phytochemicals especially grape seeds and skin including flavonoids, anthocyanins, polyphenols, and stilbene derivatives resveratrol **(Çetin and Saðdýç, 2009; Nassiri-Asl and Hosseinzadeh, 2009; Yadav et al., 2009; Yang and Xiao 2013; Mendesa, Joana et al., 2013; Georgiev et al., 2014; Silva and Queiroz, 2016 and Ferri et al., 2016)**. Lately, it was discovered that even grape handling byproducts (pomace, skins, seeds, and seed oil) had significant nutritional value and were offered in different types as powders, granulates, dry or concentrate extracts, and other advanced packaging methods **(Georgiev et al., 2014)**; in which the pomace, which makes up about 20 to 30% of the processing grapes mass , is primarily a by-product chiefly contains of pressured skins, stems and seeds, and these massive quantities of byproducts pose a significant environment and waste problem **(Mendesa, Joana et al., 2013 and Ferri et al., 2016)**. Grape skins are the major grape pomaces component donating roughly to a half of material weight **(Mendesa, Joana et al., 2013)**. Several scientific studies and epidemiological evidence have linked the consumption of grapes or grape's skin and seed extracts with many therapeutic and biological impacts as antioxidative, anti-inflammatory, antidiabetic, antimicrobial, antiviral, anticarcinogenic, antiaging properties, additionally to possessing hepatoprotective, cardioprotective and neuroprotective actions **(Çetin and Saðdýç,2009; ; Yadav et al., 2009; Xia et al., 2010; Yang and Xiao,2013; Georgiev et al., 2014 and Silva and Queiroz, 2016)**. Since grapes biomass has a comparable unique mixture of physiologically active components to those present in typical growing grapes but with larger concentrations, it is possible to anticipate that it will be related to the production of natural goods with higher added value, and then it accepted as beneficial diet supplements which would be promising functional foods for health care of people to treat and stave off illnesses **Deng et al., 2011; Mendesa, Joana et al., 2013; Georgiev et al., 2014 and Ferri et al., 2016)**.

Today, there are several educations to recognize effective natural anti-hyperuricemic products without toxicity or negative effects **(Hwa et al., 2011 and Chen et al., 2013)**. There are no knowledge or sufficient previous studies have been investigated whether red grape skin (RGS), as byproduct, had a beneficial health effect on hyperuricemia. Therefore, this investigate was operated to study the possible impacts and mechanism of RGS on hyperuricemia get by fructose.

Materials and Methods

Materials:

Red grape and cake components

Red grape (*Vitis vinifera, L.*) and cake components of flour, egg, oil, sugar, baking powder and vanilla were bought at the neighborhood market in Egypt, Menoufia, Shiben El-Kom.

Chemicals

Biochemical assay kits were obtained from the Company of Alkan Medical, St. El-Doky, Egypt). MDA (Malondialdehyde) and the activity Kits of CAT (catalase), SOD (superoxide dismutase) and GSH.Px (glutathione peroxidase) were got from Company of Biodiagnostic, El-Doky, Egypt. Other chemicals were obtained from Company of El-Gomhoria, Cairo, Egypt.

Animals

The 24 albino rats (adult male), Rattus norvegic, being 155 ± 5 g weight were got from National research institute, Animal House (Cairo, Egypt). Rats were kept in groups in well-ventilated cages under sanitary conditions in Biological Laboratory, Home Economics Faculty, Nutrition and Food Sci. Department, Shibin El-kom (Menoufia), Egypt and consumed standard diet AIN-93 as reported by **Reeves et al., (1993)** for a seven-day adaptation period. This investigate was ethically accepted by the Institutional Animal Ethics committee. Menoufia University (Reg. No, MUFHE /F/NFS/12/23).

Methods

Preparing of dried red grape skins (DRGS)

Red grape skin as a byproduct during the grape juice production was dried at 50°C in an Alab Tech vacuum oven. Following that, it was pulverized in an electrical mill and put through British standard 80 mesh screens. Prior to usage, the pure powder was placed in plastic bags and refrigerated around -20°C.

Identification of main chemical composition, total phenolics, anthocyanins, and antioxidant activity

Main chemical composition of RGS as moisture, ash, fiber, fat and crude protein were measured according to the A.O.A.C. methods (2012). Total carbs were determined using difference as following:

% Carbs = 100 - (moisture%+% fiber+%Ash%+protein+% fat).

Total phenolics of DRGS was determined by the Folin– Ciocalteu (FC) reagent-based colorimetric test as showed by **Singleton and Rossi (1965)** which was given as mg/g DM and estimated as gallic acid equivalent (GAE). Total anthocyanins contents of DRGS were determined utilizing PH-differential technique explained through **Wrolstad (1976)**. Total antioxidant action was detected using the phosphomolybdenum technique **(Prieto et al., 1999)**.

Experimental protocol

The 24 albino rats (adult male), Rattus norvegic, being 155 ± 5 g weight were kept in an environment that is humidity- and temperature-regulated plus a 12-hour cycle for light and dark. The rats receive unrestricted supply of food or water. The rats were separated into 2 primary groups, in which the first was control group (as n=6) received drink water only and fed on basic diet while the second primary group, high fructose intake group (18 rats), had 8 weeks of consuming water with 10% fructose and divided into three subgroups(n=6) after 4 weeks of receiving fructose. Subgroup (1), served as a control positive, received water with 10% fructose and given a basal diet for 8 weeks while subgroups (2) and (3) had drinking water with 10% fructose for totally, 8 weeks and given diet containing 2.5% and 5% DRGS at last 4 weeks respectively. The fructose dose and period of this study done in accordance with previous animal investigations as **Fan et al., (2014)**.

Blood and tissue samples collection

All rats underwent an overnight fast at the conclusion of the trial. Blood samples were taken from the portal vein of the liver after scarification by ether anesthesia in cleaned centrifuge tubes. Blood was centrifuged at - 4^0C for 10 minutes at a speed of 4000 rpm to obtain serum samples. Then, until analysis, the serum was placed in the plastic vial and maintained frozen at -20˚C **(Schermer, 1967)**. Both at once, kidney tissues were dissected quickly on ice for biochemical assays.

Biochemical analysis

Via commercial kits, urea, uric acid and creatinine levels in serum were evaluated accordance to **Patton and Crouch (1977), Fossati et al., (1980) and Tietz (1986)**, regulatory. Serum cholesterol, HDL.c (High Density Lipoprotein) and triglycerides were detected as**, Allain (1974), Lopez (1977) and Fossati and Prencipe (1982)**, in arrange. LDL.c (Low Density Lipoprotein) and VLDL.c (Very Low Density Lipoprotein) were estimated according to the following equations of **Lee and Nieman (1996)**: VLDL (mg/dl) = Triglycerdes / 5 and LDL (mg/dl) = Total cholesterol – (HDL+VLDL). GSH.Px (glutathione peroxidase) and SOD (superoxide dismutase) activities plus lipid peroxide as evaluated MDA (malondialdehyde) levels were assayed in both sera plus renal tissues using a modified method published with **Necheles et al. (1968), Masayasu and Hiroshi (1979) and Ohkawa et al., (1979)**, respectively. Nitric oxide (NO) in renal tissues was determined according to **Hu et al., (2009)**. Serum glutathione (GSH) was determined according to **Beutler et al., (1963).** Also, serum LDH (lactate dehydrogenase) and liver function as aminotransferases, were evaluated accordance method of **Wroblewski and Ladue (1955)** and **Reitman and Frankel, (1957)**, regulatory.

Technological techniques

Preparation and Sensory evaluation of cake

Creamy cake were made using the recipe of **Saba,Nargis (1996)**. Sensory evaluation for cake samples was achieved by fifteen of public members from Shiben El-Kom, City, Menoufia, Egypt. The judges were invited to assess the cakes' general acceptability as well as their look, taste, texture, color and compressibility. 10 = outstanding, 9 = like very, 8 = like very lot, 7 = like moderately, 6 = like somewhat, 5 = neither like nor dislike, 4 = dislike slightly, 3 = dislike moderately, 2 = dislike very much, and 1 = detest severely) were used to grade the items according to **Mehrabi et al., (2017)**. Statistics were used to evaluate precision and accuracy. The cake was assessed 6 hours after baking. The panelists assessed a single piece of each type of cake system that was simultaneously presented in an open area at 25 °C, a normal temperature without additional lighting. Water was available for rinsing.

