THE PROTECTIVE EFFECT OF ROYAL JELLY ON ROUNDUP-INDUCED IMMUNOTOXICITY IN ALBINO RATS

BY

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ABSTRACT

Roundup is a widely used herbicide because of its broad spectrum and high water solubility. It is a glyphosate-based organophosphate containing mixture of surfactants. Interference of such herbicide with immune system function can induce immune suppression and decrease of disease resistance. The objective of this study is to evaluate the effect of this herbicide on the rats immune system and to assess the potential role of Royal jelly as an immune protective in Roundup-exposed rats. Eighty male albino rats were randomly divided into four equal groups. Animals of groups I and II were given one daily dose of Roundup (1500 mg/kg BW) for four weeks. Royal jelly (300 mg/kg BW once daily) was added during the last seven days of Roundup administration in group II. Group III animals received royal jelly (300 mg/kg BW) once daily, for seven days. Animals of group IV served as a control group. All animals were given the daily doses by gastric gavage. At the end of the treatment period, all rats were subjected to biochemical analysis for serum IL-4 and INF-γ levels. The results of this study revealed significant reduction of serum IL-4 and INF-γ levels in Roundup-treated animals. Royal jelly administration during the last seven days of Roundup treatment has improved IL-4 levels, but this improvement wasn't statistically significant. However, it has significantly improved INF-γ levels compared to Roundup-treated animals. This study signifies the immune depressant effect of Roundup. Furthermore, it refers to the role of Royal jelly administration as a protective agent against such immune suppression.

Key words: *Roundup, Royal jelly, IL-4, INF-γ, Rat , Immune.*

INTRODUCTION

Pesticides are economically important chemicals, which are used in public health programs, agriculture and for non-agricultural purposes (Abdollahi et al., 2004). Although pesticides have reduced vector-born diseases and offered lower cost and better quality foodstuffs, yet they can persist in the agricultural products and in the environment, posing health hazards to humans and animals (Dallegrave et al., 2007).

Herbicides are distinctive group of pesticides and are considered as selective

weed killers. Roundup is a widely used herbicide because of its broad spectrum and high water solubility. It is an organophosphate, which contains glyphosate (n-phosphonomethylglycine) as the active ingredient and polyoxyethyleneamine (POEA) as the surfactant agent (Releya, 2005). It is used to control weeds in emerged grasses, pastures as well as rice, corn and soy plantations (Williams et al., 2000).

The proportion of glyphosate to surfactant in the Roundup formulation varies according to the country in which the product is marketed. In Egypt, Roundup is available as 48% (w/v) isopropylamine salt of n-phosphonomethylglycine and 52% (w/v) polyoxyethyleneamine (the surfactant) which is produced by Monsanto Company (El-Shenawy, 2009). Recently, the comparative effects of the Roundup and glyphosate on mitochondrial oxidative phosphorylation were studied, and it was reported that mitochondrial alterations caused by Roundup cannot be exclusively attributed to the active ingredient, but may as well be the result of other chemicals, e.g. POEA, or due to the possible synergy between glyphosate and roundup formulation products (Peixoto, 2005).

Many studies have shown that glyphosate has a low toxicity (Marc et al., 2002; Howe et al., 2004), however, an increased risk for non-Hodgkin's lymphoma following exposure to certain pesticides including Roundup has been reported by some authors (Hardell et al., 2002; De Roos et al., 2003). Virtually, every pesticide product contains ingredients other than those identified as the "active" ingredients, which are misleadingly called "inert". Commercial glyphosate formulations have been reported in both in vivo and in vitro studies to be more toxic than glyphosate, thus indicating a synergy between glyphosate and Roundup formulation products (Martinez and Brown, 1991; Marc et al., 2002).

The immune system is likely to be one of the most sensitive physiological systems to pollutants that can interact with immune system components and interfere with protection function inducing immune suppression and reducing disease resistance (Wong et al., 1992). Glyphosate has been reported to have biochemical and immunological effects on plants, fishes, amphibians, arthropods and snails (Mohamed, 2011). However, its immunotoxic effects on rats have never been studied.

