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Research Article

Counterfeit Probiotic Drugs

Probiota İlaçlarinda Sahtecilik

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Abstract

Aim: Counterfeit drugs are a threat to human health worldwide. It can be seen that insufficient research has been conducted on the subject of counterfeit drugs related to potentially addictive drugs seized by the authorities. The aim of this study was to investigate whether or not there are drugs for sale in the Turkish market, which are counterfeit drugs under the heading of probiotics which are defined as micro-organisms with a positive effect on health when taken in certain quantities.

Material and Method: : A total of 17 different probiotic products in capsule, drops or sachet form, which were permitted for sale, were obtained from randomly selected chemist's shops in the province of Malatya.

Results: There was nothing missing or counterfeit on the packaging of the 17 products examined. When the contents were investigated, no deficiencies or excess micro-organism production was determined in the first 12 products. In product #13, there was no production of one of the mentioned micro-organisms. In products # 14,15, 16, and 17, more than one micro-organism stated in the prospectus could not be obtained.

Conclusion: As the checking of products sold in chemist's but controlled by the Ministry of Food, Agriculture and Livestock is not easy, there is a need for tighter supervision. This can be provided by sending the samples taken during audits to the correct laboratories, making detailed examinations, and evaluation the amount of active substance.

Keywords: Probiotic, counterfeit drugs, drug evaluation

Öz

Amaç: Dünya genelinde sahte ilaçlar insan sağlığını tehdit etmektedir. Yapılan çalışmalar göz önüne alındığında; sahte ilaç konusunda adli olarak ele geçirilmiş, bağımlılık potansiyeli bulunan ilaçlar ile ilgili çalışmalar yapıldığı ancak diğer ilaç grupları ile ilişkili yeterli çalışma yapılmadığı görülmektedir. Biz bu çalışmamızda Türkiye piyasasında; belirli miktarlarda alındıklarında sağlığı olumlu yönde etkileyen mikroorganizmalar şeklinde tanımlanan; probiyotikler başlığı adı altında satılan ilaçların sahte olup olmadıklarını araştırmayı amaçladık.

Materyal ve Metot: Malatya ilinde randominize bir eczaneden kapsül, damla ve şase formu bulunan ve satışı için izinleri bulunan 17 adet farklı marka probiyotik ürün alındı.

Bulgular: İncelenen 17 ürüne ait kutular ve kutu üzerinde olması gereken bilgiler açısından herhangi bir eksiklik ve sahtecilik göze çarpmadı. İçerikleri açısından yapılan araştırmada ilk 12 üründe herhangi bir eksik ya da fazla organizma üremesine rastlanmadı. On üç numaralı üründe içerikte bahsedilen mikroorganizmalardan 1 tanesi üremedi. On dört on beş, on altı ile on yedi numaralı ürünlerde prospektüste belirtilen birden fazla mikroorganizma ise elde edilemedi.

Sonuç: Eczanelerde satılan ancak Gıda Tarım ve Hayvancılık Bakanlığı tarafından kontrolü yapılan ürünlerin kontrolleri kolay olmayıp sıkı denetimlerin yapılması gereklidir. Bu ürünlerin denetimleri esnasında alınan numunelerin doğru laboratuvarlara gönderilerek detaylı incelemeleri yapılmalı aynı zamanda ilaç etken maddelerinin de miktar yönünden değerlendirilmesi sağlanmalıdır.

Anahtar Kelimeler: Probiyotik, sahte ilaçlar, ilaç değerlendirmesi

INTRODUCTION

In recent years, counterfeit drugs have become a serious problem in both developed and developing countries. Although there is no clear definition of exactly what counterfeiting is, each country has a definition according to their own laws. Drugs accepted as counterfeit in one country may not be accepted as such in other countries (1).

The World Health Organization (WHO) has defined counterfeit drugs as fake brands that have been deliberately mis-labelled in respect of identity or source, and drugs on the market with the correct content but without the active substance or which do not contain sufficient active substances (2).

The Turkish Ministry of Health defines counterfeit drugs as a product produced or imported with a different

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composition from the formulation of the product licensed and permitted by the Ministry of Health (eg, deficient amount of active substance, containing too much or none of the active substance, or containing a different auxiliary substance) (3). The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) accepts that 7% of all the medications sold throughout the world are counterfeit (4).

According to the WHO definition, the active substances and doses contained in these types of products may be different from the information on the label, or products may not even contain any active substance (5). The concept of counterfeit and smuggled drugs changes from country to country, and as there is no full explanation and consensus has not yet been reached on this subject, studies related to the frequency of these drugs have determined frequency rates in a wide range of 1%-50% (6).

However, there are drug groups that are used by many patients and are not thought to be counterfeited. Probiotics, which are classified as containing foodstuff, are licensed for manufacture and sale by the Turkish Ministry for Food, Agriculture and Livestock, and are sold in chemist's, and are evaluated as in this group (7). Probiotics are defined as micro-organisms that have a positive effect on health when taken in certain quantities (8). The nutritional sources of probiotics are fermented yoghourts, cheese, koumiss, kefir, bread, beer and wine, which use Lactobacilli, Bifidobacteria, Enterococci, and Streptococci (9). Probiotics are used on a broad scale and may be purchased either on prescription or over the counter in chemists'.