Statistical analysis

Statistical program SPSS for Version 10 Windows was used to evaluate the findings, which were presented as Means ± Standard Deviation. The statistics package program's one-way ANOVA testing was utilized to analyze the variances between groups, and Duncan's multiple comparison test was utilized as a post hoc test to evaluate the levels of significance at a significance level of $P \leq 0.05$ as the statistics package program **(Artimage and Berry, 1987)**.

Results and Discussion

The main chemical components, total phenols, anthocyanin plus antioxidant activity of red grape skins (RGS)

The main nutrient composition, total phenols, anthocyanin and antioxidant activity of red grape skin (RGS) as well as % RGS fraction of whole red grape fruit are presented in Table (1). Generally, RGS fraction was 21.96% of whole red grape fruits. The main nutrient composition of RGS as Moisture, Ash, Fat, Protein, Carbohydrate and Fiber were 80.87, 1.79, 0.225, 0.5, 10.57 and 6.045 (g /100 g) respectively. Depending on dry matter (DM), these nutrient values are concentrated by 5 times on basis of about 80% moisture. At the same time, total phenols (mg/100g), anthocyanin (mg/100g) and antioxidant activity (PPm BHA equivalent) achieved levels of 86.82, 21.41 and 20381, respectively.

Table (1): The main chemical components, total phenols, anthocyanin and antioxidant action of red grape skin (RGS)

Parameters	RGS (Fresh weight) M ± SD
% Skins fraction of whole grape fruit	21.96 ± 1.32
Basic components (g /100 g)	
Moisture	80.87 ± 0.435
Ash	1.79 ± 0.091
Fat	0.225 ± 0.105
Protein	0.5 ± 0.31
Carbohydrate	10.57 ± 0.055
Fiber	6.045 ± 0.085
Total phenols (mg/100g)	86.82 ± 0.15
Anthocyanin (mg/100g)	21.41 ± 0.12
Antioxidant activity (PPm BHA equivalent)	20381

Each result within the table reflects the average of 3 replicates ± the standard deviation.

Grapes, come in the most economically important and extensively grown and eaten fruits worldwide which used in making juices, jelly, wines, and other products. The pomace, which makes up about 20 to 30% of the processing grapes mass, is primarily a by-product chiefly contains of pressured skins, stems and seeds, and these massive quantities of byproducts pose a significant environment and waste problem **(Ferri et al., 2016)**. Grape skins are the major grape pomaces component donating roughly to a half of material weight **(Mendesa, Joana et al., 2013)**. Red grapes pomace is described by a high source of polyphenol components (mostly in skin and seed) with high antioxidant activity **(Ferri et al., 2016 and Silva and Queiroz, 2016)**. During grape juice processing, only limited quantities of anthocyanins (about 2%) are extracted but most of the flavonoids are primarily found in the grape skin. Anthocyanins, the most common flavonoids present in grapes, are only present in red grapes type, and primarily gather in the skins. Also, over 70 percent of grapes polyphenols are still present in pomace, a byproduct of the production of wine and grape juice especially in seeds. Therefore, due to their chemical and biological properties of such biomass which contain higher levels of biological active components than those of typical growing grapes, it becomes a considerable source of health promoting nutraceuticals **(Georgiev et al., 2014)** and may use in many applications as ingredients of functional foods; as natural colorants and preservatives of foods **(Ferri et al., 2016)**.

The chemical structure of grapes pomace is known to varying and the wide ranges depending partly on varietal and cultural differences, growth climates, and processing conditions, so in important study by **Deng et al., (2011)** The DF

(dietary fiber) content of the skin of 2 WWGP (white wine grape pomace) and three RWGP (red wine grape pomace) from the US was examined, principal and phenolic components and the results showed that DF in RWGP (51.1–56.3% DM) was significantly greater than WWGP (17.3–28.0%), but significantly less in soluble sugars (1.3-1.7% versus 55.8-77.5% DM). Addition to this, RWGP skins had higher principal contents than those of WWGP skins as following protein (11.26 to 12.34 vs. 5.38 to 6.54 % DM), fat (3.35 to 6.33 vs. 1.14 to 2.64 % DM) and ash (6.1 to 7.59 vs. 2.53 to 3.31 % DM). Also, RWGP as Compared with WWGP had higher levels of total phenols (21.4–26.7 versus 11.6–15.8 mg GAE/g DM) and (32.2–40.2 versus 20.5–25.6 mg AAE/g DM) for DPPH radical scavenging activity. Moreover, anthocyanins found only in RWGP by ranges of 0.29 to 1.42 mg mal.3.glu/g DM. The total proanthocyanidin and flavanol levels were varied from 8.0 to 24.1 and 31.0 to 61.2 mg/g DM, regulatory for the 5 WGP kinds. Insoluble DF of 5 WGP types had greater than 95.5% from total DF which made up of lignin, neutral sugars and uronic acid (as 7.9–36.1%, 4.9–14.6% and 3.6–8.5% DM respectively). They are also good sources of, cellulose, hemicellulose and Klason lignin, then have potential to be highly supportive materials that are environmentally friendly. The high number of soluble sugar in skins of WWGP may allow them to create novel, excellent flexible and biodegradable packaging substances. Overall, the RWGP skins with high contents of dietary fiber, total phenols, total flavanol, proanthocyanidins, anthocyanin, and high antiradical scavenging activity becomes an excellent ingredient for nutraceutical, medical, and food applications. These finding providing that the grape skins of pomace generally can be excellent DF sources that are abundant in bioactive chemicals, since DF is well known as a valuable element for healthy diet related to reductions risks of many diseases. In other study by **Dávalos et al., (2005)**, the commercial red grape juice showed higher antioxidant activity than that of white grape juice.

Also, **Mendesa, Joana et al., (2013)** provide the valorization of red grape skins by the chemical composition and the structural features. The richest substances in grape skins were structural polysaccharides as 20.8% cellulose & 12.5%hemicelluloses, following proteins (18.8%), aliphatic substances (fatty acids, wax, cutin, etc., totaling 14%), tannins (13.8%), sugars (mostly fructose and glucose, totaling 12.3%) and 7.8% ash. Grape skins wasn't contained lignin which come in adverse to the previous finding by **Deng et al., (2011)** that grape pomace (GP) skins are good source of good sources of Klason lignin as well as cellulose and hemicellulose. Moreover, the results by **Mahmoud, Maha et al., (2020)** showed that GP contains 8.75% protein, 7.38% lipids, and 46.63% all dietary fiber. K, Na, Ca, Mg, S and P were present in higher levels. The GP lipid include 85.75% of unsaturated fatty acid (66.60% polyunsaturated fatty acid and 19.14% monounsaturated). Linoleic acid was the main fatty acid as

65.29%. All phenolics were about 50.35 mg gallic acid equivalent (GAE) /g, total flavonoids as mg rutin equivalent (RE)/g were 22.25 and 51.92% of the DPPH radicals were scavenged. The most opulent polyphenol was gallic acid (9.76 mg/100g), while the richest flavonoids component was catechin (52.5 mg/100g) and stilbene content of resveratrol was 14.11 mg/100g. And **Yadav et al., (2009)** demonstrated that water, acids and sugars are the principal grape composition. It is contained 81-87 % water, 12–18 % carbohydrates, 0.5–0.6 % proteins and 0.3–0.4 % fat. Additionally, considerable quantity of potassium, vitamin C and vitamin A as 0.1–0.2 %, 0.01–0.02 % and 0.001–0.0015 % in regular. Furthermore, the results from studding 16 red grape cultivars by **Orak (2007)** showed that anthocyanin content varied between 40.3 and 990.8 mg/l as fresh weight and total sugar content ranged between 13.29 and 24.46%. Also, **Varandas et al., (2004)** examined the grape skins sugar as fructose and glucose for 5 Portuguese grape types compared with that of entire grapes and grape juice, the results showed that grape skin glucose was higher than fructose, however both substances elevated from the green berry stage in July to veraison in August and then slightly decreased until harvest in September. As anticipated, the total sugar (fructose and glucose) in the complete grapes was more than that of juice and much greater than that of grape skins itself which record on average, 10±5% and in veraison being 30 ±7%.

