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Raisin Syrup Consumption Has Hematological Improvement In Mice

Yusur Falah Faraj[1] , Shatha Salah Asad[2] , Jamela Jouda[3*] , Khalid M Salih[3] , Luma A. Qasim[3] and Sundus Q. Mohammed[3]

[1]National Center of Hematology, Mustansiriyah University, Baghdad, Iraq.

[2]Al-Kindy College of Medicine, University of Baghdad, Baghdad, Iraq.

[3]Department of Biology, College of Science, Mustansiriyah University, Baghdad, Iraq.

Abstract:

Based on our last study that suggested many hematological impact of changing diet style and since raisin contains many useful materials which may have many benefits for hematological parameters, this work aims to study the curative effect of raisin extract on the hematological changes and histopathological changes of spleen resulting from changing the diet style in mice. In this study, 32 adult male Balb/c mice aged 8 weeks old were conducted. They were divided into four groups (n=8 for each); first group (abbreviated G_B) fed on normal diet containing10% sheep brain extract and drink tap water, second group (abbreviated G_R) fed on normal diet and drink raisin syrup at a concentration of 0.5mg/ml ad libitum, third group (abbreviated G_{B+R}) fed on normal diet containing10% sheep brain extract and drink raisin syrup at a concentration of 0.5mg/ml ad libitum, and fourth group act as control group that fed on normal diet and drink tap water ad libitum. After 7 days, blood samples were collected from the eye of all mice and transferred into EDTA tubes to determine complete blood count, then mice were sacrificed by cervical dislocation and spleens were obtained to investigate their histopathological changes. Results showed that the deviations in the values of complete blood count as well as histopathological changes in spleen that occur in mice of G_B group are improved in mice of G_R and G_{B+R} groups when compared with control group. These results indicate the beneficial effect of raisin on health status and need further investigation.

Key words: raisins, nutritional style, fat-rich diet, brain extract.

Introduction:

Raisins are dried grapes produced in many regions of the world. It can be eaten raw or used in cooking, baking, and fermentation [1]. Since Iraq, Iran, and turkey have a perfect weather for planting raisins, the best kind of raisins can be found there. The finest Iraqi raisins are the yellow kind which come from Al-Hoss, Diyala, Malwiya, and Al-Sa`is [2].

Raisins contain up to 72% sugars, most of which are glucose and fructose [3], 3% protein, and 3.7% -6.8% dietary fibers [4]. Raisins are also high in boron [5, 6], omega 3 [7], E and C vitamins [5], and antioxidants, but they are low in sodium and do not contain cholesterol [2]. This total nutritional

value of raisins is very important for controlling weight and maintaining good human health due to controlling glucose and cholesterol, which helps in good functioning of the digestive system, regulating blood pressure [8], and a moderate glycemic index [9], reducing the risk of malignancies [10], and improvement of many other health biomarkers.

It is known that blood cells, red and white blood cells, and platelets are very important to the health of the body, and any imbalance in the value of these cells can cause many complications and diseases [11]. Whereas, changing from a diet high in fiber and low in fat to a diet low in fiber and rich in saturated fats can affect the erythrocyte membranes [12] and count [13], and the white blood cell count [13] associated with cardiovascular disease [14] and inflammation that may also result from eating a high-fat diet [14, 15], and a platelet count [14] whose activation and aggregation are among the key processes typically controlled in the pathophysiology of cardiovascular disease [16]. On the other hand, our previously research demonstrated several pathological changes in the spleen, which it plays important roles in regard to blood containing [17], of mice because of diet style changing [14].

The best way to normalize this anomaly is by using natural materials as they have limited side effects [18]. It is believed that raisins can increase the red blood cell count because it is the best natural source of iron and vitamins B-12 and C, so it is recommended to use it to treat anemia [2]. There is no study proving this result and to our knowledge, there is no information about the effect of raisins on WBCs and PLTs except our previous study that referred to increase RBC, decrease PLTs, and no changing in WBCs by consumption of raisin extract [2].

According to our previous researches, changes in nutritional style rather than a conventional diet caused hematological impacts [13] and raisin consumption affect differently on hematological parameters [2] So this work aims to study the curative effect of raisin extract on the hematological changes and histopathological changes of spleen resulting from changing the diet style in mice.