Royal jelly (RJ) is a secretion of the hypopharyngeal and mandibular glands of worker honeybees, and it directs the development of honeybee larvae into queen bees. RJ is composed of proteins (12-15%), sugars (10-16%), lipids (3-6%), vitamins,

and free amino acids, and has been used for medical and nutritional purposes in folk medicine (Howe et al., 1985). Recently, five types of major royal jelly proteins (MRJPs; MRJP1-5) have been characterized by cDNA cloning and sequencing. The biological functions of some components of RJ have been described e.g. MRJP3 has been proved to show immunomodulatory effects in vivo (Okamoto et al., 2003).

Thus, because the use of commercial roundup has dramatically increased in recent years and many of the adverse effect are related to oxidative stress and a likely effect on the immune response, the present study was undertaken to evaluate the immunological responses of albino rats to the effect of sublethal concentration of roundup herbicide and to evaluate the potential protective effect of royal jelly.

MATERIAL AND METHODS

Animals and experimental design:

This study was carried out on 80 adult male albino rats. Their weight ranged between 150 - 200 grams. The animals were maintained on standard laboratory conditions, 10 rats per cage and were fed ad libitum with commercial diet. The animals were divided into the following groups:

1. G I (Roundup-intoxicated): It included 20 rats; they received oral Roundup (1500 mg/kg BW) once daily for 4 weeks (Williams et al., 2000).

2. G II (Roundup-intoxicated and royal jelly-treated): It included 20 rats; they received oral Roundup (1500 mg/kg BW) once daily for 4 weeks. Oral royal jelly (300 mg/kg BW) was added once daily during the last 7 days of treatment (Zamami et al., 2008).

3. G III (Royal jelly-treated): It included 20 rats; they received oral royal jelly (300 mg/kg BW) once daily for 7 days.

4. G IV (normal healthy control): It included 20 rates; they served as a control group.

Chemicals:

Roundup (Isopropylamine salt of glyphosate N- (phosphonomethyl) glycine 48%) was obtained from Agrochemical Company for Chemicals and Medical Trading. It is available as water based solution of the glyphosate salt. Roundup contains 480 g mono (isopropyleammonium) glyphosate/liter. Royal jelly was purchased from Pharma Cure Pharmaceutical Company in the form of Unovit syrup (each 5ml contained 300 mg of natural royal jelly preserved in pure bee's honey).

Methods:

At the end of the experimental period, animals were sacrificed by cervical dislo-

cation. Blood samples were obtained from the heart by needle puncture. The blood samples were kept in plain glass tubes in a water bath for 30 minutes at 37ºC till coagulation occurred, then the serum was separated from the blood clots by centrifugation (5000 rpm) and was stored in aliquots at -20 ºC for determination of serum interferon-γ (INF-γ) and Interleukin-4 (IL-4).

Commercial INF-γ and IL-4 ELISA kits (Mabtech AB, Sweden) were used for determination of serum INF-γ & IL-4 according to the manufacturer instructions.

Statistical analysis:

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows (SPSS Inc., Chicago, IL, USA, Version 16.0). The results were provided as mean ± standard deviation for each group. The difference between two means was statistically analyzed using the Students' t-test. For comparison between more than two means, the F value of analysis of variance (ANOVA) was calculated and Tukey's post-hoc test was performed to compare between each two means if F value was significant. Significance was adopted at $p < 0.05$.

RESULTS

Serum IL-4

The serum level of IL-4 showed non-significant (p=0.86) change in its mean value in the royal jelly-treated group (0.40±0.22) compared to the control group (0.39±0.25). On the other hand, Roundup-treated animals showed a significant (p=0.01) reduction in the mean value of serum IL-4 (0.27±0.14) compared to the control animals. Administration of royal jelly with Roundup resulted in a slight elevation in the mean value of serum IL-4 (0.33±0.16), however the difference was non significant (p=0.50) as compared to roundup-treated animals (Tables 1 & 2).

