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Evaluation of Effect and Modulatory Action of Black Pepper *(Piper nigrum)* and Praziquantel, Schistosomicidal Drug, On Selected Hepatic Aspects

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The research work was conducted to investigate the effect of intragastric administrations (five days a week) of praziquantel in a dose of 142mg kg^{-1} body weight (bw) for 85 days and black pepper in doses of 160 and 320 mg kg^{-1} bw for 36, 71, and 99 days on liver contents of DNA, total proteins, number and size of the liver cells and histopathological changes in the liver tissues of male and female albino rats. Non-significant changes were revealed that regarding the effect of both praziquantel, on DNA and cell numbers, and black pepper, on all the studied parameters, in male and female groups. Significant increase in liver total proteins and cell size was observed after praziquantel treatments. Modulating potential effect of black pepper, in a dose of 160mg kg^{-1} bw, on the changed hepatic aspects induced by praziquantel was proved. Hepatic histopathological studies also showed lower percentage of animals manifesting moderate pathological changes in the group of animals treated with black pepper 160 mg kg^{-1} bw followed by praziquantel 142mg kg^{-1} bw when compared to the praziquantel group. The higher dose of black pepper showed the moderate and marked hydropic degeneration and portal tract inflammation throughout the used intervals in both male and female groups. The tested doses of praziquantel and black pepper throughout the used intervals could not cause malignant transformation, necrosis, or fatty degeneration.

Key words: Praziquantel, blackpepper, liver, albino rats

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Introduction

Praziqantel is a drug of choice in treatment of both types of schistosome infections. Schistosomiasis is an endemic disease in Egypt. The prevalence of schistosoma mansoni in rural population of five governorates in Lower Egypt ranged from 17.5 to 42.9% and in Upper Egypt reached 4.3% in Fayoum, whereas the prevalence of schistosoma haematobium in four governorates in Upper Egypt ranged from 4.8 to 13.7% (El-Khoby *et al.*, 2000). Praziquantel is rapidly absorbed after oral administration and is extensively metabolized in the liver (Diekmann and Buhring, 1976). Although praziquantel seems to be almost the ideal schistosomocidal drug, however at the cytogenetic level, many authors claim that praziquantel has induced genotoxic damage, mutagenic, or coclastogenic effects *in vivo* and *in vitro* (Billings and Heidelberger, 1982; Anwar *et al.*, 1989; Montero *et al.*, 1994; Herrera *et al.*, 1994 and Hanna *et al.* 1996 a and b).

Pipper nigrum, a kind of spices with a common name of black pepper, is widely used in Egyptian diet for the source of flavor. This product is commonly used in the manufacture of variety of commercially prepared food such as meats, soups, pickles, condiments and others. An estimate of average human intake of black pepper is about 2 mg kg^{-1} per day (Concon *et al.*, 1979). Extracts of black pepper have induced genotoxic damage *in vitro* (Madrigal-Bujaidar *et al.*, 1997). Safrol, tannins, terpenes, and alkaloid are of the constituents of black pepper and known to be carcinogenic or procarcinogenic (Concon *et al.*, 1979 and Roe and Field, 1965).

The aim of this investigation was to study the effect of long term treatments with praziquantel and black pepper, the interaction between them on the hepatic transformation system in albino rats.

Materials and Methods

147 clinically healthy adult albino rats *Rattus ratus CH3* (84 males and 63 females, about 120gm at the start of experiments) were housed in plastic cages with wire top side and provided water and food ad libitum.

Praziquantel (Alexandria Co., under the licence of Bayer) was suspended in water, using an electromagnetic stirrer, and expressed in mg kg^{-1}bw. The LD_{50} of praziquantel for rats is 1420mg kg^{-1} (bw) (Frohberg, 1984).

Black pepper, the dry mature berries without evidence of mold or insect infestations were grounded to fine powder and suspended in water overnight, using an electromagnetic stirrer and expressed in mg kg^{-1} bw.

Two experiments were carried out in parallel:

The first experiment: Twenty one male albino rats were divided into three groups:

1. Seven rats were served as control group.
2. Seven animals were administered a daily oral dose of praziquantel (142mg kg^{-1} bw, 1/10 LD_{50}) for 5 successive days /week up to 12 weeks.
3. Seven rats were given a daily oral doses of black pepper (160mg kg^{-1} bw) followed by praziquantel (142mg kg^{-1} bw) for 5 successive days/week up to 12 weeks.