In different parts of grape, the total phenolic content (TPC) of skin, seed and leaf vs. flesh being about 374.6, 2178.8 and 351.6 vs. 23.8, mg/g gallic acid equivalent (GAE) regularly **(Xia et al., 2010)**. TPC changed for grape skins with cultivar, geographic origin, climate, soil characteristics, and farming methods or exposure to pathogens; and the mainly compounds included phenolic acids, anthocyanins, proanthocyanidins, flavonols, flavanols, and resveratrols **(Xia et al., 2010; Deng et al., 2011 and Ferri et al., 2016)**. The main phenolic chemicals in grape seeds and skins are proanthocyanidins. Anthocyanins are mainly pigments found in skin, and are absent in flesh **(Xia et al., 2010 and Georgiev et al., 2014)**. By different methods to evaluate antioxidant activity, grape skin showed 12.8 μmol TE/g (TEAC, Trolox equivalent antioxidant capacity) and 15.7 - 113.3 mmol TE/g (as DPPH, 1,1-diphenyl-2-picryhidrazyl) and 36.40 mmol TE/g (ORAC, oxygen radical absorbance capacity). Among different grape parts, seeds had the greatest antioxidant capacity followed by grape skin, while the least antioxidant action was found in the flesh **(Pastrana-Bonilla et al., 2003)**. Although, **Arnous et al., (2002) and Orak (2007)** appeared that flavanols were responsible for anti-radical activity more than anthocyanin; in which similar anti-radical activity was possessed by flesh as skin despite of the fact that grape phenolic index of flesh was less than skin because the absent of anthocyanins for the flesh **(Falchi et al., 2006)**. Grape or its parts extracts could decrease biological system

oxidative stress as well as prevent food spoilage (Xia et al., 2010). The other study results by **Lago-Vanzela et al., (2011)** showed that the edible parts of Bordô grape cultivated in South Brazil (flesh with skin) included 1130 mg/kg phenolic chemicals (considering as gallic acid), primarily presented in skin. Skin anthocyanins level was high (1359 mg/kg, principally a malvidin 3,5-diglucoside). 154 μmol/kg of total flavonols were found largely within the skin and the principal flavonol in both grape parts was myricetin 3-glucoside. Low amounts of flavanol and proanthocyanidins were present in grape skin, while derivatives of hydroxycinnamic acid principally produced across caffeic acid were ten times more within skins than that of flesh (all: 483 μmol/kg). Lastly, grapes produced a significant amount of resveratrol (10.91 mg/kg) as well as shown a high level of antioxidant activity (37.6 1.0 mmol/kg, like Trolox).

Effects of red grape skin on hyperuricemia and renal injury in rats fed fructose

As present within Table 2, compared with control group, fructose treated rats as 10% in drinking water for 8 weeks gave significant increases in serum UA (uric acid) values, as serum creatinine and urea levels. Also, excess fructose intake resulted in significant decreased levels of renal NO (nitric oxide) in rats as compared to normal group; in which renal NO marker reflects endothelial dysfunction.

Table (2): The effect of red grape skin on hyperuricemia and kidney injury in rats fed fructose

Parameters / Groups	Serum uric acid (mg/dl)	Serum creatinine (mg/dl)	Serum urea (mg/dl)	Renal NO (nmol/mg wet tissue)
control	$1.43^{c} \pm 0.14$	$0.66^{b} \pm 0.03$	$34.27^{b} \pm 1.97$	$5.41^{a} \pm 0.5$
Fructose	$2.2^{a} \pm 0.18$	$0.73^{a} \pm 0.02$	$40.87^{a} \pm 3.6$	$3.5^{c} \pm 0.23$
F+ DRGS (2.5% of diet)	$1.87^{b} \pm 0.17$	$0.68^{ab} \pm 0.02$	$36.67^{ab} \pm 3.56$	$4.42^{b} \pm 0.24$
F + DRGS (5% of diet)	$1.83^{b} \pm 0.15$	$0.67^{ab} \pm 0.05$	$35.87^{ab} \pm 2.29$	$5.14^{ab} \pm 0.48$

The data is presented like mean ± SD. The market letters show significant differences between dietary treating groups as revealed by one-way ANOVA followed by Duncan's range multiple test (a > b > c > d > e), where values within a column with dissimilar superscripts are meaningfully different ($p \leq 0.05$).

F, Fructose makes about 10% of the drinking water.

DRGS, Dried Red Grape Skin. 2.5% and 5% DRGS serve as 12.5% and 25% FRGS (Fresh Red Grape Skin) according to about 80% moisture content.

NO, nitric oxide.

The supplementation by DRGS (Dried Red Grape Skin) at 2.5% and 5% of diet significantly lowered serum uric acid levels than that of fructose treated

rats. Also, RGS supplementation caused nonsignificant reduction in serum creatinine and urea levels than fructose group, but at the same time these levels of creatinine and urea did not significantly different from normal group. Furthermore, RGS groups showed higher renal NO levels than fructose treated rats and reached in group of high dose (5% of diet DRGS) to levels that showed insignificant changes from normal group. Also, it is worthy observed that there were no significant differences between two experimental doses of RGS in all previous parameters.

These results indicated that RGS has anti-hyperuricemic effect which restore NO-mediated renal endothelial dysfunction; in which consumption of high fructose caused metabolic syndrome(MS; as hypertension, insulin resistance with dyslipidemia), hyperuricemia has a pathogenic role and considered as an autonomous danger factor for the development of kidney injury caused by UA-intervened endothelial dysfunction through consequent impairment of NO generation as explained by **Hu et al., (2009); Zhang et al., (2012) and Essawy et al., (2012)**. In fact, UA-induced oxidative stress decreases endothelial NO biovailability **(Yu et al.,2010)**. Decrease in NO levels of serum can be recovered by decreasing urate causes in hyperuricaemia as showed by **Zhang et al., (2012)**. Blocking oxidative stress or increasing NO substrate prevent produce glomerular and general hypertension and kidney cortical vascular constriction (**Tapia et al., 2013).**

A variety cells, include endothelial cells plus macrophages, create nitric oxide (NO) **(Nijveldt et al., 2001)**. In spite of the early release of No which created from L-arginine by constitutive NO synthase (NOS) activity is vial as vasodilators (remaining the dilatation of blood vessel) **(Nijveldt et al., 2001 and Wu and Meininger, 2002)**, the substantially greater amounts of NO produced via macrophages inducible NOS can cause oxidative injury as a radical itself or by its reacts with free radicals, resulting in the highly damaging peroxynitrite which can directly oxidize LDLs, causing irreversible cell membrane damage **(Nijveldt et al., 2001)**. NO has many actions and plays very important jobs in nearly each body cell or organ function. Several dietary agents, involving amino acids, protein, fructose, glucose, fatty acids, cholesterol, phytoestrogens, minerals, vitamins, polyphenols and ethanol, are either useful for health or partially relate to the development of chronic illnesses via control of NO creation by constitutive or inducible NOS **(Wu and Meininger, 2002)**.

Administration 10% fructose within drinking water during 8 weeks in rats found to induce significant elevation in uric acid, creatinine and urea, in addition to renal histopathological changes **(Hu et al., 2009; Zhang et al., 2012; Chen et al., 2013 and Fan et al., 2014)**, also, significant reduction in renal NO **(Hu et al., 2009 and Zhang et al., 2012)**, as well as MS involving

hypertension, insulin resistance and dyslipidemia **(Hu et al., 2009; Zhang et al., 2012 and Fan et al., 2014)**.

