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The Genetic Effect of the Combined Action of Vincristine and Fennel Plant Extract on the Germ Cells of *Drosophilla melanogaster*

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Abstract. This study was designed to investigate the mutagenic potentiality of the anticancer drug vincristine and fennel plant extract on *Drosophilla melanogaster* using two test systems, the sex linked recessive lethal (SLRL) and estimating the activity of cholinesterase enzyme (ChE) in F1 and F2 bar eye females and F2 wild types males. A wild type Strain Oregon-R (or-R) male flies of *D. melanogaster* were treated on a medium containing a concentration of one of individually of the two agents, followed by combined treatment in an alternative way of fennel extract followed by vincristin, then vincristin followed by fennel extract and finally the two agents together. The results showed no significant increase in the percentage of the S.L.R.L in all stages of spermatogenesis in all treatments. Meanwhile, vincristine and fennel plant extract showed a genotoxic effects in the three categories of the two generations of S.L.R.L, F1 females heterozygous F2 bar eye females and F2 wild type males on the genetic background of ChE in all treatments.

Introduction

In the past, most of the studies on the genetic effects of anticancer drugs have concentrated on cytogenetic damage[1]. However, it is obviously important to learn more about the different types of mutagenic lesions induced by anticancer drugs. Marselos and Vainio[2] reported that most of the cancer chemotherapeutic agents are mutagenic and carcinogenic. Vincristine (VCR) a widely used anticancer drug in Saudi Arabia contains the active substance vincristine sulphate.

Vincristine sulphate is a dimeric alkaloid found in the leaves of the plant *Catharanthus roseus*[3]. The natural vinca alkaloids and their synthetic derivatives are used as antineoplastices. These agents act by reacting with tubulin,

altering the microtubule organization and dynamics disturbing the mitotic spindle and subsequently causing cell aneuploidy[4,5]. The genotoxicity of VCR has been tested several times in vitro systems and in vivo in lower organism. Various aspects of its effects have been reviewed on several occasions[6,7]. The available information on its genotoxicity is found to be contradictory to each other. Moreover in most of the earlier studies, either the doses tested were unusually high or the data generated were after chronic exposures to the chemical. Furthermore, Gonzalez-Cid *et al.*[8], found that VCR and vinorelbine (VRB) induced a significant increase in micronuclei (MN) frequencies in binucleated (BN) cells, and produced a slowing of the cell cycle, causing a decrease in the percentage of BN cells in cultured human lymphocytes. Also, Tiburi *et al.*[9], reported that vincristine (VCR), vinblastine (VBL) and vinorelbine (VNR) induced genetic toxicity causing increments in the incidence of mutational events, as well as in somatic recombination in *Drosophila melanogaster.*

Now, the world is directed to depend on nature to decreasing from the side effects of the drugs. Herbal medicine is the oldest form of healthcare known to mankind. Herbs had be used by all cultures throughout history. It was an integral part of the development of modern civilization, the plant kingdom has provided an endless source of medicinal plants first used in their crude form as herbal teas, syrups, infusions, ointments, liniments, and powders. With the development of chemistry and western medicine, the active substances of many species have been isolated and in some cases, duplicated in the form of synthetic drugs, thus, herbs have been used for their therapeutic or medicinal value. Herbs are plants or plant part valued for their medicinal, aromatic or savory qualities. Herb plants produce and contain a variety of chemical substances that act upon the body. Therefore, discovery and exploration of compounds possessing antimutagenic and anticarcinogenic properties are of great importance. Many substances with antimutagenic activity have been found by several investigators[10-17]. The present study was designed to detect the mutagenic effects of vincristine (VCR) anticancer drug and antimutagenic effects of fennel plant extract in *Drosophila melanogaster* using two test systems, the sex liked recessive lethal mutations test (SLRL) and the estimation of the activity of Cholinesterase enzyme (ChE).

Materials and Methods

1. Strains

Two strains of *D. melanogaster* were used in the present study:

a – Muller-5 (M-5)

A marker strain of *D. melanogaster* used for the detection of Sex Linked Recessive Lethal mutations. Its X-chromosome carries a dominant marker bar

eye (B) and a recessive mutant eye color, white apricot (W^a). It has also two inversions, the first is scute (Sc^{8r}) inversion and the second designated (in-s), is included in the first inversion.

b – Oregon-R (O-R)

This stock is a wild type strain that has always been used in *Drosophila* laboratories. It was obtained from the department of Genetics, Ain Shams University, Cairo, A.R.E. This strain was repeatedly tested to determine its spontaneous Sex-linked recessive lethal (S.L.R.L).

