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Research article

Microbial evaluation of some syrups in Syrian pharmacies

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ABSTRACT

Microbial contamination of syrups can bring clinical hazards to patients as well as physical and chemical changes in the product.

Aims: Studying the influence of the war on the Syrian pharmaceutical industry from a microbiological point of view by assessing the microbiological quality of syrup samples taken from Syrian pharmacies.

Methodology: Fifty different syrups from 29 different companies having various manufacture dates were collected during validity period between 9-2019 and 6-2021 in Aleppo, Syria. Membrane filtration technique was performed to quantify microbial contamination of the collected syrup samples. This involved passing the samples through filter nitrocellulose membrane disks with a pore size of 0.45 μm then transferring the filter disks alongside any collected microorganisms into Tryptone Soya Agar, Sabouraud Dextrose agar, Xylose lysine Deoxycholate agar and Eosin Methylene Blue agar plates. Colonies observed on these plates were counted and the number of viable microbes in the original sample was expressed as colony forming units per milliliter (CFU/mL). Investigation of *Escherichia coli* in all syrup samples and Salmonella in herbal syrup samples was also performed.

Results: This study revealed that 28 syrups (56%) had no growth of either bacterial or fungal colonies; 33 syrups (66%) had no growth of bacterial colonies; 43 syrups (86%) had no growth of fungal colonies. On the other hand, 7 syrups (14%) exceeded the pharmacopoeial limit for bacterial growth and 6 syrups (12%) exceeded that for fungal growth. Furthermore, 5 syrup samples (10%) were on the high permissible limits for bacterial contamination and none for fungal contamination.

All syrups were free from *E. coli* and all herbal syrups were free from *Salmonella*. Taken together, out of the fifty syrups examined 13 syrups (26%) exceeded the pharmacopoeial limits and therefore pharmacopoeial accepted syrups constitute a percentage of (74%).

Conclusion: Although the majority of samples tested showed compliance with the pharmacopoeial limits of microbiological contamination, the small proportion of syrups in the Syrian market exceeding the pharmacopoeial limit is still concerning and reveals the implications of post-war conditions on the quality of manufacturing in the Syrian pharmaceutical industry. That said, it remained within the proper limits compared to studies conducted in other countries in similar situations.

This study, therefore, highlights the need to apply the Good Manufacturing Practice (GMP) rules more strictly in order to limit microbiological contamination in pharmaceutical syrups to ensure the quality of products and safety of users. We suggest that further quality control studies are conducted on a larger scale and repeated more frequently.

1. Introduction

In microbiological terminology, pharmaceutical products can be divided into two categories: sterile and non-sterile [1]. Sterile production demands manufacturing drugs in an area free from microorganisms, such as production of intravenous injections and eye drops, while the production of non-sterile pharmaceuticals (NSP) demands a clean area which is not completely free from microorganisms and permits the presence of microorganisms within permissible limits. NSP include oral dosage forms (syrups, suspensions, and emulsions) and topical dosage forms (creams, gels, and ointments [2] (. Non-sterile pharmaceutical products are not required to be completely sterile, but are subject to some boundaries in terms of the number and types of acceptable microorganisms to ensure their effectiveness and safety for the consumer [3].

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One of the most common non-sterile pharmaceutical forms are syrups which are defined as a non-sterile liquid dosage form that contain active ingredients and constitute the most convenient dosage form for babies, children and the elderly [3]. Flavored and medicated syrups are the preferred dosage forms for both children and the elderly as they are easily swallowed and absorbed through the gastrointestinal tract. Patients usually use multi-dose syrups and for this reason, manufacturers should use preservatives to prevent accidental contamination resulting from repeatedly opening the same bottle of syrup. Preservatives are widely employed in a variety of manufacturing industries [4, 5, 6]. The contamination of syrups with microorganisms may bring changes in their physiochemical characteristics, including the fermentation of syrups and appearance of turbidity, besides producing possible odors and color changes [7]. In some cases, the presence of a small amount of microbial doses in pharmaceutical products was shown to pose a potential hazard to the consumer's health [7, 8]. For example, the presence of *Salmonella* causes typhoid fever and contamination with *Escherichia coli* may cause intestinal infections and is considered an indicator of fecal contamination. Microbiological contamination of syrups can cause the spoilage of the medication and lead to serious clinical risks particularly in children and elderly people. The presence of microbial and fungal contaminants becomes a major health concern when their number exceeds the acceptable limit (10^2 CFU/mL) for bacteria and (10 CFU/mL) for fungi as recommended by the European pharmacopoeia 2010 [9].