Diminished NO production in relation to impaired endothelium-dependent relaxation, elevated reacting oxygen species production and increased uric acid (UA) concentration have been shown to linked to the pathogenesis of hypertension induced by fructose **(Tran et al., 2009)**. Endothelial NO decrement by uric acid may contribute to insulin resistance and then this later partly relate to the promoting of hypertension induced by fructose in rats **(Nakagawa et al., 2006; Tran et al., 2009 and Zhao et al., 2009)** which produced by 2-5 weeks of fructose intake as 10% of drinking water **(Zhao et al., 2009)**; also, reactive oxygen species as superoxide anion are involved in the pathogenesis of endothelial dysfunction through annihilate NO, which relates to the promoting of hypertension **(Song et al., 2008)**. Moreover, **Tapia et al., (2013)** demonstrated that chronic hyperuricemia can result in kidney and metabolic changes, as postprandial hypertriglyceridemia, glomerular and general hypertension, as well as hepatic TG buildup. Fructose caused metabolic syndrome (MS) as hypertension, hyperuricemia, and hypertriglyceridemia is contributed to the damage of renal microvascular and glomerular hypertension in rats, while adverse effect on MS and renal function were linked to the quantity of fructose intake in which fructose used either in diet (60%, F60) or drinking water (10%, F10) for 8 weeks and these changes are best observed for high doses (F60%), whereas a obvious increase in water intake therefore, volume increase in F10 may cause a kidney vasodilatory impact; also a linear link was found between caloric intake from fructose vs. absolute consentrations of uric acid and TG and between plasma uric acid and systolic blood pressure in which as calculated, rats consumed about 38% and 66% of their daily calorie intake from fructose in F10 and F60 regularly as studied by **Sánchez-Lozada et al., (2007)**, who also hypothesized that variable routes of fructose intake in rats may induce different consumption of fructose and then various metabolic syndrome levels that could result in different morphological and physiological renal responses. As well as the probably effect of administration period in which some effects as hyperuricemia, hypertension and insulin resistance may early induce then renal affects. All these respects may need more specific research. Anyway, there is increasing evidence that MS induced by elevated fructose consume is a danger factor for renal damage and dysfunction **(Sánchez-Lozada et al., 2007; Fan et al., 2014 and Ma et al.,2015)**.

Many prior researches were successful in highly block the symptoms of MS induced via fructose by reducing serum UA and improve NO **(Nakagawa et al., 2006, Hu et al., 2009; Zhang et al., 2012 and Essawy et al., 2012)**, and this discovery is even more pertinent because people lack uricase then acquire hyperuricemia more sensitive to diet than mammals that do not express uricase

or rodents that have an active uricase so high fructose levels needed to cause great metabolic alterations and kidney impairment in rats whereas people lack uricase seem to be considerably more sensitive to fructose impacts; and then lower levels of fructose would be necessary in humans **(Sánchez-Lozada et al., 2007; Johnson et al., 2009 and Tapia et al., 2013)**. In this regard, the mean fructose intake especially from sweetened beverages (SB) may reach 10–20% from total calorie intake among young adults **(Sánchez-Lozada et al., 2007 and Vos et al., 2008)**. Fructose consumption has elevated dramatically due to the intake of high fructose SB and foods which associated with hyperuricemia in nondialysis-dependent chronic kidney disease (CKD) patients as observed in 55.8 % of patients **(Vieira et al., 2015).** There is increasing evidence that great fructose consumption in (SB) elevates the danger for cardiorenal and metabolic injuries, which are partly caused by a subsidiary rise in UA and associated with incidence and development of CKD in humans and animals **(Tapia et al., 2013; Fan et al., 2014 and Ma et al.,2015)**. Moreover, a key finding in studies on rats by **Tapia et al., (2013)** was the observation that SB + uricase inhibitor (UI) induced a significant increase in glomerular hypertension reaching to levels that showed in models of extensive chronic renal damage, and actually the degrees for glomerular pressure produced by SB + UI were significantly greater compared SB alone by +33% and also UI alone by 14%, also it seems that the increase in general blood pressure (BP) interrelated with poor autoregulation produced by kidney microvascular arteriolopathy and oxidative stress which leading to elevated hypertension of glomerular in SB + UI animals thus, mixing SB and UI greatly speeding up renal impairment progression.

Several studies explained how fructose induced hyperuricemia by deficiency of renal UA / creatinine excretion in the urine via urate transporters system which might be associated with reduced NO in the kidney, insulin resistance and dyslipidemia playing a significant role in this pathogenesis which contribute to kidney dysfunction, hyperuricemia, and other metabolic syndrome symptoms; and reducing UA levels by either a uricosuric agent or an inhibitor of xanthine oxidase normalized NO levels, enhanced renal function and insulin responsiveness **(Nakagawa et al., 2006; Sánchez-Lozada et al., 2007; Hu et al., 2009 and Zhang et al., 2012).** Moreover, in important concern **Hu et al., (2009)** pointed to that lack regulation of kidney organic ion and cation transporters which concurrent with renal dysfunction and hyperuricemia (urate underexcretion) may elevate the body's clinical exposure to medicines and can result in undesirable side effects as long as elevated fructose consumption.

Peoples with gout or hyperuricemia are typically treated with substances that inhibit uric acid biosynthesis or improve the excretion of uric acid, as well as with anti-inflammatory compounds; while synthetic products used in clinical

practice have several adverse side effects; So, there is a requirement for new, safe and effective natural agents, as supplements in contemporary food **(Hwa et al., 2011 and Dwibedi et al., 2022)**. Some studies about grapes or its proceeding wastes as grape pomace (GP) which including seeds and skins or grapes bioactive compounds showed useful effects which can related to possible hypouricemic effect. **Batu and Kirmaci (2007)** showed that red grape is among the highest flavonoids sources and the polyphenols in its skins can help regulate blood pressure, act as antioxidants, and prevent blood clots.

At first, grapes are an excellent source of potassium, which enhances an alkaline blood balance and stimulates the renal and regulates heartbeat. The restorative power of grapes is cleansing the liver and removing uric acid from the body **(Batu and Kirmaci, 2007)**. And **Lucia et al., (2023)** showed a slight diuretic action, an increase of the uric acid elimination by grape aqueous extracts from the skin, seeds, and pulp in rats. Moreover, **Dwibedi et al., (2022)** encapsulated the grape bioactive components' ability to block the actions of human disease-related enzymes including xanthine oxidase related to gout. In addition to, **Decendit et al., (2013) and Mossalayi et al., (2014)** showed that grape anthocyanins inhibited inflammatory mediators from human macrophages and reduced arthritis score in arthritic experimental rats. Also, **Mahmoud, Maha et al., (2020)** found that rats consumed a diet high in fat with 15% GP (grape pomace) was the most healthful, in which a non-significant alteration in UA and creatinine levels, compared to healthy control rats was noticed. Therefore, GP can be regarded as a supplier of healthy substances that can be used in food and pharmacological industries. As well as, **Abdel-Hamid, Ghada (2014)** demonstrated that adding red grape juice to the diet can protect against kidney impairment and abnormal serum lipids connected by national hypercholesterolemia. However, **(Ohno et al., 2008)** showed that grape juice, which include substantial quantities of glucose and fructose, with exercise accelerated adenine nucleotide breakdown plus lactic acid construction which are crucial in elevating plasma levels of urate. But it is worthy observed that phytochemicals of grapes vary among different varieties **(Yang and Xiao, 2013)**; and grape biomass contain higher levels of important biological active compounds than in regular growing grapes **(Georgiev et al., 2014)**. Also, Comparative antioxidant and hypolipidemic effects of red and white grapes in adult hypercholesterolemic humans showed that consumption of red grapes has more effects than white grapes **(Rahbar et al., 2015)**.