2. Chemicals

a – Vincristine sulfate (Oncnvin)

Tablets produced by Faulding Pharmaceuticals Plc / Warwickshire CV31 3RW, United Kingdom.

It is a dimeric alkaloid found in the leaves of the plant *Vinva rosea* and widely used as anticancer drug because VCR has spindle poisoning properties and also exerts lethal effects on cells during division.

(Foeniculum vulgare Mill)

b – Fennel

The essential oil of the most important fennel variety (var. dulce) contains anethole (50 to 80%), limonene (5%), fenchone (5%), estragole (methyl-chavicol), safrole, ?-pinene (0.5%), camphene, ?-pinene, ?-myrcene and p-cymene. In contrast, the uncultivated form (var. vulgare) contains often more essential oil, but since it is characterized by the bitter fenchone (12 to 22%), it is of little value.

c – Kit for Cholinesterase

This kit was obtained from QUIMICA CLINICA APLICADA for the estimation of the activities of the enzyme Cholinesterase (CHE).

3. Methods

Two test systems were employed in this study:

a – Mullar[18] and Brusick[19] for *Drosophila* Sex-linked recessive lethal (SLRL) assay.

b – The estimation of the activity of the enzyme Cholinesterase (ChE) in *Drosophila.*

In this investigation, Oregon-R of *D. melanogaster* males were treated as follows:

a. Single treatment of VCR with one concentration 2ml/100ml of medium.

b. Single treatment of fennel with one concentration 2ml/100ml of medium.

c. Combined treatments with VCR and fennel extract by the arrangement of vincristin then fennel extract, fennel extract followed by vincristin and finally the two agents together.

SLRL have been estimated and three categories were analyzed for enzyme activity, F1 and F2 females heterozygous and wild type males.

Cholinesterase estimated by using spectrophotometric analysis.

Sample prepared by homogenizing the whole body of 100 adults in 1.0 ml of refrigerated phosphate buffer (pH 7.2) with glass homogenizer, after that centrifugated at 8.000 rpm for about 1 minute at 4ºC and the particulated material was discarded, and then 40 µl of the supernant was transferred in test tube. The kit of ChE was added and the mixture was shaken vigorously to avoid bubble formation during the measurement of transmission. The transmission was then measured at 405 mu using spectronic spectrophotometer model.

4. Statistical Analysis

1 – Kasten Baum and Bowman test was used to test significance of sex-linked recessive lethal results[20].

2 – ANOVA test (SPSS programe) was applied for significancy of enzyme estimation.

Results and Discussion

1. Induction of Sex-Linked Recessive Lethal

a – The results obtained from the SLRL test after treatment with the one concentration of VCR (2ml/100ml of medium) are summarized in Table 1 and presented graphically in Fig. 1. Among 1079 tested chromosomes, four lethal was detected at the first brood (0.37%) while among 847 tested chromosomes, one lethal was detected at the second brood (0.11%), but 0.10% (one among 941 chromosomes tested) of induced SLRL mutations were detected at the third brood, and percent-

age of 0.10% (one lethal among 926 tested chromosomes), at the fourth brood, was obtained. These frequencies for all broods were not significantly different from the control frequencies. Thus, it would be considered as conclusive results. This is in agreement with the results obtained by Tood *et al.*[21], who found that the VCR produces many chromosomal effects, but mainly, not mutagenic. Also, Clements *et al.*[1], found that vincristine did not give positive results in the white-ivory somatic mutation test in *Drosophila.* However, positive results have been observed for vincristine in somatic mutation and recombination test (SMART) of *Drosophila melanogaster*[9]. Similarly, treated males with the extract of fennel plant (2ml/100ml medium) as a single treatment induced lethal mutation with a frequency of about 0.0% in the first brood, and in the second brood about 0.12%, and about 0.40% in the third brood, with no lethality at the fourth brood. These frequencies for all broods were not significantly different from the control frequencies, this indicates that the extract of fennel plant has no mutagenic effect on *D. melanogaster*, this is in agreement with the results obtained by Zheng *et al.*[22], who isolated five natural compound products from Umbelliferae, these compounds induced the detoxifying enzyme glutathione S-transferase (GST) in several mouse target tissues, and the tumor was reduced from 68 to 11%. Also, the antioxidant activity of the fennel oils was evaluated as well as antimicrobial activity[23]. However, these results disagree with the results obtained by Sanchez-Lamar *et al.*[24], who found that *Phyllantus orbicularis* plant extract induced micro nuclei and abnormal anaphase in Chinese hamster ovarian (CHO) cells (Fig. 1).