Animals were sacrificed 85 days later, after 18 hours fasting.

The second experiment: Sixty three male and 63 female albino rats were divided as follows:

1. Twenty one males and twenty one females were served as control, seven for each interval.
2. Twenty one males and twenty one females were administered a daily oral dose of 160mg kg^{-1} bw black pepper for 5 successive days a week up to 5, 10 , and 14 weeks
3. Twenty one animals of each sex were given a daily oral dose of 320mg kg^{-1} bw black pepper for 5 successive days /week up to 5, 10, and 14 weeks.

Sacrifices were made after 36, 71, and 99 days, using 7 rats at each interval. Animals were fasted 18 hours before decapitation. Animals of the two experiments were weight daily to adjust the dose given and dosing was attempted using gastric intubation. Livers were removed for the biochemical analysis and for histopathological investigations.

Biochemical analysis: Determination of liver deoxyribonucleic acid (DNA) was done as described by Burton (1956), liver total proteins according to Armstrong and Carr (1964), cell size by Robinson (1971) and the estimated cell number from the equation: Number of nuclei (million), total DNA(mg) x 10^9/9.47, where DNA is almost exclusively located within the nucleus of the cell with constant amount per diploid nucleus of 9.47mg x 10^{-9}/nucleus of rat liver (Osman, 1978).

Tissue processing: The liver were fixed in 10% natural formalin for 24 hours. Processing into paraffin was performed by the standard histopathological laboratory method. Sections were prepared from the paraffin blocks. The histologic sections were cut at 5μ thickness. From each block 5 sections were prepared. he histologic sections were stained by Haematoxylon and Eosin (Cook, 1974) examined under the light microscope (Will/Leitz microscope).

Statistical analysis was performed according to Bahn (1972).

Results

The data are tabulated as mean values ± standard deviations ($\bar{x} \pm SD$) or ± standard error of the means (± SEM) and percentage difference from the corresponding control. The levels of significant differences were tested using either one-way or two-way analysis of variances. Histopathological changes are tabulated as percentage of animals who developed portal tract inflammation and hydropic degeneration throughout the three intervals used.

Treatments with praziquantel, in a dose of 142 mg kg^{-1} bw for 85 days, slightly reduced the levels of DNA in the livers of male rat group to -15% when compared to the normal control group. Treatments with black pepper in a dose of 160mg kg^{-1} bw followed by praziquantel 142 mg kg^{-1}bw corrected this decrease to almost the normal value of -0.36% (Table 1). This also reveals non-significant difference between the three tested groups, using one-way analysis of variance.

Treatments with both doses of black pepper (320 and 160 mg kg^{-1} bw) showed non-significant increases in the levels of DNA at 36 and 71 day intervals, then decreased at 99 days in both male and female rat groups when compared to the normal control group (Table 2). Effect of higher dose of black pepper (320 mg kg^{-1} bw) on the level of DNA was more pronounced than the lower dose (160mg kg^{-1} bw). Two-way analysis of variance revealed that non-significant difference between the groups (A) and between the time intervals (B).

Table (3) illustrates the treatment effect of praziquantel 142mg kg^{-1} bw) with and without black pepper (160 mg kg^{-1} bw), for 85 days, on the content of liver total proteins. Treatment with praziquantel increased the liver content of total proteins to +53.4 % whereas treatments with black pepper followed by praziquantel decreased the level to almost the normal value of +0.99 % when compared to the normal control group. One-way analysis of variance between the three tested groups revealed significant increase at $P < 0.01$. Duncan's multiple range "t" test reflected significant differences between the group of rats treated with praziquantel against both of the normal control group

Table 1: Effect of black pepper and/or praziquantel treatments (mg kg^{-1} bw) on the levels of DNA in the livers of male albino rats.

Sex	Groups(mg kg^{-1} bw)	x̄ ± SD (mg gm^{-1})	% diff.	F	Duration (days)
Male	Control	2.806 ± 0.279	-	NS	85
	Praziquantel 142	2.381 ± 0.613	-15.2		
	Black pepper 160 followed by praziquantel 142	2.796 ± 0.103	-0.36		

x̄ mean; SD, standard deviation; % diff., percentage difference from the control; F, one - way analysis of variance; NS, non-significant .