Secondary, grape juice provide a vasorelaxation effect by stimulate the production of nitric oxide (NO) in endothelial cells, since it is known that NO is important in the body’s natural system for upholding flexible and healthy blood vessels and then helps encourage normal blood pressure. Both systolic as well as diastolic of blood pressure showed reductions of nearly six points in

hypertensive men drinking grape juice **(Batu and Kirmaci, 2007)**. Also, whole red grape juice reduced blood pressure during rest as well as improving hypotension after exercise in hypertensive individuals **(Neto et al., 2017)**. It appears that the benefits of grape skin extract (200 mg/kg/day) are mediated in part by vasodilator action depending on the endothelium and antioxidant effect in experimenting condition of preeclampsia, where symptoms included decreased nitric oxide generation and increased oxidative stress **(Nassiri-Asl and Hosseinzadeh, 2009)**. In addition to, **Çetin and Saðdýç (2009)** who revealed that resveratrol pretreatment as 10 mg/kg/day per oral, primarily present in skins and seeds of grape, limits the oxidative stress that restrains NO (nitric oxide) production essential for vasorelaxation as well as restrains vasoconstrictor activity stimulated by oxidative stress. Moreover, of red grape berries - cultured cells (RGC) lower blood pressure for metabolic syndrome rats induced by fructose in which increase NO levels, signaling a positive action of RGC on vasodilatation and these useful effects related to highly rich with polyphenols and resveratrol **(Leibowitz et al., 2014)**.

Thirdly, Positive health benefits as antioxidant, hypolipidemic, and anti-inflammatory effects by the consumption of red grape juice have exerted in both hemodialysis patients and healthy subjects without affecting on uric acid levels **(Castilla et al., 2006; Nassiri-Asl and Hosseinzadeh, 2009 and Lasuncio´n et al., 2003)**. Also, useful effects of the consumption of red grape juice or anthocyanidins in grape seeds and skins have reported, such as improvement of the endothelial function by modulate the decrease in NO levels, increase antioxidant capacity, protection of LDLs oxidation and improve lipid profile, reduce oxidation of plasma native protein, and decrease platelet accumulation, which pointing cardioprotective and vaso-protective properties including vasorelaxation, antiatherosclerosis and antiarrhythmic actions **(Batu and Kirmaci, 2007; Leifert and Abeywardena, 2008 and Alnahdi, Hanan and Ayaz, Najla, 2012)**.

Therefore, from the obtained results and important findings of all previous studies it could be concluded that RGS with several effects as antioxidant action, regulation NO production and improve lipid profile can reduce serum UA levels, and hence improve impaired effects related to NO unregularly which associated with fructose induced MS (involved in hypertension and dyslipidemia, as well as oxidative stress); indicated to the potential applications for functional food part RGS due to its anti-hyperuricemia and renal protective actions against high fructose consumption.

Effects of red grape skin on oxidative parameters in fructose -fed rats

Results of Table 3 summarize the antioxidant action of RGS in fructose treated rats.

High fructose consumption (10% in drinking water for 8 weeks) enhanced the significant reduction in the activities of SOD (superoxide dismutase) plus GPX (glutathione peroxidase) in each of renal tissue and serum, as well as renal content of GSH (glutathione), as an endogenous antioxidant against free radicals, in addition to significant elevating levels of MDA (malondialdehyde), the lipid peroxidation marker, in both renal tissue and serum as compared with control group.

Two experimental doses of RGS (2.5% and 5% of diet DRGS) significantly reversed the reduction in each of renal GSH content and the activity of renal SOD plus GPX, as well as the increase in renal MDA by fructose consumption. As regard to serum parameters, it could be noticed significant reduction in MDA for two RGS doses and significant elevating in SOD for high RGS dose compared to fructose group, while the elevating in each of serum SOD for low RGS dose and serum GPX for two RGS doses come by insignificant changes from fructose group but at the same time reached to levels did not significantly difference from normal group.

The levels of each of renal GSH and serum SOD and GPX for two experimental doses of RGS, in addition to renal and serum MDA for high experimental dose of RGS reached to levels that did not significantly change from normal group. Although high experimental RGS dose appeared to be more effective in some oxidative parameters as renal and serum MDA and serum SOD, but no significant differences were detected between both two experimental doses of RGS for oxidative parameters except for serum MDA in which high RGS dose (5% of diet DRGS) was significantly favorable than low RGS dose (2.5% of diet DRGS), reaching to normal level. This may be indicated that the two experimental RGS doses can serve as good choice and may be no need to higher dose with this model; anywise more studies are needed to prove and detect the perfect dose, period, and type of grape toward these respects in different experimental animal models and in humans.

Table (3): Effects of red grape skin on oxidative parameters in fructose - fed rats

Parameters / Groups	Renal				Serum		
	MDA (Mmol/g)	SOD (U/g)	GPX (U/mg)	GSH (µmol/g)	MDA (nmol/ml)	SOD (U/l)	GPX (ng/ml)
control	$24.95^{c} \pm 2.42$	$66.9^{a} \pm 5.8$	$19.61^{a} \pm 1.71$	$29^{a} \pm 2.02$	$7.14^{c} \pm 0.65$	$48.34^{a} \pm 4.77$	$41.98^{a} \pm 3.5$
Fructose (F)	$42.75^{a} \pm 3.99$	$40^{c} \pm 3.61$	$12.25^{c} \pm 0.97$	$20^{b} \pm 1.95$	$12.8^{a} \pm 0.92$	$35.32^{b} \pm 2.06$	$35.84^{b} \pm 3.1$
F + DRGS (2.5% of diet)	$30.7^{b} \pm 1.9$	$55.28^{b} \pm 4.49$	$16.3^{b} \pm 1.39$	$25^{a} \pm 2.41$	$9.28^{b} \pm 0.8$	$42.14^{ab} \pm 2.78$	$40.81^{ab} \pm 2.57$
F + DRGS (5% of diet)	$26.65^{bc} \pm 2.55$	$55.41^{b} \pm 4.66$	$15.3^{b} \pm 0.86$	$28^{a} \pm 2.26$	$7.54^{c} \pm 0.79$	$46.76^{a} \pm 4.22$	$40.12^{ab} \pm 2.79$

The data is presented like mean ± SD. The market letters show significant differences between dietary treating groups as revealed by one-way ANOVA followed by Duncan's range multiple test (a > b > c > d > e), where values within a column with dissimilar superscripts are meaningfully different ($p \leq 0.05$).
F, Fructose makes about 10% of the drinking water.
DRGS, Dried Red Grape Skin. 2.5% and 5% DRGS serve as 12.5% and 25% FRGS (Fresh Red Grape Skin) according to about 80% moisture content.
MDA, malondialdehyde; SOD, superoxide dismutase; GPX, glutathione peroxidase; GSH, glutathione.

High intake of fructose which cause a common experimental MS model also exhibit developed renal abnormalities, elevated amounts of peroxidation final outcomes, decreased status of antioxidants as lower in the activities of enzymatic antioxidants (SOD, CAT, GPx and GST), and lipid accumulation and peroxidation in the kidney **(Taleb-Dida et al., 2011)** and also **Wang et al., (2015)** found decreased SOD amount and action, as well as increased H_2O_2 plus O_2 generation in renal cortex and glomeruli in Fructose feeding rats. Also, a decline in GSH as an endogenous antioxidant against free radicals and activity of antioxidant enzyme (SOD), in addition to marked higher level of MDA (lipid peroxides) in the renal tissues of fructose-treated rats observed by **Palanisamy et al., (2008) and Chen et al., (2013)**. Moreover, a significant lower in total antioxidant capacity (TAC) showed in Fructose-fed rats **(El Mesallamy et al., 2010)**.