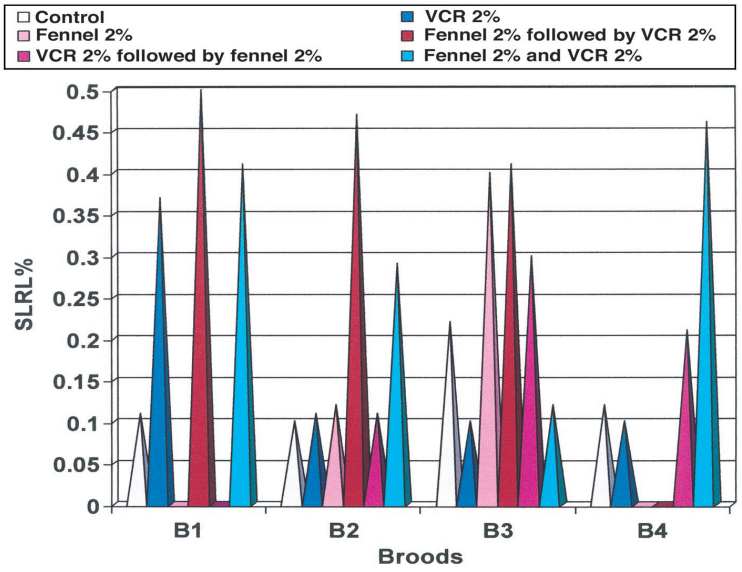

Fig. 1. Sex-linked recessive lethals in four broods of *Drosophila melanogaster* occurring spontaneously and after treatments of vincrestine and fennel plant extract.

b – The combined treatment with the same concentration with extract of fennel plant followed by vincrestine, induced lethal mutation with a frequency of about 0.50% in the first brood, and in the second brood about 0.47%, and about 0.41% in the third brood, with no lethality at the fourth brood. This frequencies for all broods were not significantly different from the control frequencies. The results indicate that the extract of fennel plant followed by VCR has no mutagenic effect on *D. melanogaster*. Although the protective effects of coffee against somatic mutation and mitotic recombination induced by cyclophosphamide (CPH), mitomycin C (MMC) and urethane (URE) were evaluated in the wing spot test in *Drosophila melanogaster*, coffee showed significant dose-related inhibitory effects on the genotoxicity of MMC. The same protective effect was also observed with one concentration of coffee in combination with CPH[25].

On the other hand, the combined treatment with vincrestine followed by extract of fennel plant, induced lethal mutation with a frequency of about 0.0% in the first brood, and in the second brood about 0.11%, and about 0.30% in the third brood, and about 0.21% lethality in the fourth brood, but these frequencies for all broods were not significantly different from the control frequencies. This indicates that the treatment of vincrestine followed by extract of fennel plant has no mutagenic effect on *D. melanogaster*.

Moreover, the combined treatment with vincrestine and extract of fennel plant together, induced lethal mutation with a frequency of about 0.41% in the first brood, and in the second brood about 0.29%, and about 0.12% in the third brood, and about 0.46% lethality in the fourth brood, but these frequencies for all broods were not significantly different from the control frequencies.

The data obtained in these study showed that the single and combined treatments using sex-linked recessive lethal mutations are inactive, producing a statistically insignificant increase in the frequency of total SLRL (Table 1).

Vincristine has been reported to be cytotoxic, namely as far as accumulation of mitotic figures, arrest of cells at metaphases with highly contracted chromosomes but failing of chromatid separation C-mitotic effects, inhibition of tubulin polymerization, disruption in the formation of microtubules and movements of chromosome[6,7&26]. Thus simultaneous measurement of genotoxicity and cytotoxicity at different doses and exposure times may be an important consideration in the evaluation of genotoxicants. Also, the small numbers of biochemical and genetic investigations do not permit establishment of an exact mechanism of herbal therapies and antimutagenic action.

Further experiments are required to determine whether these substances are scavengers of genotoxic species or if their antimutagenic potential is demonstrated in more complicated ways[17, 27].

