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# Kinetics of Hesperetin for Liver Fortification in γ-Irradiated Mice

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HESPERETIN (3`,5,7-trihydroxy-4`-methoxyflavonone), the aglycone of the flavanone glycosides hesperidin, exerts pharmacological properties such as antioxidation, anti-inflammation, blood lipid and cholesterol lowering is effectively used as a supplemental agent in the treatment protocols of complementary settings.

Four groups were prepared: Control group: received 0.5 ml normal saline for 7 days. Hesperetin group: Mice received 7 doses of hesperetin injections (100 mg/ kg body wt/ day). Irradiated group: Mice submitted to total body irradiation with 4 Gy γ-rays. Protected group (Hesperetin plus irradiation): Mice received hesperetin for 7 days and then submitted to 4 Gy of γ-rays. The mice were sacrificed at 24 h, 1 week and 2 weeks after the end of the experimental treatments.

Irradiated mice exhibited significant hyperglycaemia and augmented hepatic glycogen after the first day and 1 week but significant hypoglycemia and reducing hepatic glycogen after 2 weeks. Also, they exhibited significant increased serum total cholesterol (TC) and triacylglycerols (TG) and decreased hepatic TC and TG after 1 & 2 weeks. This treatment also resulted in a significant dropped in hepatic glucokinase (GK), glucose-6-phosphatase (G6P) and phosphoenolpyruvate carboxykinase (PEPCK) activities after 1 & 2 weeks.

Hesperetin injections modulated the serum glucose and hepatic glycogen, adjusted TC and TG in both serum and liver and ameliorated the lessening in hepatic GK, G6P and PEPCK.

The attending results demonstrated that hesperetn treatment modulated the biochemical symptoms of radiation disorders in mice.

In conclusion, administration of hesperetin may have a useful role in modulating oxidative stress induced by exposure to γ-radiation by improving the natural antioxidant mechanism and fortification liver functions.

***Keywords:*** Hesperetin, liver, protection, γ-rays, mice.

Increasing attention has been given to the roles of free radicals generated through the oxidative stress, especially induced by ionising radiation (Riabchenko *et al.,* 2011). Interest has increased in the possible health benefits of flavonoids owing to their potent antioxidant and free-radical scavenging activities (Jain *et al.,* 2011). Attempts have recently been made to find biological activities among citrus flavonoids. It was shown that the administration of hesperetin and its metabolites significantly lowered the total cholesterol (TC) and triacylglycerols (TG) concentrations in plasma (Hwang *et al.,* 2012 and Kim *et al.,* 2003). Hesperetin bioflavonoid exhibited biological and pharmacological properties, such as anti-inflammatory, anticarcinogenic and antioxidant activities (Gardana *et al.,* 2007). In addition, Kawaguchi *et al.* (2004) showed that pre-treatment with hesperetin could suppress infection-induced endotoxin shock in mice and a significant reduction of bacterial numbers during infection due to the activation of host defence mechanisms. Furthermore, it protects rat neurons cells against various types of insults associated with many neurodegenerative diseases (Hwang and Yen, 2011). Results indicate that hesperetin glucuronides protects against UV-A radiation-induced necrotic cell death (Tvrrell and Rice-Evans, 2003) and treats symptoms of radiation sickness (Saad, 2005). Recently, Fu *et al.* (2010) concluded that hesperetin may be used as a potent radio protector against radiation damage.

The radio protective properties of hesperetin were studied in this report using the kinetics of γ-rays-induced oxidative injury. A series of tests was conducted to explore the changes in mouse liver and mechanisms of radioprotection.

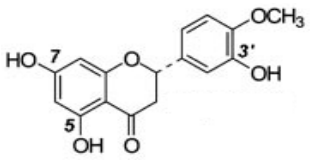
## Material and Methods

### *Animals*

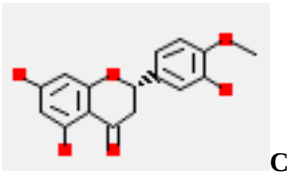
Thirty male mice per group, 5 weeks old (20-23 g), were purchased from the Holding Company for Biological Products and Vaccines (Helwan, Cairo, Egypt). All mice were housed in stainless-steel cages in a room with controlled temperature (20-22 °C and 60± 5 % relative humidity) and lighting (alternating 12-h periods of light and dark). Mice had free access to food and water.