Table 2: Effect of black pepper treatments (mg kg^{-1} bw) on the levels of DNA in the livers of male and female albino rats.

Sex	Groups	Duration: 36 days		71 days		99 days		F	
	(mg kg^{-1} bw)	x̄± SD (mg gm^{-1})	% diff.	x̄± SD (mg gm^{-1})	% diff.	x̄± SD (mg gm^{-1})	% diff.	A	B
Male									
	Control	2.289 ± 0. 81	-	2.163 ± 0.372	-	3.005 ± 1.277	-	NS	NS
	160	2.323 ± 0.519	+1.5	2.380 ± 0.524	+10.0	1.977 ± 0.225	-34.2		
	320	2.501 ± 0.225	+9.3	2.207 ± 0.212	+2.0	1.842 ± 0.220	-38.7		
Female									
	Control	2.040 ± 0. 60	-	2.193 ± 0.313	-	3. 154 ± 0. 545	-	NS	NS
	160	2.393 ± 0.662	+17.3	2. 997 ± 0. 383	+36.7	2. 319 ± 0. 372	-26.5		
	320	3.043 ± 1.011	+49.2	2. 615 ± 0. 27	+19.2	1. 665 ± 0. 362	-47.2		

x̄, mean; SD, standard deviation; % diff., percentage difference from the control; F, Two-way analysis of variance; A, groups; B, time intervals; NS, non-significant.

Table 3: Effect of black pepper and/or praziquantel treatments (mg kg^{-1} bw) on the levels of total proteins in the livers of male albino rats.

Sex	Group(mg kg^{-1} bw)	x̄±SD (gm %)	% diff	F	Duration (days)
Male	Control	20.074±2.413 (1)	-	P<0.01	85
	Praziquantel 142	30.783±4.909 (2)	+53.4		
	Black peper 160 followed by praziquantel 142	20.273±3.482 (3)	+0.99		

(1) vs. (2) P< 0.01 and (2) vs. (3) P < 0. 01, using Duncan's multiple range "t"test.
x̄, mean; SD, standard deviation; % diff., percentage difference from the control; F, one-way analysis of variance .

Table 4: Effect of black pepper treatments(mg kg^{-1} bw) on levels of total proteins in the livers of male and female albino rats.

Sex	Groups	Duration: 36 days		71 days		99 days		F	
	(mg kg^{-1} bw)	x̄± SD (gm%)	% diff.	x̄± SD (gm%)	% diff.	x̄± SD (gm%)	% diff.	A	B
Male									
	Control	22.671±2.947	-	25.337 ± 3.968	-	23.488 ± 2.746	-	NS	NS
	160	22.482 ± 3.714	-0.84	24.018 ± 1.433	- 5.2	27. 5 ± 5.283	+18.6		
	320	21.698 ± 2.262	- 4.3	30.712 ± 3. 88	+21.2	22.408±2.979	-4.6		
Female									
	Control	18.74 ± 4.735	-	27.699 ± 3.496	-	25.727 ± 2. 74	-	NS	NS
	160	23.61 ± 4.804	+23.1	26. 049±5. 439	- 6. 0	27.636 ± 5.122	+ 7.4		
	320	23.645 ± 4.843	+24.6	32.669 ± 0.350	+17.9	21.146 ± 3.219	-17.8		

x̄, mean; SD, standard deviation; % diff., percentage difference from the control; F, Two-way analysis of variance; A, groups; B, time intervals; NS, non-significant.

Table 5: Effect of black pepper and/or praziquantel treatments mg kg^{-1} bw on number and size of cells in the livers of male albino rats.

Sex	Groups	x̄± SEM: cell number (million)	cell size (μm)	% diff.: Cell number	% diff.: cell size	F: Cell number	F: cell size	Duration (days)
	(mg kg^{-1} bw)							
Male								
	Control	295.737± 10.691	7.197± o.400 (1)	-	-	NS	P<0.01	85
	Praziquantel 142	251.461± 26.424	13.314± 0. 956 (2)	-15.0	+85.0			
	Black pepper 160 followed by praziquantel 142	295.275± 3.840	7.250± 0.432 (3)	-0.16	+0.74			

(1) vs. (2) P< 0.01 and (2) vs. (3) P< 0.01, using Duncan's multiple range "t" test.
x̄, mean; SEM, standard error of the means; % diff., percentage difference from the control; F, One-way analysis of variance; NS, non-significant.