Table 1. Identification of sex-linked recessive lethals occurring spontaneously and after different treatments with vincrestine and fennel plant extract in *D. melanogaster.*

Treatments	Sperms B1			Spermatides B2			Spermatocytes B3			Spermatogonia B4			Total		
	N.	L.	%	N.	L.	%	N.	L.	%	N.	L.	%	N.	L.	%
Control	906	1	0.11	913	1	0.10	88	2	0.22	815	1	0.12	3540	5	0.14
VCR 2%	1079	4	0.37	847	1	0.11	941	1	0.10	926	1	0.10	3793	7	0.18
Fennel plant extract 2%	784	0	0.0	792	1	0.12	744	3	0.40	912	0	0.0	3232	4	0.12
Fennel 2% followed by VCR 2%	983	5	0.50	839	4	0.47	964	4	0.41	975	0	0.0	3761	13	0.34
VCR 2% followed by Fennel 2%	852	0.	0.0	847	1	0.11	986	3	0.30	915	2	0.21	3600	6	0.16
VCR 2% and Fennel 2% together	955	4	0.41	1018	3	0.29	820	1	0.12	1074	5	0.46	3867	13	0.33

N. = Number of tested chromosomes, L. = Number of lethal mutations (SLRL), % = Frequency of SLRL.

2. Estimation Activity of ChE Enzyme

The second part of this investigation was carried out to estimate the activities of the enzymes ChE in some insects of two generations of SLRL:

F1 females, F2 bar eye females and F2 wild type male. Table 2 shows that VCR caused change in ChE activities due to its mutagenic potentiality. The mean values of ChE activities in females F1 were for the control of 22846 units, and females F2 36969.5 units, and in males F2 42613.2 units.

While in the treated experiments with VCR they dropped to 18314 units for females F1 and 21659.2 units for females F2, and 32331.2 units for males F2, statistical analysis indicated that the difference of F1 females, F2 females and F2 males with the control were significant. This result is in agreement with Kozik & Szczech[28], who observed that administration of therapeutic doses of vincristine to young rats brings about a drop of the neuronal AChE activity.

Meanwhile, the single treatment with fennel plant extract induced significant difference from the control for both generations in all broods except the female of the first generation of spermatid brood. The activity of enzyme in females F1

were 38515.7 units, in female F2 were 38651.5 units, and males F2 were 21014.5 units (Fig. 2).

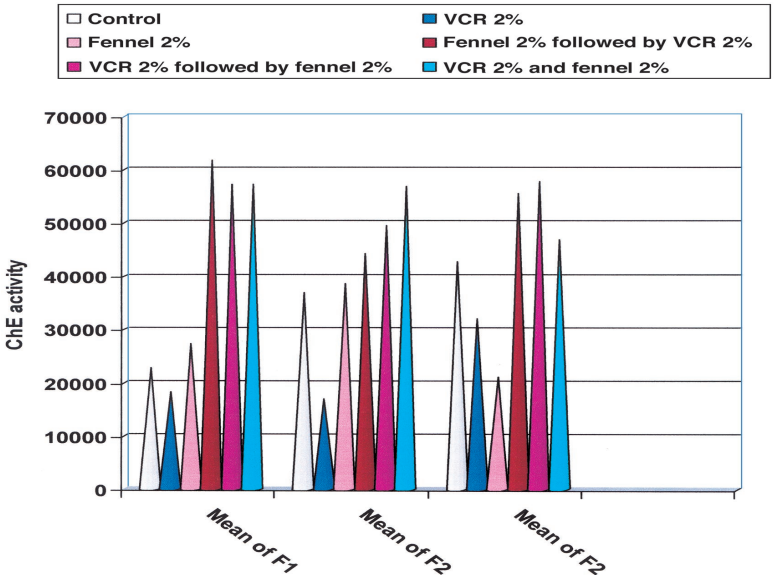

Fig. 2. Effect of vincrestine and fennel plant extract with different treatments on cholinesterase ChE activity in three categories of *D. melanogaster.*

The result shows a significant increase in enzyme activity, which is in accordance with the finding of Atta-ur-Rahman *et al.*[29], who mentioned that five steroidal alkaloids isolated from etheethanolic extract of *Savcococca saligna*, all compounds were found to possess cholinesterase inhibitory potential. Also, Orhan *et al.*[30], found that, the fumaria extracts displayed high potentinhibition against both of the activities of AChE (Acetylcholinesterase) enzymes.

The combined treatment with fennel plant extract followed by vincrestine also showed a significant increase in enzyme activity for both generations in all broods, in females F1 were 61645 units, and females F2, 44300 units, and in males F2, 55459.5 units (Table 2).

The combined treatment with vincrestine followed by fennel plant showed a significant increase in enzyme activity for both generations in all broods, in females F1 were 57184.7 units, and females F2, 49543.5 units, and in males F2, 57822.7 units.

The combined treatment with vincrestine and extract of fennel plant together showed a significant increase in enzyme activity for both generations in all broods, in females F1 were 57118 units, and females F2, 56761.2 units, and in males F2, 46798.5 units.