Table 1 shows the quantitative specifications of bacteria, fungi and organisms that must be absent in oral pharmaceutical preparations according to the European Pharmacopoeia 2010.

Metabolic polymorphism of bacteria helps them to consume and transform a variety of ingredients included in the pharmaceutical formulations. Therefore, it is important to determine the microbial load of all pharmaceutical products to ensure that quality of the final product is satisfactory [7, 8]. During the manufacturing stages, drugs are subjected to several processing steps that increase the risk of contamination with microbiological and physiochemical pollutants. These contaminants can enter the products from several sources such as poor facility design, the air entering through the ventilation system, staff, workers' hands, the machinery and other equipment utilized in the manufacturing process [7, 10]. Microbiological quality of non-sterile pharmaceutical products should be evaluated as an important quality control step particularly in developing countries where the climatic conditions may encourage the proliferation of microorganisms in medical products. Moreover, many products may be stored or dispensed under uncontrolled conditions [2].

As a result of the war that passed on Syria and left a lot of regression on various levels, this study was conducted to investigate the influence of this war on the Syrian pharmaceutical industry from a microbiological point of view, especially in light of the absence of such studies in this field in Syria.

2. Experimental procedures

2.1. Sample collection

Fifty syrups from 29 different companies with a variety of manufacture dates were collected randomly from different pharmacy stores in Aleppo, Syria. Tables 2 and 3 show the different syrup samples used along with their manufacture and expiry dates. Four syrups of fifty were herbal. Table 3 shows herbal syrup samples. All samples were examined during validity period between 9-2019 and 6-2021.

2.2. Materials and methods

The following media were used in the current study: MacConkey agar, MacConkey broth, Tryptone Soya Agar (TSA), Tryptone Soya Broth (TSB), Sabouraud Dextrose agar (SDA), Sabouraud Dextrose broth (SDB), Xylose lysine Deoxycholate (XLD) agar, Eosin methylene blue (EMB) agar and Brilliant Green Bile (BGB) broth.

Table 1. Acceptance criteria of microbiological quality of non-sterile dosage forms (European pharmacopoeia 2010).

Route of administration	[1]TAMC (CFU/mL)	TYMC (CFU/mL)	Specified micro-organisms
Aqueous preparations for oral use	10^2	10^1	Absence of *E.coli* (1 g/mL)
Herbal medicinal products to which boiling water is added before use	10^7	10^5	Not more than 10^3 *E coli* (1 g/mL) Absence of *Salmonella* (1 g/mL)

[1] TAMC: Total Aerobic Microbial Count.

All media were prepared according to the manufacturer's protocol (HiMedia, Mumbai, India).

2.3. Determination of total microbial counts

Membrane filtration technique was performed to quantify microbial contamination of the collected syrup samples. This involved passing the samples through filter nitrocellulose membrane disks with a pore size of 0.45 μm under biological safety cabinet in order to collect any potential contaminants (bacteria or fungi) on the filter membrane disk. The following steps were performed according to the European pharmacopoeia 2010: after preparing the media (TSA and SDA), two dilutions (1/10 and 1/100) were made of each syrup (using physiological serum as the diluent) in order to reach a dish with a density of countable colonies [11]. After filtering the samples, the membrane filter disks were washed three times with hundred milliliters of sterile physiological serum. Each membrane was then placed on the surface of a dish of culture media so that the germ carrying face is up while avoiding air reservation between the membrane and the middle surface. When the dishes were incubated, the germs pulled nutrients through the membrane and formed colonies. Three replicate dishes were cultured of each dilution along with the original sample concentration.

TSA dishes were incubated at 35 °C for 2 days in the bacterial incubator for the detection of bacterial growth and SDA dishes were incubated in the fungal incubator at 25 °C for 7 days for the detection of fungal growth. Colonies were counted and the number of viable cells in the original sample and in each dilution was expressed as colony forming units per milliliter (CFU/mL). Colony forming units per milliliter were calculated using the following equation. CFU/mL = CFU/plate × dilution factor [12]. (N.B. The dilution factor in the previous equation represents that of the dish on which colonies were of a countable density).