Table 6: Effect of black pepper treatments(mg kg^{-1} bw) on number and size of cells in the livers of male and female albino rats.

Sex	Group	x̄ ± SEM % diff.					
		36 days		71 days		99 days	
	(mg kg^{-1} bw)	cell number (million)	cell size (μm)	cell number (million)	cell size (μm)	cell number (million)	cell size (μm)
Male							
	Control	241.711±15.201	9.989±0.326	228.423±16.021	12.504±0.461	317.410±47. 672	8.472±1. 036
	160	245.266±22.384 +4.0%	10.112±0.389 +1.2%	251.303±22.570 +10.0%	10.646±1.299 -14..9%	208.795± 8. 978 -34. 2%	13.439±0.749 +58. 6%
	320	264.097± 8.968 +9.3%	8.667± 0.066 -13.2%	233.016±9.125 +2.0%	13.990±0. 568 +11.9%	194.539±8. 196 -38.7%	12.180±0. 317 +43.8%
F	A	NS	NS				
	B	NS	NS				
Female							
	Control	215.432±10.384	9.346±0.820	231.539±13.479	13.165±0.725	333.039±22.607	8. 217±0.770
	160	252.679±24.428 +17. 3%	9.741 ± 1.460 +4. 2%	316.473±16.525 +36.7%	9. 02±0.798 -25.6%	244.864±14.839 -26.5%	12. 287±1.285 +49.5%
	320	321.348±43.70 +49..2%	8.301± 1.004 -11.2%	276.170±14.107 +19.3%	12.565±0. 527 -4.6%	175.773±14.455 -47.2%	12. 078±0.920 +47.0%
F	A	NS	NS				
	B	NS	NS				

x̄ mean; SEM, standard error of the means; % diff., percentage difference from the control; F, Two-way analysis of variance; A, groups; B, time intervals; NS, non-significant.

Table 7: Effect of black pepper and/or praziquantel treatments (mg kg^{-1} bw), for 85 days, on the % of male albino rats who developed focal hydropic degeneration and portal tract inflammation.

Groups	% of animals with focal hydropic degeneration.		% of animals with portal tract inflammation.	
(mg kg^{-1} bw)	Mild	Moderate	Mild	Moderate
Control.	40	0	0	0
Praziquantel 142	0	67	67	33
Black pepper 160 followed by praziquantel.	0	40	40	20

N.B. No malignant transformation, no necrosis and no fatty degeneration were detected in livers in any section.

Table 8: Effect of black pepper treatments, in doses of 160 and 320 mg kg^{-1} bw for 36, 71, and 99 day intervals, on the percentage of male and female albino rats who developed focal hydropic degeneration and portal tract inflammation.

Sex	Groups	Focal hydropic degeneration							Portal tract inflammation						
		36 days		71 days		99 days			36 days		71 days		99 days		
	(mg kg^{-1} bw)	Mild %	Moderate %	Mild %	Moderate %	Mild %	Moderate %	Marked %	Mild %	Moderate %	Mild %	Moderate %	Mild %	Moderate %	Marked %
Male	Control	100	0	50	0	40	0	0	50	0	50	0	0	0	0
	160	0	50	0	0	40	0	0	50	0	-	-	40	0	0
	320	0	67	0	67	29	29	29	33	33	0	67	29	29	29
Female	Control	50	0	50	0	40	0	0	40	0	50	0	20	0	0
	160	50	0	33	17	43	0	0	50	0	33	17	43	0	0
	320	50	25	29	71	29	29	29	75	0	14	86	29	43	14

N.B. No malignant transformation, no necrosis, and no fatty degeneration were detected in livers in any section.

and the group of animals treated with black pepper followed by praziquantel. Table 4 showes a non-significant fluctuations of liver total proteins in male and female groups after treatments with two doses of black pepper throughout 36, 71, and 99 day intervals using two-way analysis of variance. Tables 5 and 6 demonstrate the estimated number and size of the liver cells after treatments with praziquantel and / or black pepper in male and female albino rats, respectively. The number of the liver cells showed non-significant changes between the groups treated with praziquantel , black pepper followed by praziquantel , and the normal control, using one way analysis of variance (Table 5). Treatment with praziquantel increased size of the liver cell to +85.0 % whereas black pepper modified this increase to + 0.74 % in the group of males treated with black pepper followed by praziquantel, when compared to the normal control group. Duncan's multiple range test reflected significant difference at $P<0.01$ between the group treated with praziquantel against both of the group treated with black pepper followed by praziquantel and the normal control group (Table 5).