### *Drug*

Hesperetin was purchased from (Sigma-Alderch Chemicals, St. Louis, MO, USA). A daily intra-peritoneal (ip) administration of hesperetin, dissolved in 0.5 ml sterilised normal saline, at dose of 100 mg/ kg body wt was given for 7 days, alone, or prior to γ-irradiation according to (Hosseinimehr and Nemati, 2006) protocol.




**3`,5,7-trihydroxy-4`-methoxyflavonone**



**C$_{16}$H$_{14}$O$_6$**

**Fig. 1. Hesperetin structure.**

***Irradiation***

A single whole body γ-irradiation dose of 4 Gy at a dose rate 0.42 Gy/ min using a $^{137}$Cs source (Gamma Cell-40) belongs to the NCRRT, Nasr City. Egypt.

***Experimental design***

Four groups of mice (n= 30) were treated as follows: Control group: Each mouse received 0.5 ml normal saline ip, per day for 7 days. Hesperetin group: Mice received 100 mg/kg body wt/ day of hesperetin drug for 7 days. Irradiated group: Mice were exposed to a single dose of 4 Gy total body γ-rays irradiation. Protected group (Hesperetin plus irradiation): Mice received hesperetin for 7 days and then submitted to 4 Gy of γ-irradiation. Mice were sacrificed by cervical dislocation at 24 h, 1 week and 2 weeks after the end of treatments. Blood samples were collected and sera separated. Livers were removed, rinsed with physiological saline solution and immediately stored at -80°C. Sera of glucose (GS), total cholesterol (TC) and triacylglycerols (TG) were determined using Dubowski (1962), Richmond (1973) and Spayd *et al*. (1978) methods, respectively.

Hepatic lipids were extracted quantitatively with an ice-cold mixture of chloroform and methanol (2:1, v/v) by the method of Folch *et al.* (1957). The hepatic TC and TG were analysed with the same enzymatic methods used in the sera analysis. Hepatic glycogen concentration was determined as described by Seifter *et al.* (1950).

Hepatic glucokinase (GK), glucose-6-phosphatase (G6P) and phosphoenolpyruvate carboxykinase (PEPCK) activities were measured using the spectrophotometric assays according to Davidson and Arion (1987), Alegre *et al.* (1988) and Bentle and Lardy (1976).

***Statistical Analysis***

All data are presented as means+ SE. Statistical analyses of the results were calculated using ANOVA-test according to Knapp and Miller (1992). Acceptable significance was recorded when the P-values were less than 0.05.

## Results

No significant changes appeared between control and hesperetin groups of all tested parameters at the 3 experimental time periods.

**TABLE 1. Serum glucose and hepatic glycogen levels in mice given hesperetin and/ or 4 Gy γ-rays.**

| Experimental periods | **Glucose** (mmol/ L) | **Glycogen** (mg/ g liver) |
|---|---|---|
| **Control group** | | |
| **1st day** | 21.3± 1.12 | 63.4± 3.43 |
| **1 week** | 20.9± 1.14 | 63.1± 3.25 |
| **2 week** | 21.1± 1.16 | 63.3± 3.45 |
| **Hesperetin group** (100 mg/ kg) | | |
| **1st day** | 20.8± 1.13 | 65.2± 3.44 |
| **1 week** | 20.7± 1.17 | 65.5± 3.28 |
| **2 week** | 20.8± 1.13 | 65.1± 3.37 |
| **Irradiated group** (4 Gy γ-rays) | | |
| **1st day** | 30.9± 1.45[a,b] | 79.1± 4.10[a,b] |
| **1 week** | 26.9± 1.18[a,b] **A** | 75.7± 3.68[a,b] |
| **2 week** | 17.1± 0.91[a,b] **A,B** | 50.7± 2.58[a,b] **A,B** |
| **Hesperetin plus irradiation group** | | |
| **1st day** | 23.8± 1.03[c] | 66.4± 4.06[c] |
| **1 week** | 22.2± 124[c] | 64.1± 3.65[c] |
| **2 week** | 20.6± 1.07[c] | 59.3± 2.85[c] **A,B** |

[a]= Statistical significant as compare to control group.

[b]= Statistical significant as compare to hesperetin group.

[c]= Statistical significant as compare to irradiated group.