Serum INF-γ

The serum level of INF-γ showed non-significant (p=0.16) change in its mean value in royal jelly-treated group (45.02±7.11) compared to the control group (47.50±8.41). On the other hand, Roundup-treated group showed a significant (p=0.0001) reduction in the mean value of serum INF-γ (31.75±6.89) compared to the control group. Administration of royal jelly with Roundup resulted in significant (p=0.001) elevation in the mean value of serum INF-γ (38.62±6.02) compared to Roundup-treated animals (Tables 3 & 4).

DISCUSSION

The immune system is known to have a critical role in maintaining human and animal health. It is one of the most sensitive targets for environmental pollutants, since they can modulate several immunological mechanisms at various cellular and subcellular levels (Wong et al., 1992). The abil-

ity of pesticides to stimulate or suppress lymphocyte proliferation and to induce genotoxic activity and chromosomal aberrations in cultured lymphocytes were proposed as possible mechanisms explaining their adverse effects on the immune system. In addition, exposure to pesticides was found to alter the production of cytokines, which play a crucial role in activation, proliferation and differentiation of lymphocytes (Medjdoub et al., 2011).

Interleukin-4 is an immunoregulatory cytokine, produced by activated T cells, mast cells and basophils. It plays a central role in regulation of B-cell and T-cell mediated immune responses (Paul, 1991; Paul and Seder, 1994). In the current study, sublethal Roundup exposure was associated with significant serum IL-4 reduction. However, different studies on serum IL-4 levels in a range of pesticides exposure displayed conflicting results. Serum IL-4 has shown significant elevation after propanil and lindane exposure (Seth et al., 2005; Corsini et al., 2007). More recent studies reported unaltered IL-4 secretion in cultured lymphocytes in the presence of organophosphorus pesticide metabolite (Esquivel-Senties et al., 2010).

However, Medjdoub et al. (2011) recorded significant reduction in serum IL-4 levels on exposure to mancozeb and metribuzin. According to Schneider et al. (1995) reduction of serum IL-4 could be explained by suppression of NF-AT, the most critical transcription factor for IL-4 production. Consequently, Roundup might have an inhibitory effect on T-cell specific transcription factor NF-AT resulting in T-cell dysfunction, which leads to a diminution in IL-4 gene transcription with subsequent serum IL-4 reduction. Moreover, Roundup exposure possesses potent oxidative effect with liberation of reactive oxygen species as reported by Amimoto et al. (1995) and Abdel-Wahhab and Aly (2003). Several studies have provided evidences for reactive oxygen species and oxidative stress involvement in pesticide-induced immunotoxicity (Li and Kawada 2006; Saulsbury et al., 2008). This could be attributed to the induction of pesticides-mediated peroxisomal oxidation with subsequent elevation of intracellular hydrogen peroxide radicals and other reactive oxygen species (ROS), which could result in alteration in cell signaling pathways involved in cell growth and cell death (Gonllez et al., 2005; Antherieu et al., 2007).

The serum level of INF-γ showed significant reduction in Roundup-treated group. Likewise, Seth et al. (2005), Corsini et al. (2007) and Esquivel-Senties et al. (2010) have reported a decrease in INF-γ level after exposure to different pesticides. Such reduction may be attributed to decreased INF-γ synthesis. It is well known that

increased intracellular cyclic adenosine monophosphate (cAMP) concentrations will lead to suppression of INF-γ production. It has been shown that cAMP reverses mitogen- or antigen-induced T cell proliferation, with corresponding reduction in cytokine synthesis (Mary et al., 1987; Snijdewint et al., 1993).