Table 2. Effect of vincrestine and fennel plant extract with different treatments on cholinesterase (ChE) activity in the three categories of *D. melanogaster.*

Category		ChE activity (units)*					
		Control	**VCR**	**Fennel**	**Fennel then VCR**	**VCR then fennel**	**VCR and fennel**
F1 ♀	B1	22827	14332**	68067**	49419**	27148**	40551**
	B2	24637	16518**	21338	90171**	65967**	46229**
	B3	13767	13756**	52262**	60206**	66868**	79104**
	B4	30153	28650**	12390**	46784**	68756**	62588**
	Mean	22846	18314	38515.7	61645	57184.7	57118
F2 ♀	B1	37616	19866**	51536**	38774**	47288**	47311**
	B2	26000	21002**	18889**	33430**	77540**	76087**
	B3	52753	19023**	35334**	16048**	18342**	16874**
	B4	31509	26746**	48847**	88948**	55004**	86773**
	Mean	36969.5	21659.2	38651.5	44300	49543.5	56761.2
F2 ♂	B1	53054	31311**	25873**	45176**	72481**	48606**
	B2	50227	43459**	16946**	76124**	42499**	40377**
	B3	32363	21645**	27702**	50637**	50499**	55493**
	B4	34809	32910**	13537**	49901**	65812**	42718**
	Mean	42613.2	32331.2	21014.5	55449.5	57822.7	46798.5

*One unit of ChE activity is expressed as one Ug of acetylcholine (substrat) reacting with ChE in on ml of 100 flies homogenate in one hour incubation at 37ºC.
*P0.05 **P0.01

In conclusion, vincrestine drug failed to increase the percentage of SLRL mutations and gave a non-conclusive result. In contrast, it did record a significant difference when estimating the enzymatic activity of ChE which proves its ability to cause mutations. The treatment with extract of fennel plant didn't cause any significant increase in the SLRL mutations, but gave a high significant difference when estimating the enzymatic activity of ChE, which brings to attentions the necessity of codification of its use because it might have dangerous effects on humans when using it in high doses, but we can't judge its mutagenic effect before using higher sensitive tests more than those used in this experiment.

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التأثير الطفري للمعاملة المفردة والمشتركة لمستخلص نبات الشمر وعقارالفينكريستين في حشرة *الدروسوفيلا ميلانوجاستر*

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المستخلص. يهدف هذا البحث إلى دراسة التأثير الطفرى للمعاملة المفردة والمشتركة لمستخلص نبات الشمر وعقارالفينكريستين، وذلك باستخدام سلالات ذبابة الخل دروسوفيلا ميلانوجاستر *Drosophila melanogaster* باستخدام اختبارين ، اختبار الطفرات المميتة المتنحية المرتبطة بالجنس (SLRL)، و تقـــدير النشـــاط الإنزيمي لإنزيم الكولين استيريز (ChE) لإناث الجيل الأول الخليطة (F1)، وإناث الجيل الثاني ذات العيون الحمراء العودية (F2)، وذكور الطراز البري للجيل الثاني بهدف مقارنة حساسية كلا الاختبارين .

عوملت ذكور الدروسوفيلا البرية من سلالة (Or-R) بمعاملة مفردة من نبات الشمر وعقارالفينكريستين، وكذلك عوملت بثلاث معاملات مشتركة اشتملت الواحدة منها على خليط من كل من مستخلص الشمر أولاً ، ثم عقارالفينكريستين ، والمعاملة الثانية عقارالفينكريستين ، ثم مستخلص الشمر ، والمعاملة الثالثة الاثنان معًا، ثم تم تقدير الطفرات المميتة المتنحية المرتبطة بالجنس ، كما تم تقدير النشاط الإنزيمي لإنزيم الكولين استيريز. ولم تظهر المعاملات المفردة والمشتركة لكل من نبات الشمر وعقار الفينكريستين أي تأثير معنوي في نسبة طفرات (SLRL).

أظهرت نتائج تقدير النشاط الإنزيمي للكولين استيريز (ChE) أن المعاملة المفردة لكل من مستخلص نبات الشمر وعقارالفينكريستين أدت إلى اختلاف معنوي عال في النشاط الإنزيمي ، يتراوح ما بين الارتفاع والانخفاض لكلا الجيلين في جميع الفترات التزاوجية، باستثناء الفترة التزاوجية الثانية الممثلة لمرحلة الطلائع المنوية لإناث الجيل الأول المعاملة بمستخلص الشمر، لم تكن الاختلافات معنوّية كما ظهرت فروق معنوّية عالية عند المعاملة المشتركة لجميع الفترات التزاوجية لكلا الجيلين ذكوراً وإناثًا.