**(A)**= Significantly different from value after 1st days.

**(B)**= Significantly different from value after 1 week.

Irradiated mice exhibited a significant hyperglycaemia with a value of 30.9± 1.45 mmol/ L after the first day. The observed increase in glucose concentration decreased significantly to 26.9± 1.18 mmol/ L after a week, however, it was still significantly elevated as compared with the control value. In contrast, after 2 weeks the glucose level exhibited a significant hypoglycaemic value of 17.1± 0.91 mmol/ L (Table 1). The hepatic glycogen of the irradiated mice was significantly augmented as compared to the control, with values of 79.1± 4.10 and 75.7± 3.68 mg/ g liver after the first day and a week post-irradiation. After 2 weeks, the glycogen level exhibited a significant

reduction to 50.7± 2.58 mg/ g liver. There were significant differences between the glycogen values after 2 weeks as compared to the first day and one week sampling times (Table 1).

Hesperetin drug injections for 7 days prior to irradiation showed marked protection of the glucose/ glycogen parameters studied for mice at all experimental periods. There were significant differences between the glycogen value after 2 weeks and after the first day and one week time samples (Table 1).

As shown in Table 2, the TC and TG levels in serum and hepatic tissues were significantly higher in γ-irradiation-exposed mice than in the normal matched-controls after a week and 2 weeks of the experimental periods. There were significant differences between serum TC values at 1 week and 2 weeks and its value at 24 h while only serum TG values at 2 weeks were significantly different from the 24 h values. Significant differences between hepatic TC values at first week versus values at 24 h and hepatic TG values at 2 weeks versus values at 24 h were also detected.

**TABLE 2. Serum and hepatic lipids levels in mice given hesperetin and/ or 4 Gy γ-rays.**

| Experimental periods | **Serum** (mg/ dl) | | **Hepatic** (mmol/ g) | |
|---|---|---|---|---|
| | **TC** | **TG** | **TC** | **TG** |
| **Control group** | | | | |
| **1st day** | 3.34± 0.221 | 1.44± 0.092 | 0.20± 0.010 | 0.12± 0.003 |
| **1 week** | 3.29± 0.192 | 1.49± 0.112 | 0.22± 0.014 | 0.12± 0.005 |
| **2 week** | 3.27± 0.253 | 1.41± 0.124 | 0.21± 0.012 | 0.13± 0.009 |
| **Hesperetin group** (100 mg/ kg) | | | | |
| **1st day** | 3.31± 0.182 | 1.42± 0.082 | 0.19± 0.012 | 0.12± 0.008 |
| **1 week** | 3.27± 0.204 | 1.48± 0.131 | 0.21± 0.016 | 0.12± 0.007 |
| **2 week** | 3.24± 0.210 | 1.41± 0.102 | 0.21± 0.017 | 0.13± 0.006 |
| **Irradiated group** (4 Gy γ-rays) | | | | |
| **1st day** | 3.59± 0.178 | 1.52± 0.084 | 0.19± 0.012 | 0.12± 0.007 |
| **1 week** | 4.42± 0.232[a,b] **A** | 1.72± 0.103[a,b] | 0.16± 0.009[a,b] A | 0.10± 0.006[a,b] |
| **2 week** | 4.71± 0.263[a,b] **A** | 1.90± 0.110[a,b] **A** | 0.17± 0.011[a,b] | 0.09± 0.005[a,b] A |
| **Hesperetin plus irradiation group** | | | | |
| **1st day** | 3.36± 0.218 | 1.48± 0.037 | 0.20± 011 | 0.12± 0.004 |
| **1 week** | 3.45± 0.217[c] | 1.51± 0.098[c] | 0.21± 0.011[c] | 0.11± 0.005 |
| **2 week** | 3.35± 0.241[c] | 1.49± 0.104[c] | 0.21± 0.010[c] | 0.12± 0.008[c] |

Legends as in Table 1.

Hesperetin injections prior to irradiation caused marked protection for mice as shown in both TC and TG levels after 1 week and 2 weeks of the experimental periods, except for TG after 1 week, (Table 2).

The hepatic enzyme activities showed no significant differences in the γ-irradiated group after the first day, but showed significant diminution in their activities after a week and 2 weeks, Table 3.