It was also reported that ROS play a pivotal role in the regulation of T-cell activation, energy and apoptosis. T-cell activation induces low but significant level of ROS that is crucial for T-cell proliferation, whereas high levels of ROS induce apoptosis (Tripathi and Hildeman, 2004; Williams and Kwon, 2004). Thus, fine-tuning of the redox status is critical to T-cell reactivity. Suppression of INF-γ production induced by hydrogen peroxide radical was observed at concentrations less than that required to induce cell death. Hence, Roundup-induced suppression of INF-γ might be due to elevation of cellular hydrogen peroxide levels (Malmberg et al., 2001).

It is well known that T-helper 1 cells are responsible mainly for phagocyte-mediated host defense. These cells are the principal effectors of cell-mediated immunity, delayed-type hypersensitivity reactions and chronic inflammation via IL-2, INF-γ, the T-helper 1 cytokines. Therefore, significant reduction in INF-γ levels could enhance infection risk in pesticide-exposed individuals. T-helper 2 lymphocytes are responsible for the immune defense not mediated by phagocytes, the recruitment of eosinophils and allergic reactions promoting humoral immunity via the T-helper 2 cytokine (IL-4) (Medjdoub et al., 2011). Therefore, in light of the central role of both IL-4 and INF-γ in immune response regulation, chronic Roundup exposure may have important implications in different clinical settings, for example, autoimmunity, tolerance induction and infectious diseases.

Based on the role of ROS and the involvement of oxidative stress in pesticide-mediated immunotoxicity, Royal jelly (RJ) was selected as a protective agent against Roundup-induced immunomodulation. Royal jelly was shown to exhibit antioxidant effect in addition to anti-inflammatory and immunomodulatory effects (Cemek et al., 2010). Administration of RJ with Roundup resulted in slight elevation in serum IL-4, however the difference was non significant as compared to Roundup-treated animals. At the same time, RJ administration induced significant elevation in serum INF-γ as compared to Roundup-treated animals. This immunological improvement may be attributed to the anti-oxidative activities of RJ proteins (Guo et al., 2009). Moreover, RJ-induced protection against immunosuppression has been demonstrated in the literature by several in vivo and in vitro

studies (Kohno et al., 2004; Oka et al., 2001).

In conclusion, the results of the current study indicate that Roundup sublethal exposure has an immunosuppressive effect on rats. Besides, the potential protective effect of RJ against Roundup-induced immune suppression was observed. Because Roundup and other agrichemicals are ubiquitously used in modern crop production, all humans on the vicinity of agricultural areas should be protected and periodically monitored.

Table (1): Comparison between the mean values of serum IL-4 in the studied groups in relation to the control group.

Group	*t*-test		
	Mean ± SD	***t***	***p***
Group I (Roundup)	0.27±0.14	-2.55	0.01*
Group II (Roundup& Royal jelly)	0.33±0.16	-1.19	0.23
Group III (Royal jelly)	0.40±0.22	0.17	0.86
Group IV (Control)	0.39±0.25	--	

**Significant (P-value < 0.05)*.

Table (2): Comparison of mean values of serum IL-4 of treated rats, within the studied groups.

Group	ANOVA	
	Mean ± SD	***p***
Group I (Roundup)	0.27±0.14	0.02*
Group II (Roundup & Royal jelly)	0.33±0.16	
Group III (Royal jelly)	0.40±0.22	
Group IV (Control)	0.39±0.25	
Tukey's test		
Groups		***p***
Group I (Roundup) & Group II (Roundup & Royal jelly)		0.50
Group I (Roundup) & Group III (Royal jelly)		0.02*
Group II (Roundup & Royal jelly) & Group III (Royal jelly)		0.46

**Significant (P-value < 0.05)*

Table (3): Comparison of mean values of serum INF-γ between the studied groups.

Group	*t*-test		
	Mean ± SD	***t***	***p***
Group I (Roundup)	31.75±6.89	-8.54	0.0001*
Group II (Roundup & Royal jelly)	38.62±6.02	-5.24	0.0001*
Group III (Royal jelly)	45.02±7.11	-1.39	0.16
Group IV (Control)	47.50±8.41	--	

**Significant compared to the control group (P-value < 0.05)*

Table (4): Within groups comparison of mean values of serum INF-γ of treated rats.