2.4. Detection of E. coli

Syrups were analyzed according to the European pharmacopoeia 2010 with additional steps for the presence and absence of *E. coli*. 10 ml of each syrup was passed through a filter membrane which was then washed three times with sterile physiological serum to eliminate the efficacy of the preservative and any excipients that might have an antimicrobial effect. Each membrane was then cultured in a tube containing sterile MacConkey broth as an enrichment medium. The tubes were then incubated for 48 h at 35 °C. Subsequently, by the culture loop after inflaming it, an extract was taken from each tube of a particular syrup and spread on three EMB agar plates and three MacConkey agar plates. Following a 48-hour incubation at 35 °C, the plates were visually examined to confirm each syrup was free from *E. coli* through the shape, specifications and color of the colonies after incubation.

If green metallic shine colonies appeared on the surface of EMB agar plates or bright pinky-red colonies on the surface of MacConkey agar plates that are morphologically identical to the colonies of *E. coli*, the indole test would be performed as a confirmatory biochemical test. The

Table 2. Non-herbal syrup samples of the study.

	Company	Active ingredients	Manufacture date	Expiry date
1	A	Diphenhydramine	2–2019	2–2022
2	A	Hyoscine butyl bromide	7–2018	7–2021
3	A	Ammonium chloride, diphenhydramine, drosera	11–2018	11–2021
4	A	Diphenhydramine, ammonium chloride, menthol	10–2017	10–2020
5	D	Carbocestein	3–2019	3–2022
6	E	Carbocestein	1–2018	1–2021
7	E	Bromhexin, guaifenesin, menthol, terbutaline	1–2019	1–2021
8	E	Ferrous sulfate	1–2019	1–2021
9	F	Ambroxol	1–2018	1–2021
10	F	Hyoscine butyl bromide	5–2020	5–2023
11	F	Paracetamol	5–2018	5–2021
12	F	Metoclopramide HCl	2–2018	2–2021
13	G	Levocetrizine	4–2018	4–2021
14	G	Ambroxol	11–2018	11–2021
15	G	Ammonium chloride, bromhexin HCl, dextromethorphan HBr, pseudoephedrine HCl	10–2020	10–2023
16	H	Pizotifin	10–2017	10–2021
17	I	Sodium bicarbonate, dill seed oil	10–2017	10–2020
18	I	Dicyloverin	5–2018	5–2021
19	I	Carbocestein	7–2018	7–2021
20	I	Carbocestein	8–2018	8–2021
21	I	Oxybutynin	6–2020	6–2023
22	J	Multivitamins & mineral	10–2018	10–2020
23	K	Prednisolone	10–2017	10–2020
24	L	Paracetamol	4–2019	4–2022
25	L	Desloratadin	2–2019	2–2020
26	M	Levetiracetam	2–2019	2–2022
27	M	Sodium valproate	3–2020	3–2023
28	M	Salbutamol, guaphensin	11–2019	11–2022
29	N	Cetrizin	2–2018	2–2021
30	N	Bromhexine, guaiphenesin, terbutaline, menthol	1–2020	1–2023
31	O	Hydroxyzine	1–2019	1–2022
32	O	Lactulose	10–2018	10–2021
33	P	Loratadine	10–2018	10–2021
34	Q	Diprophylline	1–2019	1–2022
35	R	Phenylephrine, guaiphensine, paracetamol	1–2019	12–2021
36	S	Bromhexine, pseudoephedrine, dextromethorphan, ammonium Cl, menthol	5–2019	5–2022
37	S	Paracetamol, pseudoephedrine, dextromethorphan, chlorpheniramin	5–2019	5–2022
38	T	Aminophylline	5–2018	5–2021
39	T	Codein phosphate, glyceril gayacolate	9–2019	9–2022
40	V	Oxomemazin, paracetamol, guaiphensine, sodium benzoate	7–2020	7–2023
41	W	Iron	10–2019	10–2021
42	X	Levocetrizine	11–2017	11–2020
43	Y	Diphenhydramine	3–2018	3–2021
44	Z	Piracetam	10–2019	10–2022
45	A	Clorpheniramine, phenylephrine	12–2020	12–2023
46	C	Iron elemental, folic acid, Vitamin B12	9–2019	11–2021

Table 3. Herbal syrup samples of the study.