**TABLE 3. Hepatic enzyme activity (nmol/ min /mg protein) levels in mice given hesperetin and/ or 4 Gy γ-rays.**

| Experimental periods | GK | G6P | PEPCK |
|---|---|---|---|
| **Control group** | | | |
| **1st day** | 267.5± 8.71 | 847.7± 57.69 | 130.1± 5.19 |
| **1 week** | 259.3± 7.98 | 830.8± 53.17 | 128.4± 4.81 |
| **2 week** | 262.6± 7.77 | 834.6± 51.54 | 126.9± 4.62 |
| **Hesperetin group** (100 mg/ kg) | | | |
| **1st day** | 275.4± 7.88 | 879.6± 56.39 | 124.2± 3.28 |
| **1 week** | 268.4± 9.67 | 864.5± 51.31 | 123.6± 4.40 |
| **2 week** | 275.7± 6.68 | 871.7± 52.71 | 118.1± 4.73 |
| **Irradiated group** (4 Gy γ-rays) | | | |
| **1st day** | 235.4± 10.23 | 761.2± 45.03 | 118.4± 7.34 |
| **1 week** | 168.5± 8.42[a,b] **A** | 583.2± 40.81[a,b] **A** | 93.7± 5.06[a,b] **A** |
| **2 week** | 204.8± 9.22[a,b] **B** | 600.9± 34.85[a,b] **A** | 100.2± 5.38[a,b] |
| **Hesperetin plus irradiation group** | | | |
| **1st day** | 262.3± 9.23 | 846.5± 46.44 | 122.9± 5.54 |
| **1 week** | 256.6± 10.10[c] | 808.1± 46.47[c] | 122.2± 5.11[c] |
| **2 week** | 258.3± 10.32[c] | 758.9± 44.88[a,b,c] **A,B** | 120.1± 6.22[c] |

Legends as in Table 1.

The hesperetin intake significantly elevated hepatic, G6P and PEPCK activities when compared with the irradiated group, respectively (Table 3).

There was a significant difference between G6P values after 2 weeks and after the first day and 1 week of the experimental periods.

## Discussion

Hesperetin is bio available from the fruit and vegetables diet in human subjects (Erlund *et al.*, 2002). Pharmacokinetic analysis showed that hesperetin

was rapidly absorbed and their concentrations in human plasma observed 20min after dosing and reached a peak in 4 h (Kanaze *et al.,* 2006).

Glucose level in serum and glycogen content in hepatic tissue were significantly higher than normal value after the 1st day and a week post irradiation, while a remarkable hypoglycaemic condition was recorded after 2 weeks of irradiation as shown in Table 1. These findings agreed with results of Ragab and Ashry (2004), they explained that, the cause of hyperglycaemia could be attributed to the diminished utilization of glucose by the tissues after irradiation while, the causes of hypoglycaemia later on, could be attributed to the direct effect of radiation on the β-pancreatic cells, stimulating a sudden rise in insulin or due to the increased activity of the thyroid gland leading to an increase in glucose oxidation or due to retardation of glucose absorption by damaged intestinal epithelium.

The data obtained revealed that intake of hesperetin before γ-rays exposure resulted in amelioration of the alterations in glucose and glycogen. Jung *et al.* (2004) suggested that it plays important role in preventing the progression of hyperglycaemia, partly by increasing hepatic glycolysis and glycogen concentration and/ or by lowering hepatic gluconeogenesis. In addition, the hypoglycaemic effect of hesperetin seemed to be mediated by changes in the hepatic glucose regulating-enzyme activities that were observed in Table 3. In addition, Jung *et al.* (2004) reported that, hepatic GK is the most sensitive indicator of the glycolytic pathway in mouse diabetes and its decrease can delay the utilization of blood glucose for glycogen storage in the liver.

A recent study (Attia *et al.*, 2007) has shown that low blood glucose and glycogen that appeared 2 weeks post γ-irradiation due to oxidative stress of the pancreatic-cells in rats could ameliorate by an antioxidant. Kaneto *et al.* (2001) showed that antioxidants could have beneficial effects on pancreatic-cells by neutralizing the oxidative stress. Hesperetin displayed a significant cytoprotective effect against oxidative stress (Chen *et al.,* 2012). Accordingly, in the current study, the potent antioxidant, hesperetin has been found to preserve the pancreatic-cell functions and maintain the level of blood glucose and liver glycogen.

This study has identified increased serum TC and TG concentrations and decreased concentrations in hepatic tissues in mice exposed to γ-rays after 1 & 2 weeks of the experimental period. Several studies reported that the hyperlipaemic effect and the reduction of hepatic lipids following whole body γ-irradiation were attributed to a combination of different mechanisms related to decrease lipoprotein-lipase activity and cholesterol-efflux from peripheral tissue due to plasma membrane damage and migration of fats (hepatic TG and TC) from adipose tissue (Feurgard *et al.,* 1998 and Sedelakova *et al.,* 1998).

The group of mice protected with hesperetin injections revealed reasonable protection at both experimental periods for both serum and hepatic TC and TG except for hepatic TG after a week of irradiation. Jeong *et al.* (2003) reported that hesperetin exhibited strong cholesterol-lowering effects in high cholesterol-fed mice. Furthermore, hesperetin significantly lowered TG levels in normal lipidaemic rats and hyper lipidaemic rats (Monforte *et al.,* 1995).