Sweetened beverages (SB) involved in fructose elevated protein carbonylation and lipid peroxidation in rat's renal cortex as found by **Tapia et al., (2013)**. High fructose diet is a significant contributing factor to metabolic syndrome linked to glomerular podocyte damage and oxidative strain **(Wang et al., 2015)**. Several research have shown that oxidative strain one of the factors that had a significant impact in the urate nephropathy etiology; and the nephroprotective activities and low toxic effects can achieved not only by reducing the oxidative strain that uric acid causes, but also repressing the oxidative strain-connected inflammatory cascade as lowering the intensity of iNOS proteins as showed by **(Chen et al., 2013)**. Therefore, antioxidants may represent a promising treatment approach for the mitigation MS-connected glomerular podocyte damage **(Wang et al., 2015)**; and a lot of studies on several antioxidants were discovered to reduce hyperuricemia caused by fructose and renal damage in rats **(Hu et al., 2009; Zhang et al., 2012; Chen et al., 2013; Fan et al., 2014 and Wang et al., 2015)**.

Grape includes a diversity of phytochemicals, as phenolic acids, flavonoids, anthocyanin, proanthocyanidins and stibene derivatives resveratrol, they are all powerful antioxidants however greatly varies among different varieties **(Yang**

and Xiao, 2013). Scientific investigations have demonstrated the biologic and therapeutic properties of grapes extracts, specifically grapes skin or seed as antioxidant and anti-inflammatory activities, confirming the human health benefits of grapes that commonly accepted to prevent and treat diseases **(Çetin and Saðdýç, 2009)**. Increasing serum antioxidant activity and LDL protection against oxidation by consumption of grape juice or its phytochemicals, mainly presented in seed and skin as resveratrol, protoantocyanidins and quercetin, have reported by several studies **(Batu and Kirmaci, 2007; Çetin and Saðdýç, 2009 and Alnahdi, Hanan and Ayaz, Najla, 2012)**. Flavonoids are present in abundance in Concord grapes juices (CGJ), and they exhibit more in vitro antioxidant effect than α-tocopherol. In healthy adults, increased serum antioxidant capacity and protected LDL oxidation by 10 mL CGJ $\cdot$ kg^{-1} $\cdot$ d^{-1} extent like that found by 400 IU (International Units) of α-tocopherol per day, while significantly reduced oxidation of native blood proteins more than that of α-tocopherol. Flavonoids in CGJ showed antioxidant properties which can protect from oxidative strain and lower the danger of free radicals injury and chronic illnesses **(Byrne et al., 2002)**. The NADPH in oxidase enzymes pathway is the major superoxide anions source in vascular and phagocytic cells which found to be enhanced abnormally in several chronic diseases. Recently, feeding on intense juice of red grapes with high content of polyphenols, has been found to lower superoxide anion production as oxidative strain which linked to inflammatory and/or cardiovascular disorders due to the overproduction of superoxide by NADPH oxidase **(Dávalos et al., 2009)**. The results of **Rahbar et al., (2015)** suggested that eating of whole red grape has better antioxidant and hypolipidemic impacts than white grape in adult people with hyperlipidemia. Then, whole red grape can be the perfect fruit option for preventing oxidative stress linked to metabolic problems as well as cardiovascular problems related to cholesterol, mainly for hyperlipidemic adult people.

It is normally expected that antioxidants with medical therapy is the best efficient way to manage and avoid oxidative strain damage (**Georgiev et al., 2014)**.

Effects of red grape skin on lipid profile of serum in rats fed fructose

As obvious of Table 4, high fructose intake as 10% of drinking water during 8 weeks induced dyslipidemia in rats characterized by significant elevation in serum amounts of TG (triglyceride), TC (total cholesterol), LDL-C (low-density lipoproteins of cholesterol), VLDL-C (very low-density lipoproteins of cholesterol) plus AI (atherogenic index), as well as significant reduction in serum HDL-C levels (high-density lipoprotein cholesterol) compared to control group.

RGS consumption at two experimental doses (2.5% and 5% of diet DRGS) relieved dyslipidemia by significant reducing TG plus TC, -c VLDL-c and LDL values, in addition to AI than fructose fed rats; and the levels of TC for two RGS doses reached to insignificant changes from normal group. This in addition to the increasing in serum HDL-c levels compared to fructose group by insignificant change for low RGS dose and significant change for high RGS dose but two RGS doses reaching to levels did not significantly change from healthy rats. Also, no significant differences between two RGS doses were showed for lipid profile parameters except for LDL-c levels and AI in which high RGS dose (5% of diet DRGS) showed more significant favorable effect than low RGS dose (2.5% of diet DRGS).

Table (4): Effects of red grape skin on lipid profile of serum in fructose - fed rats

Parameters / Groups	TG (mg/dl)	TC (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)	VLDL-C (mg/dl)	AI
control	$50.1^{c} \pm 4.69$	$81.8^{b} \pm 6.36$	$51.8^{a} \pm 4.95$	$19.98^{d} \pm 1.3$	$10.02^{c} \pm 0.94$	$1.58^{d} \pm 0.05$
Fructose	$89.1^{a} \pm 7.89$	$103.9^{a} \pm 6.22$	$40.7^{b} \pm 2.95$	$45.38^{a} \pm 3.14$	$17.82^{a} \pm 1.58$	$2.55^{a} \pm 0.08$
F + DRGS (2.5% of diet)	$69.8^{b} \pm 6.93$	$90^{b} \pm 7.06$	$46.5^{ab} \pm 4.25$	$29.54^{b} \pm 1.78$	$13.96^{b} \pm 1.38$	$1.94^{b} \pm 0.05$
F + DRGS (5% of diet)	$66.2^{b} \pm 5.5$	$88.5^{b} \pm 7.2$	$49.7^{a} \pm 4.81$	$25.56^{c} \pm 1.68$	$13.24^{b} \pm 1.1$	$1.78^{c} \pm 0.04$

The data is presented like mean ± SD. The market letters show significant differences between dietary treating groups as revealed by one-way ANOVA followed by Duncan's range multiple test (a > b > c > d > e), where values within a column with dissimilar superscripts are meaningfully different ($p \leq 0.05$).

F, Fructose makes about 10% of the drinking water.

DRGS, Dried Red Grape Skin. 2.5% and 5% DRGS serve as 12.5% and 25% FRGS (Fresh Red Grape Skin) according to about 80% moisture content.

TG, total triglyceride; TC, totals of cholesterol; HDL-C, high-density lipoproteins cholesterol; LDL-C, low-density lipoproteins cholesterol; VLDL-C, very low-density lipoproteins cholesterol; AI (TC/HDL-C), atherogenic index.

The prevalence of metabolic syndromes is increasing globally, and it is linked to a rising serum level of uric acid and a high fructose intake that boosts uric acid, whereas the latter limits the bioavailability of nitric oxide **(Essawy et al., 2012)**. A high-fructose consumption exhibited clustering features of metabolic syndrome including hyperuricemia, hypertension, dyslipidemia (by significant increase in serum TGs, TC and LDL-c plus significantly reduce of serum HDL-C), insulin resistance, lowered renal cells nitrite plus elevated adiposity score in

rats **(Hu et al., 2009; El Mesallamy et al., 2010; Zhang et al., 2012 and Essawy et al., 2012)**. Also, **Kho et al., (2014)** found that overconsumption of fructose results in dyslipidemia, lipid metabolism and endothelial dysfunction, increasements of epididymal_fat weight and adipocyte size, raising levels of plasma TGs, TC and LDL-c, hepatic accumulation of triglycerides, impaired vascular endothelial function, and endothelium NO synthase levels (eNOS) expression in the aorta of fructose-treated rats. Moreover, Fructose-fed rats showed disrupted lipid profile by significantly hypercholesterolemia and hypertriglyceridemia as well as significant high levels of LDLc, VLDLc and atherogenic index, compared to control diet fed rats **(El Mesallamy et al., 2010 and Ibrahim et al., 2015)**; Also, impaired glucose tolerance and insulin sensitivity, higher nitric oxide metabolites (NOx) levels, and lower total antioxidant capacity (TAC) were observed by **El Mesallamy et al., (2010)**.