Group	ANOVA	
	Mean ± SD	***p***
Group I (Roundup)	31.75±6.89	0.0001*
Group II (Roundup& Royal jelly)	38.62±6.02	
Group III (Royal jelly)	45.02±7.11	
Group IV (Control)	47.50±8.41	
Tukey's test		
Groups		***p***
Group I (Roundup) & Group II (Roundup & Royal jelly)		0.001*
Group I (Roundup) & Group III (Royal jelly)		0.0001*
Group II (Roundup & Royal jelly) & Group III (Royal jelly)		0.001*

**Significant (P-value < 0.05)*

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التأثير الوقائى لغذاء ملكات النحل على التسمم المناعى الناجم عن التعرض للراوند آب فى الجرذان البيضاء

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الراوندآب هو أحد المبيدات المستخدمة على نطاق واسع بسبب أتساع الطيف الميكروبى الخاص به و قدرته العاليه على الذوبان في الماء. وهو نوع من الفوسفات العضوي القائم على الغليفوسات و الذي يحتوي على خليط من المذيبات. و تداخل هذه النوعيه من المبيدات مع وظيفة جهاز المناعة من الممكن أن يسبب ضعف المناعة وانخفاض المقاومة للأمراض. و لقد كان الهدف من هذه الدراسه هو تقييم تأثير هذا المبيد على جهاز المناعة فى الجرذان البيضاء و كذلك تقييم الدور الذى يمكن أن يقوم به غذاء ملكات النحل (الهلام الملكى) فى وقاية جهاز المناعة في الجرذان التي تعرضت له.

وقد أجريت هذه الدراسة على ثمانين من ذكور الجرذان البيضاء التي قسمت عشوائيا إلى أربع مجموعات متساوية (٢٠ جرذا لكل مجموعة). أعطيت الحيوانات من المجموعة الأولى والثانية جرعة يومية من الراوندآب (١٥٠٠ مغ/كغ) لمدة أربعة أسابيع. أضيف الهلام الملكي بجرعة تبلغ (٣٠٠ مغ/كغ) يوميا خلال الأيام السبعة الأخيرة فى جرذان المجموعه الثانية. و أعطيت الحيوانات من المجموعة الثالثة الهلام الملكي بجرعة تبلغ (٣٠٠ مغ/كغ) يوميا لمدة سبعة أيام. بينما استخدمت الحيوانات من المجموعة الرابعة كمجموعة ضابطة. تم اعطاء الجرعات المقررة لجميع الجرذان بالتزقيم المعدى. و في نهاية فترة التجربة تم إجراء تحليل لمستويات الأنترليوكين ٤- و الأنترفيرون-جاما في مصل الدم لجميع الجرذان.

و قد أسفرت نتائج هذه الدراسة عن انخفاض إحصائى ملحوظ في مستويات الأنترليوكين ٤- و الأنترفيرون-جاما في مصل الدم للجرذان المعالجة بالراوندآب. وقد أظهر العلاج بالهلام الملكي القدره على تحسين مستويات الأنترليوكين ٤- و الأنترفيرون-جاما فى مصل الدم للجرذان المعالجة بالراوندآب مع الهلام الملكى لمدة سبعة أيام، ولكن هذا التحسن لم يكن ذو دلاله إحصائية فى مستوى الأنترليوكين ٤- بينما كان التحسن الأحصائى ملحوظا فى مستوى الأنترفيرون-جاما. و تبين هذه الدراسة تأثير الراوندآب الذى يؤدى إلى إنخفاض قدرة الجهاز المناعى. كما أنها تشير إلى دور غذاء ملكات النحل كعامل وقائي ضد الإحباط المناعي الناجم عن التعرض لهذا المبيد.