Table 6 shows non-significant changes between groups treated with the two doses of black pepper and the corresponding controls in concern to number and size of the liver cells of male and female albino rats.

Histopathological investigations reflected no-malignant transformations, no-necrosis, and no-fatty degenerations in the livers of any section after treatments with praziquantel and /or black pepper. Percentage of animals manifested hepatic degeneration, portal tract inflammation and the intensity of the liver cell changes are expressed in tables 7 and 8. Mild hydropic degeneration and mild portal tract inflammation were predominant in most of the tested groups. In Table 7, praziquantel treatment reflects moderate hydropic degeneration and mild portal tract inflammation in 67 % and moderate portal tract inflammation in 33% of male albino rats. The male animals treated with black pepper followed by praziquantel showed decrease in the percentage of animals manifesting moderate hydropic degeneration and mild portal tract inflammation from 67 to 40 %, for both, also animals manifesting moderate portal tract inflammation decreased

from 33 to 20 %. Treatment of animals with 160mg kg^{-1} bw black pepper showed moderate hydropic degeneration in 50 % of males at 36 days and in 17 % of females at 71 days whereas moderate portal tract inflammation was reflected in only 17 % of female rats at 71 day interval (Table 8), taking in our consideration that the histopathological changes of male albino rats treated with 160mg kg^{-1} bw black pepper for 71 days could not be investigated, because samples were badly processed. The effect of 320mg kg^{-1} bw black pepper on the liver is more pronounced than the effect of 160mg kg^{-1} bw. Treatments with 320mg kg^{-1} bw black pepper reflected moderate hydropic degeneration at 36, 71, and 99 days and marked hydropic degeneration at 99 days in both male and female animals, moderate portal tract inflammation in 33, 67 and 29 % of the males at 36, 71, and 99 day intervals, respectively, and in 86 and 43% of the females at 71 and 99 day intervals, respectively, in addition to marked portal tract inflammation at 99 day interval in 29% of the male and 14% of the female albino rats (Table 8).

Discussion

The obtained results have shown that praziquantel and / or black pepper have no-significant effect on the liver content of DNA (Tables 1 and 2) which may reflect the non-significant changes in the activities of the enzymatic system involved in DNA synthesis and repair of damaged DNA. Earlier studies have proved that neither praziquantel nor black pepper have significant effect on the hepatic drug - metabolizing enzyme system (Kheir *et al.*, 1995 and Dalvi and Dalvi 1991).

It is noteworthy that the non-significant decrease of 15 % in the level of DNA in a group of animals treated with praziquantel is modulated to almost the normal control level of -0.36 % in a group of animals treated with black pepper followed by praziquantel, when compared to the normal control group (Table 1).

Neither praziquantel nor black pepper have significant effects on the liver cell numbers (Tables 5 and 6). *In vitro* studies have proved that praziquantel up to dose of 60μg ml^{-1} shows non-significant effect on the number of V-79 and FAF-28 cells (Hanna *et al.*, 1996a) and SHE cells (Herrera *et al.*, 1994). However, praziquantel in a dose of 50μg ml^{-1} reduces the number of V-79 cells by 40 % and in a dose of 100μg ml^{-1} reduces 95 % from the cells (Billings and Heidelberger, 1982). Powder of black pepper in diet of mice has no impact on carcinogenesis (Shwaireb *et al.*, 1990).

Praziquantel shows significant increases in both liver total proteins and liver cell size whereas black pepper treatments, in two doses, reflect non-significant fluctuations in both of total proteins and cell size. Kheir *et al.*, (1995) reported significant increases in liver total proteins after 800, 1600, and 2000mg kg^{-1} bw respectively praziquantel treatments.