Materials and Methods:

A fat-rich diet was prepared as described in our previous study [14] and raisin syrup was also prepared as described in our previous study [2]. In this study, 32 adult male Balb/c mice aged 8 weeks old were obtained from the preventive research center, Baghdad, Iraq and divided into four groups (n=8 for each); first group (abbreviated G_B) fed on normal diet containing10% sheep brain extract and drink tap water, second group (abbreviated G_R) fed on normal diet and drink raisin syrup at a concentration of 0.5 mg/ml ad libitum, third group (abbreviated G_{B+R}) fed on normal diet containing10% sheep brain extract and drink raisin syrup at a concentration of 0.5 mg/ml ad libitum, and fourth group act as control group that fed on normal diet and drink tap water ad libitum. After 7 days, blood samples were collected from the eye edge of all mice and transferred into EDTA tubes to determine complete blood count by using D-Cell 60 Hematology Analyzer from DIAGON®/ Diagon Ltd, Hungary, Budapest, then mice were sacrificed by cervical dislocation and spleens were obtained and fixed in 10% formalin solution to investigate their histopathological changes by using standard procedure of hematoxylin and eosin staining. Data are expressed as mean ± standard deviation (M±SD) and differences were analyzed by using Statview version 5.0 based on Fisher test and Tukey HSD test. Differences considered significant at P value less than 0.05.

Results:

Table (1) shows that mice fed on fat-rich diet (G_B) have total count of WBCs (13.9 ± 3.6 x 10^9/L) which significantly (P < 0.01) higher than 8.4 ± 2.6 x 10^9/L in control group. However, total count of WBCs in G_R and G_{B+R} groups (9.8 ± 1.9 x 10^9/L and 10.2 ± 3.6 x 10^9/L respectively) reveal non-significant difference from those in G_B and control groups.

Table (1): Total count of WBCs in different groups

WBCs count (x 10^9/L)	G_B (n=8)	G_R (n=8)	G_{B+R} (n=8)	Control (n=8)
Range	9.4 – 21.7	6 – 12.5	4.5 – 14.5	4.4 – 12.5
M±SD	13.9 ± 3.6[a]	9.8 ± 1.9[a,b]	10.2 ± 3.6[a,b]	8.4 ± 2.6[b]
Different small letters indicate significant difference between column at P<0.01				

Based on the normal range of WBCs count in mice (4.45 – 13.98 x 10^9/L), the 95% confidence interval of a proportion show that 0.375 of mice in G_B have WBCs count higher than the upper limit of normal range (0.324 at 95% CI), while those in G_{B+R} (0.125) and G_R (0.0) are within normal range (0 – 0.324 at 95% CI) as shown in figure (1).

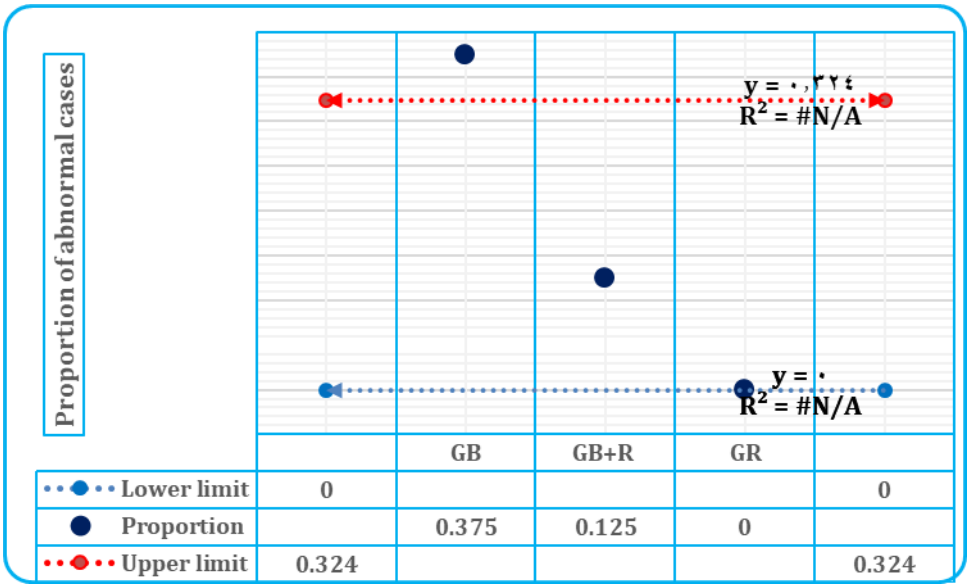


Figure (1): Proportion of mice with WBCs count higher than upper limit of normal range based on 95% confidence interval

Since there were no significantly differences among granulocytes and lymphocytes count in these four groups and they were within the normal rang, table 2 shows only the different among monocytes numbers in these groups which were significantly higher in the G_B group (2.4 ± 0.35 x 10^9/L) compared to control (0.72 ± 0.15 x 10^9/L) and G_R (0.8 ± 0.18 x 10^9/L). There was no significantly difference between its number in G_B and G_{B+R} (1.2 ± 0.44 x 10^9/L). Interestingly, monocytes numbers in G_B and G_{B+R} higher than normal rang in the mice (0.15-0.94)