1	B	Thymol	8–2019	8–2023
2	C	Thymol	8–2019	8–2023
3	U	Ivy leaft dry extract	11–2020	11–2023
4	B	Thymol extract, Ivy leaft dry extract	4–2021	4–2024

A, B, C…. a symbol for the companies from which the syrup samples were taken.

syrup would pass the test if such colonies were not seen or if the confirmatory biochemical test was negative.

2.5. Detection of Salmonella

Salmonella is only investigated in herbal syrups according to European pharmacopoeia 2010 with additional steps. 10 ml of each syrup was passed through a filter membrane that was then washed three times with sterile physiological serum. Each membrane was cultured in a tube containing sterile Brilliant Green Bile (BGB) broth as enrichment medium and the tubes were incubated for 48 h in 35 °C. Subsequently, by the culture loop after inflaming it, an extract was taken from each tube of a particular syrup and was spread on three XLD plates. The plates were incubated for 48 h at 35 °C, then visually observed to confirm that each syrup was free from *Salmonella* through the shape, specifications and color of the colonies after incubation.

If red colonies appeared on the surface of XLD plates and were morphologically identical to the colonies of *Salmonella*, we would move to reactions characteristic of Salmonella on Triple Sugar Iron (TSI) agar. If the former colonies belong to one of the *Salmonella* strains, colonies will appear red in color with black centers; at that point, a urease test would be performed as a confirmatory biochemical test. A negative urease test indicates the presence of *Salmonella*.

2.6. Negative control

To verify testing conditions, a negative control was utilized consisting of the chosen diluent (sterile physiological serum) in place of the test preparation. The absence of microbial growth in the negative control plate indicates successful experimental conditions.

3. Results

Tables 4 and 5 show the results of the total bacterial count and the results of the investigation of *E. coli* (and *Salmonella* in herbal syrups) in contaminated syrup samples and comparing these results with pharmacopoeial limits according to the European pharmacopoeia 2010.

Tables 6 and 7 show the results of the total fungal count in the contaminated tested syrup samples and comparing these results with the pharmacopoeial limits according to the European pharmacopoeia 2010.

Results obtained from this study revealed that only seven samples of fifty were contaminated with bacteria exceeding pharmacopoeial limits, which appeared as Gram positive bacillus genus when tinctured with Gram stain (Figure Sa, Figure Sb), Most of the colonies grown on TSA were round, rough, wrinkled, opaque and white with serrated edges, and six samples of fifty syrups were contaminated with fungi exceeding pharmacopoeial limits.

No descriptive colonies of *E. coli* appeared in the specific media and therefore all non-herbal syrups were found to be free from *E. coli*.

Furthermore, all herbal syrup samples were within the permissible limits of TAMC according to European pharmacopoeia"2010"; while one of the four herbal syrups exceeded the pharmacopoeial TYMC limits. All herbal syrups were found to be free from *E. coli* and *Salmonella* as no

Table 4. Total bacterial count and investigation of *Escherichia coli* in contaminated non-herbal syrup samples.

	Company	Active ingredients	Mean of total aerobic bacterial count CFU/mL	*Escherichia coli*	Acceptable limit (CFU/mL)
					bacteria
1	A	Diphenhydramine	100	NG	10^2
2	A	Hyoscine butyl bromide	100	NG	
3	A	Diphenhydramine, ammonium chloride, menthol	1	NG	
4	D	Carbocestein	10	NG	
5	E	Carbocestein	1	NG	
6	F	Ambroxol	300	NG	
7	I	Sodium bicarbonate, dill seed oil	200	NG	
8	I	Dicyloverin	400	NG	
9	I	Carbocestein	100	NG	
10	I	Carbocestein	100	NG	
11	L	Paracetamol	2034	NG	
12	O	Hydroxyzine	240	NG	
13	P	Loratadine	10	NG	
14	Q	Diprophylline	700	NG	
15	X	Levocetrizine	153	NG	
16	Y	Diphenhydramine	100	NG	

(NG): No Growth.
Details of calculation counts (Table S1).