Another confirmation of the above modulatory effect is also observed when the significant increase of liver total proteins has been decreased from +53.4 %, in the group treated with praziquantel, to + 0.99 % in the group treated with black pepper followed by praziquantel, when compared to the normal control group. Also the liver cell size has been decreased from +85 % to +0.74 % in the aforementioned two groups, respectively, when compared to the normal control group. These findings are in parallel with many other authors. In the study of Nalini *et al.*, (1998), the significant increases of the activities of β-glucuronidase and mucinase, as a result of the presence of colon carcinogen 1, 2-dimethylhydrazine (DHM), are decreased to more or less similar values of the control rats after supplementation with black pepper in the presence of DHM. Black pepper fed to mice in the study of Singh and Rao (1993) appears to induce liver detoxification system in chemical carcinogenesis. In the study of Unnikrishnan and Kuttan (1990), oral administration of black pepper extracts increases the percentage of life span by 64.7 % in mice in which Ehrlich ascites tumor were intraperitoneally transported.

In concern of the histopathological changes in this work, at first malignant transformations, necrosis, or fatty degenerations have not been detected in any section of livers of either male or female rats after treatments with praziquantel and / or black pepper throughout the used intervals. These are in coincide with others. In the study of Billings & Heidelberger (1982), praziquantel fails to induce transformation in $C_3H/10$ T1/2. However, praziquantel induces morphological transformation in SHE cells in the study of Herrera *et al.*, (1994). An extract of black pepper at a dose level of 2mg, 3 times a week , when given for either 5 months to male and female Egyptian toads or for 3 months to mice, result in appearance of liver tumors after 2 months in 24 % male and 36 % female toads (el-Mofty *et al.*, 1991) and a significant increase of the number of tumor-bearing mice Shwaireb *et al.* (1990).

The detected mild hydropic degenerations and mild portal tract inflammation in all tested groups (Tables 7 and 8), appear to be non-specific. These mild changes can be attributed to delay in fixation of the specimen in formalin or due to hypoxia or sudden circulatory failure at time of the animal death. Moderate hydropic degeneration and moderate portal tract inflammation in the group of animals treated with praziquantel (Table 7) may be attributed to inhibition of the enzymatic system in mitochondria or to disturbance in the metabolic process. It is worthmentioning that a group of animals treated with black pepper followed by praziquantel shows lower percentage of animals with moderate hydropic degeneration, from 67 to 40% and moderate portal tract inflammation, from 33 to 20 %, when compared to the group of animals treated with praziquantel (Table 7). These findings reflect further confirmation of the modulatory effect of black pepper on praziquantel effect.

Treatments of animals with black pepper at a dose of 160mg kg^{-1} bw reveals moderate hydropic degeneration in 50 % of male rats, at 36 day interval, moderate hydropic degeneration, and moderate portal tract inflammation in 17 % of females, at 71 day interval. On the other hand, both male and female animals showed no considerable changes at 99 day interval (Table 8). These findings may reflect that daily black pepper ingestion, at a dose of 160 mg kg^{-1} bw, may have a beneficial adaptive cytoprotictive response. Marotta and Floch (1991), in their report, have confirmed this finding. Treatment with the higher dose of black pepper (320 mg kg^{-1} bw) seriously affected the livers of both male and female rats (Table 8). Moderate and marked incidences of both hydropic degeneration and portal tract inflammation are reflected in both sexes. These findings may reflect the significant inhibition in the activities of the hepatic microsomal enzyme system. Dalvi and Dalvi (1991) have proved that the intragastric dose of 100mg kg^{-1} of piperine, a major constituent of black pepper, to adult male rats cause an increase in hepatic microsomal cytochrome P-450, benzphetamine N-demethylase, aminopyrine N-demethylase, and alanine hydroxylase, 24 hours following treatment. However the higher intragastric dose of 800mg kg^{-1} piperine produces significant inhibition in the activities of the aforementioned parameters of the hepatic drug-metabolizing enzyme system 24 hours after treatment.

In conclusion, the potential modulatory effect of

160mg kg^{-1} bw black pepper on the possible disturbances by praziquantel is suggested. In addition, further investigations of the effect of daily consumption of black pepper in high doses are needed.

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