Table (2): Monocytes count in different groups

Monocytes count (x 10^9/L)	G_B (n=8)	G_R (n=8)	G_{B+R} (n=8)	Control (n=8)
Range	2.75 – 2.0	0.62 – 0.98	1.64 – 0.76	0.57 – 0.87
M±SD	2.4 ± 0.35[a]	0.8 ± 0.18[b,c]	1.2 ± 0.44[a,c]	0.72 ± 0.35[b]
Different small letters indicate significant difference between column at P<0.05				

On the other hand, Table (3) shows that mice fed on fat-rich diet (G_B) have RBCs count (6.2 ± 0.55 x 10^{12}/L) which significantly (P < 0.01) lower than those in control group (8.96 ± 0.7 x 10^{12}/L), G_R group (8.06 ± 0.85 x 10^{12}/L), and G_{B+R} group (7.66 ± 0.97 x 10^{12}/L). However, G_R group has non-significant difference with both G_{B+R} and control groups, but RBCs count in G_{B+R} is significantly lower than in control group.

Table (3): Total count of RBCs in different groups

RBCs count (x 10^{12}/L)	G_B (n=8)	G_R (n=8)	G_{B+R} (n=8)	Control (n=8)
Range	5.25 – 6.99	7.09 – 9.37	6.63 – 9.37	7.59 – 9.85
M±SD	6.2 ± 0.55[b]	8.06 ± 0.85[a,c]	7.66 ± 0.97[c]	8.96 ± 0.7[a]
Different small letters indicate significant difference between column at P<0.0001				

Based on the normal range of RBCs count in mice (7.14 – 12.2 x 10^{12}/L), the 95% confidence interval of a proportion in control group is between (0.675 and 1). Accordingly, all mice in G_B have RBCs count lower than the lower limit of normal range (0.675 at 95% CI), thus the proportion of normal cases is (0.0), while the proportion of mice that have RBCs count within normal range of 95% CI in G_{B+R} and G_R 0.5 and 0.75 respectively as shown in figure (2).

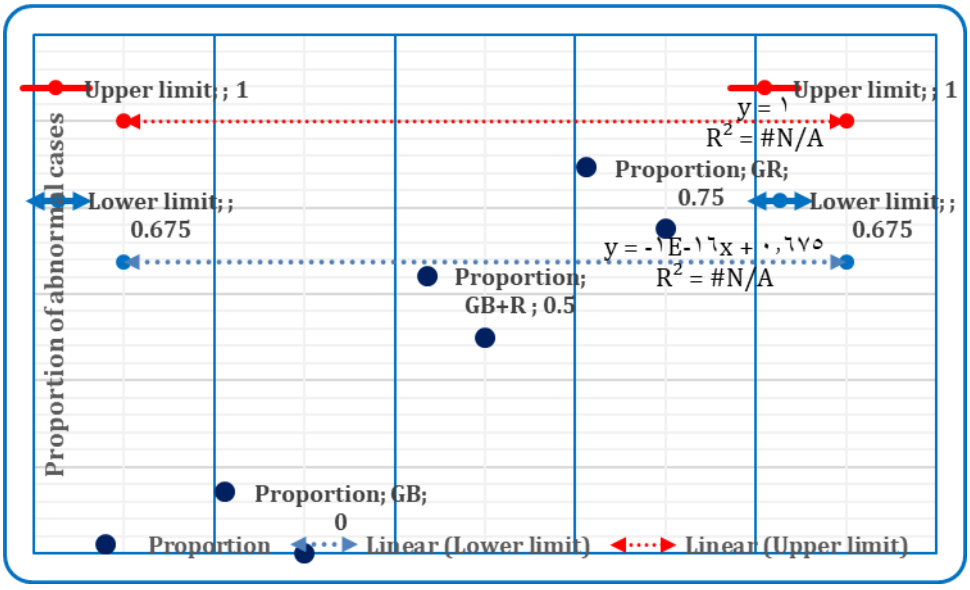


Figure (2): Proportion of mice with RBCs count less than the lower limit of normal range based on 95% confidence interval

In addition, PCV% was significantly lower in mice fed on fat-rich diet (G_B) (10.56 ± 2.88) than those in control group (37.72 ± 1.42), G_R group (39.24 ± 1.4), and G_{B+R} group (33.08 ± 1.12). However,

G_R group has non-significant difference with both G_{B+R} and control groups table 4. Based on normal value of PCV% in mice is (37.3 - 62.0), only PCV% in G_B and G_{B+R} were not within the normal range.