Table 5. Total bacterial count and investigation of *Escherichia coli* and *Salmonella* in contaminated herbal syrup samples.

	Company	Active ingredients	Mean of total aerobic bacterial count CFU/mL	*E.coli*	*Salmonella*	Acceptable limit (CFU/mL)
						bacteria
1	B	Thymol	467	NG	NG	10^7

(NG): No Growth.
Details of calculation counts (Table S2).

Table 6. Total fungal count in contaminated non-herbal syrup samples.

	Company	Active ingredients	Mean of total aerobic fungal count CFU/mL	Acceptable limit (CFU/mL)
				Fungi
1	A	Ammonium chlorid, diphenhydramine, drosera	1465	10^1
2	E	Carbocestein	2	
3	G	Ammonium chlorid, bromhexin HCl, dextromethorphan HBr, pseudoephedrine HCl	2000	
4	N	Cetrizin	206	
5	T	Aminophylline	200	
6	Y	Diphenhydramine	100	

Details of calculation counts (Table S3).

Table 7. Total fungal count in contaminated herbal syrup samples.

Company	Active ingredients	Mean of total aerobic fungal count CFU/mL	Acceptable limit (CFU/mL)
			fungi
1	Ivy leaft dry extract	2×10^6	10^5

Details of calculation counts (Table S4).

descriptive colonies of the two microorganisms appeared in the specific media.

All results of negative control plates were free of microbial growth.

From the analysis of all the results of the current study, a set of conclusions can be made which are summarized in Table 8.

Table 8. Data of results analysis.

	Number of syrups/ from fifty	Percentage
Fungal growth less than 10 CFU/mL	44	88%
Fungal growth more than 10 CFU/mL	6	12%
No fungal growth	43	86%
Fungal Contamination on the high permissible limits	0	0%
Bacterial growth less than 100 CFU/mL	43	86%
Bacterial growth more than 100 CFU/mL	7	14%
No bacterial growth	33	66%
Bacterial Contamination on the high permissible limits	5	10%
No bacterial or fungal contamination	28	56%
Syrups conforming to pharmaceutical limits of European pharmacopoeia 2010	37	74%

4. Discussion

The aim of the current study was to investigate the microbial contamination in a randomly selected sample of syrups available in Syrian pharmacies. In fact, the lack of similar studies particularly after the recent war demonstrated a pressing need for such quality control studies in order to fill this gap and ensure safety for users.

The study revealed that 28 syrups (56%) out of the fifty syrup samples examined had no growth of either bacterial or fungal colonies, while 33 syrups (66%) had no growth of bacterial colonies and 43 syrups (86%) had no growth of fungal colonies.

On the other hand, a small proportion of syrups contained viable aerobic microbial count exceeding the pharmacopoeial limits. These were seven syrups (14%) exceeding the pharmacopoeial limit for bacterial growth and six syrups (12%) exceeding the pharmacopoeial limit for fungal growth. Furthermore, the percentage of syrup samples in which contamination was on the high permissible limits was 10% (5 syrups) and 0% for bacterial and fungal growth, respectively.

All syrups were free from *E. coli*, and all herbal syrups were free from *Salmonella*. In conclusion, out of the fifty syrups examined, 13 syrups (26%) exceeded the pharmacopoeial limits and therefore pharmacopoeial accepted syrups constitute a percentage of 74%.

These results were relatively consistent with the work of other researchers including a study conducted by Salem *et al.* (2021) of non-sterile pharmaceuticals in Egypt. The later study showed that 17.03% and 19.23% of samples exceeded the maximum acceptable limit of TAMC and TYMC, respectively [2]. Similarly, to the results in our study, the Egyptian study also confirmed oral products were free from *E. coli* [2].

On the other hand, two similar studies conducted in Nigeria showed lower standards of microbial control in syrups compared to our study. Emejuru *et al.* (2013) demonstrated that 79.17% and 66.67% of syrups tested had bacterial and fungal growth exceeding the pharmacopoeial limit, respectively, with *E. coli* being isolated from several samples [13]. The second Nigerian study conducted by Daniyan *et al.* (2011) on 80 syrups including paracetamol, chloroquine phosphate and vitamin c collected from different pharmacies in Minna metropolis showed a microbiological load of 67% in chloroquine phosphate syrups, 84% in paracetamol syrups, 67% in vitamin c syrups thereby exceeding the tolerance limit of permissible microorganisms specified officially for syrups [11].