In the current study, the evaluated hepatic enzyme activities showed significant lessening in the γ-irradiated group after 1 and 2 weeks of the experimental periods. The inhibition of glucose-6-dehydrogenase ($G_6$PDH) activity, which is the last enzymatic step in glycogenolysis may be the causes of an alteration of the glucose homeostasis status. Also, the increase in the activity of liver phosphoenol pyruvate carboxykinase activity following irradiation may account for the increase formation of glycogen from non-carbohydrate sources (Slater, 1987). Moreover, Jung *et al.* (2004) reported that hepatic glycogen reserves are important for whole-body glucose homeostasis in mice. Hesperetin intake ameliorated the reduction in the protected group and increased hepatic GK, G6P and PEPCK.

Future studies will have to address, in detail, by what mechanisms hesperetin exerts these effects.

***Conclusion***

The present study demonstrated that hesperetin has powerful protective effects on radiation-induced liver disorders and suggested that this radioprotection may be afforded by reducing the toxic effects of the oxidative products of irradiation. The dose protection factor at the low dosage of hesperetin used in this study compared with known radio protectors is very

promising and it might be useful as a potent radio protector. The mechanism by which hesperetin reduces destructive effects of radiation is not well understood. We propose that it might act by a radical scavenging mechanism via enzyme catalysis.

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## نشاط الهسبيريتين في تدعيم كبد الفأر الأبيض المعرض لأشعة جاما

**سامح سليمان توفيق**

قسم البحوث الصحية الإشعاعية - المركز القومي لبحوث وتكنولوجيا الإشعاع، ص ب: ٢٩ مدينة نصر، مصر.

الهيسبيريتين (٣`،٧،٥-تراي هيدروكسيل-٤`-ميسوكسيفلافونون) عبارة عن أجليكون جلوكوسيد فلاڤانون الهسبيريتين ، ويميزه خواص دوائية منها: مضاد للأكسدة والالتهابات ، مخفض للدهون و الكوليستيرول بالدم و يستخدم بكفاءة في أنظمة العلاج التكميلي في مرحلة النقاهة.

تم أعداد ٤ مجموعات من الفئران البيضاء: الأولي ضابطة ، والثانية معالجة بالهيسبيريتين (١٠٠ مجم/ كجم من وزن الفأر لمدة ٧ أيام متتالية) ، والثالثة عرضت أجسام الفئران لأشعة جاما-جرعة ٤جراي) ، والمجموعة الأخيرة تم علاجها بالهيسبيريتين لمدة أسبوع ، ثم عرضت لجرعة ٤جراي من أشعة جاما. و تم سحب العينات من الدم والكبد بعد نهاية التجربة بيوم واحد أو أسبوع أو أسبوعين.

أدي تعرض الفئران لأشعة جاما إلى زيادة إحصائية في مستوي السكر بالدم والجليكوجين بالكبد بعد يوم وأسبوع ، ونقص إحصائي قي مستوى كليهما بعد أسبوعين ، كما أدي إلى زيادة إحصائية في مستوي كلا من الكوليستيرول الكلي والتراي آثيل جليسيرول بالدم ، ونقص إحصائي في مساويهما بالكبد بعد أسبوع وأسبوعين. وكذلك أدي إلى نقص إحصائي في نشاط أنزيمات الجلوكوكيناز (GK) وجلوكوز-٦- فوسفاتاز (G6P) ، وفوسفوأينول بيروفات كربوكيناز بالكبد (PEPCK).

أدي تناول الفئران للهيسبيريتين قبل التعرض لأشعة جاما إلى تحسين مستوي الجلوكوز بالدم والجليكوجين بالكبد ، وضبط مستوي كل من الكوليستيرول الكلي والتراي آثيل جليسيرول بالدم والكبد ، وكذلك تخفيف النقص الحادث في نشاط الأنزيمات الثلاثة المقدرة بالكبد.

أظهرت النتائج الماثلة أن الهيسبيريتين عدل التغييرات الكيموحيوية الناتجة عن تأثيرات الإشعاع في الفئران البيضاء.

وقد خلص البحث إلى أن للهيسبيريتين دور إيجابي في التخفيف من الضغط الأكسوجيني الناجم عن التعرض لأشعة جاما وذلك بتنشيط آلية منع التأكسد الطبيعية وتدعيم كبد الفئران البيضاء عن طريق وقاية أنزيمات الكبد من التأكسد.