Advance fructose consumption via sucrose and HFCS (high fructose corn's syrup) has been linked to the rising incidence of obesity plus its associated cardiometabolic consequences, as metabolic syndrome, gout, elevated blood pressure, dyslipidemia, diabetes plus NAFLD (nonalcoholic fatty liver diseases). The proofs for these associations extract heavily from animal models, ecological research, and selected human with fructose overfeeding trials. There are some physiological mechanisms to explain these relationships derived from animal models, including rises in lipogenesis and uric acid-mediated hypertension **(Ha et al., 2013)**; also, **Tapia et al., (2013)** pointed to UA as conditional prooxidant that can persuade peroxidation of LDL.

Dyslipidemia might be partly responsible for dysregulations of renal urate transporters which retarded clearance of uric acid, causing high blood uric acid values **(Hu et al.,2009)**. Treatment of hypertriglyceridemia could reduce serum uric acid concentrations **(Nakagawa et al., 2006)**.

Flavonoids, including anthocyanins, can inhibit invitro LDL-C oxidation by scavenging radicals so flavonoids may have preventive activity against atherosclerosis **(Nijveldt et al., 2001)**. Also, **Xia et al., (2010)** showed that proanthocyanidin could prevented the raise of MDA and inhibited NO synthase in rat paws with arthritis. As well as epidemiologic investigations have supported that the intake of anthocyanin reduces the dander of arthritis and cardiovascular disorders related to scavenge reactive oxygen species (ROS), chelating metals and direct binding to proteins **(Bobinaitė and Viškelis, 2013).**

The red grape pomace which including seeds and skins as by-product contained great amounts of total polyphenols, flavonoids, anthocyanins, resveratrol and tannins than in regular growing grapes which associated with many biological properties, as antioxidant, anti-hypercholesterolemia, cardioprotective, anti-inflammation, hepatoprotective activities, supporting the use of byproducts of grapes processing as elements for useful and novel

products within the pharmaceutical, nutraceutical or beautifying fields **(Çetin and Saðdýç,2009; Georgiev et al., 2014 and Ferri et al., 2016)**. Grape pomace in the diet as 1.5% and 5.0% modulated some aspects of metabolic syndromes induced by fructose in rats that reduced fasting plasma insulin, glucose, and triglyceride levels; and in parallel with our results, the greater amount of grapes pomace diet showed a little better effect than lower amount **(Khanal, Ramesh et al., 2011)**.

Hyperlipemia plus oxidative strain, a definable danger factors for atherosclerosis and peroxidation outcomes of lipids as MDA-LDL (malondialdehyde moderated LDL), could be reduced by phenolic-rich grape juice **(Xia et al., 2010)**. Also, red grape juice successfully modulated the lower in serum TAC and NO levels as well as the alteration lipids profile namely, LDL-C, HDL-C, TG and TC in ethanol intoxicated rats (**Alnahdi, Hanan and Ayaz, Najla, 2012)**; and the same effects of red grape powder on hypercholestrolestrolemic Rats was found by **Zaki, Amal et al., (2020)**. Short-term consumption of red grape juice (RGJ) improved the lipid profile by increased plasma antioxidant capacity, cholesterol-standardized α-tocopherol and HDL levels, as well as reduced the susceptibility of LDL to oxidation and LDL levels and also prevent from inflammation in both healthy persons and hemodialysis patients. These are proposed methods that grapes flavonoids may protect from cardiovascular disorders (**Lasuncio´n et al., 2003; Castilla et al., 2006**). Plus several investigations have reported that consumption of grapes or its products or extracts involving red grape skin, seed, and juice can have useful effects on cardiovascular system by enhancing endothelial and vascular function, upregulates NO synthase making vasorelaxation effect and support healthy blood pressure, lowering cholesterol, decreasing platelet aggregation, reducing LDL and native protein oxidation then lowering the risk of blood clots, elevating antioxidant capacity, altering lipids, modulating inflammatory process and increasing anti-inflammatory factors since support the lowering of atherosclerosis via any one of the abovementioned mechanisms or more **(Batu and Kirmaci, 2007; Leifert and Abeywardena, 2008; Nassiri-Asl and Hosseinzadeh, 2009; Xia et al., 2010; Yang and Xiao,2013 and Georgiev et al., 2014)**.

Comparing the cardioprotective activities of flesh varus skins of grape indicated for the first time that despite of the fact that total phenols was less within flesh than skin of grape due to absence of anthocyanins for flesh, grape flesh show similar cardioprotective effects as skin plus the potential antioxidant properties of grape flesh and skin are equivalent as well as the reduction of MDA in the heart **(Falchi et al., 2006)**; in which **Arnous et al., (2002)** showed that flavanols were responsible for anti-radical activities more than anthocyanins. While comparative antioxidant plus hypolipidemic impacts of red

and white grape for adult hypercholesterolemic peoples showed that whole red grape intake has more effects than white grapes as anti-oxidative (by lowered TBARS and elevated TAC) and hypolipidemic (by reduced Total cholesterol and LDL-C). then, the whole red grapes can be the perfect fruit option for stop oxidative strain interacted metabolic syndromes as well as cholesterol connected cardiovascular disorders **(Rahbar et al., 2015)**; In which the phytochemicals of grapes vary among different varieties **Yang and Xiao (2013)**.

Effects of red grape skin on serum liver enzymes in fructose -fed rats

As noticed in Table 5, tested serum liver enzymes levels (ALT, AST and LDH) of fructose treated rats were significantly higher than normal group. RGS treatments at two experimental doses (2.5% and 5% of diet DRGS) lead to significant reduction in ALT and AST levels, and insignificant decreases in LDH levels vs. fructose treated rats. Also, it could be noticed that there were no significant changes between either two RGS doses each other or compared to normal group for all tested serum liver enzymes.

Table (5): Effects of red grape skin on serum liver enzymes in fructose -fed rats

Parameters / Groups	ALT (U/L)	AST (U/L)	LDH (U/L)
control	$31.4^{b} \pm 2.4$	$148^{b} \pm 12.12$	$2779^{b} \pm 175.6$
Fructose	$42.4^{a} \pm 3.33$	$174.4^{a} \pm 12.24$	$3181^{a} \pm 240.3$
F + DRGS (2.5% of diet)	$34.4^{b} \pm 2.78$	$150.1^{b} \pm 7.74$	$2858^{ab} \pm 166.3$
F + DRGS (5% of diet)	$36^{b} \pm 3.33$	$154.6^{b} \pm 7.1$	$2889^{ab} \pm 182.8$

The data is presented like mean ± SD. The market letters show significant differences between dietary treating groups as revealed by one-way ANOVA followed by Duncan's range multiple test (a> b> c> d>e), where values within a column with dissimilar superscripts are meaningfully different ($p \leq 0.05$).
F, Fructose makes about 10% of the drinking water.
DRGS, Dried Red Grape Skin. 2.5% and 5% DRGS serve as 12.5% and 25% FRGS (Fresh Red Grape Skin) according to about 80% moisture content.
ALT, alanine amino transferase; AST, aspartate amino transferase; LDH, lactate dehydrogenase.

The rise in liver lipid peroxides as well as elevated liver enzymes (ALT and AST) were detected in fructose treated rats as 10% fructose within drinking water during 20 weeks as compared to control group **(Ibrahim et al., 2015)**; and also **Khalaf, Hanaa et al., (2019)** induced fatty liver by 10% fructose within drinking water during 4 weeks that manifested by significant elevation of AST, ALT and serum and hepatic TG along with high serum UA ; while results by **Chen et al., (2013)** showed that 10% fructose within drinking water during 8

weeks leaded to nonsignificant raises in the activities of serum ALT and ALT. Liver dysfunction in fructose-fed rats (as 60% of diet for different period 30 or 60 days) was evident from a significant rise in AST, ALT and LDH enzymes in plasma **(Pooranaperundevi et al., 2010 and Giriş et al., 2014)**, plus NAFLD (nonalcoholic fatty liver diseases) was found by **Jegatheesan et al., (2015)**.