On the other hand, a study conducted in Sana'a city, Yemen by Al−Kaf *et al.* (2015) concluded all cough syrup samples tested contained viable microbial load within the acceptable limits according to the Pharmacopoeia specifications [3]. Moreover, Kundo *et al.* (2018) who studied paracetamol syrups in Bangladesh, found all syrups complying with the official requirements for microbiological quality in terms of the total viable aerobic count, according to the USP (2007) and all of the analyzed analgesic syrups were found to be free from the pathogenic microorganisms thereby passing the USP (2007) specifications [14].

The low levels of microbiological contamination in most tested syrup samples is likely due to the application of Current Good Manufacturing Practice (CGMP), effective preservative agents and suitable quality control programs [15].

It is suggested that the sugar content of syrups can provide high osmotic pressure which inhibits the growth of several microorganisms and in turn plays a role in lowering microbial levels [16]. Moreover, syrups are usually filtered before packaging [17].

The complete absence of the growth of microbiological organisms is maybe due to following optimal conditions in the production process including: sterilization of the water used to prepare the syrups, filtering the syrups before filling them in their glass containers, washing and sterilization the glass containers with dry heat before primary packing, ensuring that containers are closed tightly alongside the use of the correct concentrations of preservatives.

On the other hand, the presence of some substances that have antibacterial or antifungal effects in the composition of the syrup may be another reason for the absence of microbiological growth. For example, according to previous studies, it was found that thymol, menthol, and sodium valproate are substances that have antimicrobial effects and play a role in preserving syrups. In our current study, we have seven syrups from twenty-seven (25%) which were completely free from bacterial or fungal contamination that contain within their composition one of these substances in different proportions [18].

The European Pharmacopoeia '2010'recommends *Salmonella* (for herbal syrups), *E. coli*, as indicators of pathogenic microbial contamination of syrups. All syrup samples analyzed were found to be free from the pathogenic microorganisms and

passed the European Pharmacopoeia "2010" specifications, a result that matches that of previous studies by Salem *et al.* (2021) [2] and Al−Kaf *et al.* (2015) [3].

The absence of *E. coli* contamination indicates that samples are devoid from any fecal contamination, and therefore confirms the absence of any pathogenic organisms, whether bacterial, fungal, viral or protozoan of intestinal origin.

The presence of Gram-positive bacillus may be due to the widespread of these bacilli in dust and soil which could have been transmitted to the work surfaces in contact with the product through dust traces.

On the other hand, the presence of some molds reflects the storage quality of the syrups. The presence of certain molds is harmful since they produce metabolites that may be toxic to consumers and cause rapid deterioration of the product due to the biodegradation of the different components of formulations arising from the production of toxin [19].

This indicates that the microbiological quality of the examined syrups was in general, adequate and, in most cases, excellent.

5. Conclusion

This study showed that 56% of the syrup samples tested had no growth of either bacterial or fungal colonies, but 14% exceeded the pharmacopoeial limit for bacterial growth and 12% exceeded the pharmacopoeial limit for fungal growth. Additionally, all samples were shown to be free from the pathogenic microbiological organisms (*E. coli* and Salmonella). The syrups complying with the European pharmacopoeia 2010 constituted a percentage of 74%.

We, therefore, conclude from this study that the Syrian pharmaceutical industry was mildly affected as a result of the war, from a microbiological point of view, but it remained within the proper limits compared to studies conducted in other countries. Therefore, we suggest, in order to ensure the health of patients, to apply the rules of GMP more strictly, and to repeat this study after a while on a larger number of samples.

Declarations

Author contribution statement

Fatema Nour Jazmati: Performed the experiments; Wrote the paper.
Saleh Trefi: Conceived and designed the experiments.
Ali Ibrahim: Analyzed and interpreted the data.
Yaser Bitar: Contributed reagents, materials, analysis tools or data.

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Data availability statement

No data was used for the research described in the article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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