Table (4): PCV% in different groups

PCV%	G_B (n=8)	G_R (n=8)	G_{B+R} (n=8)	Control (n=8)
Range	13.44 – 8.68	40.64 – 37.84	34.20 – 31.96	39.14 – 36.30
M±SD	10.56 ± 2.88[b]	39.24 ± 1.4[a]	33.08 ± 1.12[a]	37.72 ± 1.42[a]
Different small letters indicate significant difference between column at P<0.05				

Platelets count increase significantly from (978 ± 89 x 10^9/L) in control group to (1999 ± 777 x 10^9/L) in G_B and decrease significantly in G_R (593 ± 105 x 10^9/L). Then it return to reach (1162 ± 433 x 10^9/L) which did not have any significantly different with control group. Platelets count was two times more in G_B and two times less in G_R than control group. Interestingly, it was critical in G_B and lower in G_R compared to normal value (841 – 2156 x 10^9/L) (figure 3).

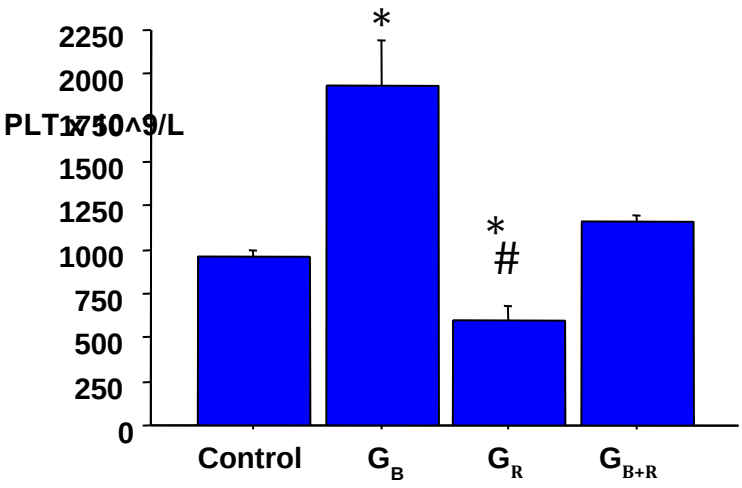
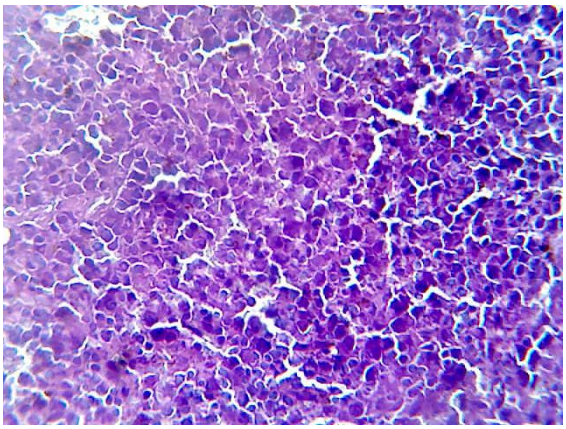
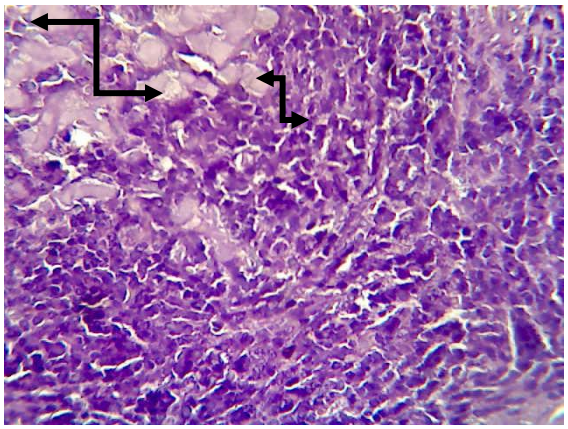


Figure (3): Platelet count in different groups. *significantly difference between Control vs. other groups. # significantly difference between G_R vs. G_B and $G_{B+R.}$

Concerning with the histological study of the spleens in all groups, the results demonstrated several pathological changes in the spleen of mice fed on fat-rich diet (G_B) which shows moderate depletion of white pulp and severe congested of red pulp compared to spleen of control group which shows no clear lesion. These changing were exactly like what was found in our last research [14]. Figure (4) shows no clear lesion in the spleen of G_R (A) and amyloid like substance deposition in red pulp of spleen in $G_{B+R.}$



A: Section in the spleen of G_R shows no clear lesions (H& E stain 400X)



B: Section in the spleen of G_{R+B} shows amyloid like substance deposition in red pulp (H & E stain 400X)

Figure (4): histological sections in the spleen of G_R (A) and G_{B+R} (B).