Rising fructose consumption via sucrose and HFCS (high fructose corn's syrup) has been linked to the rising incidence of obesity plus its associated cardiometabolic consequences, as metabolic syndrome, gout, elevated blood pressure, dyslipidemia, diabetes plus NAFLD (nonalcoholic fatty liver diseases). The proofs for these associations extract heavily from animal models, ecological research, and selected human with fructose overfeeding trials. There are some physiological mechanisms to explain these relationships derived from animal models, including rises in lipogenesis and uric acid-mediated hypertension **(Ha et al., 2013)**; also, several studies as **Tapia et al., (2013) and Khalaf, Hanaa et al., (2019)** reported that uric acid can immediately elevate accumulation of TG in liver tissue causing NAFLD by a mechanism which include oxidative strain and inflammation of mitochondria. The results by **Loza-Medrano et al., (2020)** appeared that liver fibrosis occurred via high fructose intake was connected with inflammation, hyperinsulinemia, dyslipidemia, peroxidation of lipids, dysregulation of hunger-satiety mechanism and weight gain. Several explanations for the correlation between triglycerides and fatty liver occurred by fructose including: Firstly, fructose as a lipogenic agent enhances formation of triglycerides which a direct outcome for its metabolism; Secondly, inveterate fructose intake stimulates the secretion of apolipoprotein and intestine free cholesterol plus TG manufacturing; Thirdly, insulin plus leptin, the major hormones that control energy generation and adiposity, are not increased by fructose which different from glucose **(Khalaf, Hanaa et al., 2019)**.

Liver and cardiovascular diseases related to elevate oxidative stress that are donated by cells and due to oxidative damage; it is normally expected that antioxidants with medical therapy is the best efficient way to manage and avoid oxidative strain damage **(Georgiev et al., 2014)**.

Scientific investigations have appeared the biologic and therapeutic properties of grapes extracts, specifically grapes skin or seed as antioxidant, anti-inflammatory, cardioprotective and hepatoprotective effects contributed to its several bioactive components involving flavonoids, polyphenols, anthocyanins, plus resveratrol derivatives. And resveratrol pretreatment as 10 mg/kg/day per oral, primarily present in skins and seeds of grape, prohibited oxidative injury, and reduced the ionizing radiation danger impacts on liver or ileum rat tissues as whole-body exposure to 800 cGy **(Çetin and Saðdýç,**

2009). Grape polyphenols can prevent liver due to their antioxidative plus anti-inflammatory activities **(Nassiri-Asl and Hosseinzadeh, 2009)**. Also, high polyphenols extract from grapes skins improved and protectd liver from high fat diet occurred adiposity plus liver steatosis in mice by lipids metabolism modification through organize enzymes of mRNA responsible for controlling of lipogenesis and oxidation of fatty acids **(Park et al., 2013)**.

The red grape juice successfully modulated the alteration of hepatic and cardiac biomarkers functions, including albumin, ALT (L-alanine aminotransaminase), AST (aspartate aminotransaminase), LDH (lactate dehydrogenase), CK (creatine kinase), lipid profile, and the decrease in TAC and NO levels in ethanol toxicity rats **(Alnahdi, Hanan and Ayaz, Najla**, **2012)**. As well as, red grape fruits power enhancement lipid profile and liver function in hypercholestrolemic rats **(Zaki, Amal et al., 2020)**. Also, red grape juice has beneficial effects on liver and antioxidant enzymes in pregnant and lactating rats **(Wohlenberg et al., 2015)**. Moreover, Grape pomace in the diet as 1.5% and 5.0% modulated some aspects of metabolic syndrome occurred by fructose in rats since reduced fasting plasma insulin, glucose, and triglyceride levels without affecting on elevated liver weight as a percentage of body weight (**Khanal, Ramesh et al., 2011)**.

Therefore, from the obtained results and previous studies it could be decided that RGS appeared a kind of prevention from fructose occurred NAFLD by its synergistic effects related to decreases in UA levels, oxidative stress, triglycerides, inflammation factors and the regulation of NO production. Additional animals and human investigations are required to support the current findings related to the preferable dose, period and type of grapes that should use.

Sensory evaluation of creamy cake prepared by DRGS supplementation as 2.5 and 5 % of wheat flour

Sensory assessment of creamy cake made by substituting various amounts of wheat flour with DRGS is presented in Table (6). It could be observed that cake prepared with DRGS at 2.5% replacement level recorded the favorable values in all sensory parameters and did not significantly different with usual cake. Additionally, no noteworthy variations were observed in compressibility, texture, taste, flavor and general acceptance between all cakes. While appearance and color values in cake prepared with DRGS at 5% showed significant decreases compared with 2.5% DRGS cake but did not significantly different from control cake for appearance.

Table 6. Sensory assessment of creamy cake made by substituting various amounts of wheat flour with DRGS

Parameters	Control	2.5% DRGS	5% DRGS
Appearance	$9.4^{ab} \pm 0.516$	$9.6^{a} \pm 0.699$	$8.8^{b} \pm 0.919$
Color	$9.2^{a} \pm 0.789$	$9.7^{a} \pm 0.483$	$8.3^{b} \pm 0.483$
Compressibility	$9.5^{a} \pm 0.707$	$9.6^{a} \pm 0.699$	$9^{a} \pm 0.942$
Texture	$9.3^{a} \pm 0.675$	$9.5^{a} \pm 0.707$	$8.9^{a} \pm 0.994$
Taste	$9.1^{a} \pm 0.876$	$9.1^{a} \pm 1.1$	$8.8^{a} \pm 0.919$
Flavor	$9.3^{a} \pm 0.675$	$9.1^{a} \pm 1.1$	$8.5^{a} \pm 0.707$
Overall acceptability	$9^{a} \pm 0.817$	$9.4^{a} \pm 0.699$	$8.7^{a} \pm 0.823$

The data is presented like mean ± SD. The market letters show significant differences between different cakes as revealed by one-way ANOVA followed by Duncan's range multiple test (a > b > c > d > e), where values within a row with dissimilar superscripts are meaningfully different ($p \leq 0.05$).
DRGS, Dried Red Grape Skin. 2.5% and 5% DRGS serve as 12.5% and 25% FRGS (Fresh Red Grape Skin) according to about 80% moisture value.

Also, it is important observation during cake preparation of fast height and maturity of cake in line with the levels of DRGS supplementation which may be related to soluble sugars, producing important economical and technological agents for reduce time and energy, also as a good natural colorant, flavor and height support factors. Anyway, more technological studies are needed to prove this technological orientation. This indicates that the RGS as byproduct could be applied successfully to make a cake which has high sensory features plus health benefits, making it a popular new functional food.

These findings come in agree with some investigations as **Deng et al., (2011) and (Ferri et al., (2016)** which reported that grapes pomace or its skins accepted as useful diet supplements and may use in many applications as ingredients of functional foods worthy of popularization; as natural colorants and preservatives of foods. Moreover, the search by **Nakov et al., (2020)** showed that the adding of increasing levels of grapes pomace powder (GPP) as 4%, 6%, 8% and 10% from wheat flour of cake enhanced nutritional value and antioxidant capacity by elevating ash, fibers, lipid, proteins, free phenolics, total polyphenols and anthocyanins content, while decreased moisture and PH. And the best sensory feature recorded for the cake containing 4% GPP; also its use will alleviate the ecological problems related to its disposal. Furthermore, **Bing and Chun (2015)** used the dried wild grapes as 3, 6, 9 or 12% in rice chiffon cake for evaluate quality, antioxidant, and sensory properties and concluded that grapes powder can be a useful substance which significantly increased total polyphenol content, moisture and antioxidant activity with elevating levels of grape powder, and 6% is the best amount to making rice chiffon cakes.

Conclusion

It could be concluded that low levels of fructose intake would be necessary and RGS, a largely natural byproduct with its chemical and biological properties, can be accepted as beneficial diet supplements either as colorant, flavoring, baking height supporting and/or preservatives agents of food or as novel, safe, and efficient functional food because of its hypouricemic, and renal protective actions against high fructose intake. Anywise more studies are needed to prove and detect the perfect dose, period, and type of grape toward these respects in different experimental animal models and in humans.

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