Discussion:

It is well established that any change in the diet pattern of rats can cause various pathological and immunological effects in the body [19, 20], as it can stimulate a low degree of chronic inflammation [21] leading to an increase in total white blood cells [22], inflammatory mediators [23], and monocyte concentration [24-26] associated with increased phagocytosis to get rid of foreign and toxic substances [22]. Our present research shows that the total WBCs and Monocytes number increased abnormally in the restricted group. It is well established that any immune response could increase the total WBCs and high monocyte concentration can be associated with increased phagocytosis to get rid of strange and toxic substances [22]. These results could explain the increased number of total WBCs and monocytes present in the group of mice fed a high-fat diet (G_B) in the current research compared to controls. In our current results, there was no change in WBC indicators in the group of mice that consumed a normal food and raisin extract drink (G_R) which looked like the results of the control group which agreed with our recent research while consumption of raisins could normalize the increased number of total blood cells. Leukemia and monocytes in mice fed a high-fat diet as in group G_{R+B} because raisins contain an element that is very beneficial for bone health, brain function, and immune response content [6] and omega-3 and important nutrients and have anti-oxidative stress, anti-inflammatory, and anti-urination effects [5].

Since a high-fat diet increases cholesterol levels [27], this may lead to increased osmotic erythrocyte fragility and oxidative stress [28]. These changes can cause the development of hemolytic anemia [27, 28]. This possibility was demonstrated in our recent research (), where consumption of a diet rich in high fat was shown to reduce hemoglobin, hematocrit, erythrocytes, and RDW-SD and cause little difference in MCV which may indicate the occurrence of hemolytic anemia [27, 29]. In addition, the platelet/lymphocyte ratio was three times more in the group of mice that ate a high-fat diet than the control group, which may indicate increased oxidative stress [30, 31]. In this study, the hematocrit and RBCs decreased in the forage regimen. Mice rich in fat (G_B) compared to the control group. In addition, there was no change in these parameters in the group of mice fed the regular diet and raisin extract drink (G_R) while in the group of mice normalized on a high-fat diet and raisin extract drink (G_{R+B}). The cause of the normalization of hematocrit and

erythrocytes can be due to mechanisms. The first contains raisins, vitamin C [32], vitamin B12, and iron [20]. These contents increase the number of red blood cells and have an important role in treating anemia [33, 34]. The second mechanism, grapes (a source of raisins) can enhance the antioxidant enzyme activities of the liver and red blood cells [35, 36] which may increase the number of red blood cells and treat anemia.

As was mentioned above, high-fat diet consumption increases cholesterol levels [27] and other lipoproteins concentration [37]. These changes could mediate platelet aggregation by increase arterial thrombosis tendency, increase the response of thrombin [38], change in the hematopoiesis process was [38-40], and increase white blood cell count and platelet levels due to the cholesterol-induced cytokines [41]. It is known, abnormal platelet counts are associated with cardiovascular disease [42-44], so it is recommended to treat cardiovascular disease by anti-platelet therapies [45]. On other hand, the raisins have distinct beneficial effects on CVD risk [46]. Vitseva et al, 2005; suggested decrease platelet properties of purple grape-derived flavonoids which caused uncontrolled bleeding in persons eating much purple grape [47]. These pieces of evidence agree with our results in this study that showed increase PLTs two times more in the mice group feed diet rich with fat (G_B) and decrease two times less in mice group feed normal diet and drink raisin extract (G_R) compared to control group. These changes are normalized in the mice group feed diet rich with fat and drink raisin extract (G_{B+R}).

Since consumption of a high-fat diet stimulates chronic, low-grade inflammation, and may contribute to increased levels of inflammatory serum mediators [21], our last [14] and current research has found that a high-fat (G_B) diet can cause moderate depletion of the white pulp in Agreement with other studies found that it caused many immunological and histological effects in the white pulp of the spleen [48-50], but the exact mechanism of the negative effect of the fat diet on the white pulp is still unclear [51, 52]. In addition, the current study found some deposition of amyloid-like substance in the erythroderma in the spleen of G_{R+B} which was less effective than that in the splenic section of G_B.

It can be concluded that the monocytosis, hemolytic anemia, as well as thrombocytosis caused by changing in nutritional style rather than a conventional diet could be normalized by consuming raisin extract. Therefore, the beneficial effect of raisin on health status needs further investigation particularly on immune system.

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