In a screening of literature on the subject of counterfeit drugs, studies have been conducted related to drugs with the potential for dependence, but there can be seen to have been insufficient studies on other drug groups. The aim of this study was to investigate whether or not counterfeit drugs under the heading of probiotics are being sold on the Turkish market.

MATERIAL AND METHOD

The necessary permissions for this study were obtained from the Clinical Research Ethics Committee of Inonu University. A total of 17 different brands of probiotic products in capsule, drops, or sachet form, which were permitted for sale, were obtained from randomly selected chemists in Malatya province.

The products were numbered from 1 to 17, and were evaluated in respect of points which could be counterfeited; the packaging, labelling, barcode, and contents. The examinations in respect of the active substances contained in these products were made in the Microbiology Department Laboratory of Inonu University Medical Faculty.

The form in which the products were presented for sale was evaluated in respect of whether there were any erasures or signs of damage on the barcodes and packaging. The presence or absence of any hologram on the packaging was noted, together with date of production and use-by date.

Content Analysis

The smear method described by HALKMAN was used to determine the number of micro-organisms. In this method, a 0.1ml sample was quantitatively inoculated into sheep's blood, EMB, Saboura Dextrose and chocolate (Oxoid, USA) media. After incubation for 18-24 hours, the colonies formed in the media were counted. Insufficient productions were extended for up to 48 hours. In the calculation of the colony numbers, the formula below, which was described by HALKMAN, was used. The micro-organisms were identified using Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (Maldi-Tof MS) (Bio Mérieux, France).

$$N = C / (V(n1+0,1 \times n2) Xd)$$

N = the number of micro-organisms in 1 gr or 1 ml of the sample

C = the total number of colonies in all the petri dishes where counting was applied

V = the volume (ml) transferred to the petri dishes where counting was applied

n1= the number of petri dishes counted in the count made from the first dilution

n2= the number of petri dishes counted in the count made from the second dilution

d = the greater dilution concentration from 2 consecutive dilutions applied with counting

The number obtained as a result of the count was stated as Colony Forming Unit/gr (CFU/gr). The method described by Kadir HALKMAN was used in the calculation of the colony numbers (10).

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Inonu Unıversıty Scıentıfic Research And Publıshıng Ethıcs Board Health Sciences Non-Interventional Clinical Research Ethics Committee (26.01.2021-2021/1497).

RESULTS

The results of the examinations of the packaging of the 17 products examined are shown in Table 1. The vast majority of these products were seen to be sold in the form of sachets. No missing information or signs of counterfeiting were observed in any of the information on the packaging examined.

It was found that the mean score of women in the Fertility Adjustment Scale was 23.30±1.35, and the mean score in the Spousal Support Scale was 65.41±10.41 (Table 2).

In the first 12 products investigated in respect of content, there were no deficiencies or production of extra organisms. In product no 13, only 1 micro-organşism was produced of those stated in the contents. In product nos 14, 15, 16 and 17, there was determined to be no production of at least one of the micro-organisms listed in the prospectus (Table 2).

Table 1. Findings of the evaluations of the information on the packaging of the drugs

Drug no	Damage to the packaging	Hologram	Date of production	Use-by date	Scraping or erasure on the price label	Form of sale
1	-	+	+	+	-	ampoule
2	-	+	+	+	-	sachet
3	-	+	+	+	-	sachet
4	-	+	+	+	-	drops
5	-	+	+	+	-	sachet
6	-	+	+	+	-	sachet
7	-	+	+	+	-	sachet
8	-	+	+	+	-	drops
9	-	+	+	+	-	sachet
10	-	+	+	+	-	sachet
11	-	+	+	+	-	sachet
12	-	+	+	+	-	sachet
13	-	+	+	+	-	sachet
14	-	+	+	+	-	capsule
15	-	+	+	+	-	sachet
16	-	+	+	+	-	sachet
17	-	+	+	+	-	sachet

Table 2. Results obtained from the microbiological examinations of the drugs

Drug no	Organism content stated in the prospectus	Organism obtained
1	10^9 cfu/ml Bacillus clausii	10^9 cfu/ml Bacillus clausii
2	10^9 cfu/ml Entercoccus faecium+ Lactobacillus acidophilus+ Lactobacillus rhamnosus+ Bifidobacterium longum+ Bifidobacterium bifidum	109 cfu/ml Entercoccus faecium+ Lactobacillus acidophilus+ Lactobacillus rhamnosus+ Bifidobacterium longum+ Bifidobacterium bifidum
3	10^9 cfu/ml Saccharomyces boulardii	10^9 cfu/ml Saccharomyces boulardii
4	10^9 cfu/ml Laclobacillıs yetileri	10^9 cfu/ml Laclobacillıs yetileri
5	10^9 cfu/ml Saccharomyces boulardii	10^9 cfu/ml Saccharomyces boulardii
6	10^9 cfu/ml Saccharomyces boulardii	10^9 cfu/ml Saccharomyces boulardii
7	10^9 cfu/ml Saccharomyces boulardii	10^9 cfu/ml Saccharomyces boulardii
8	10^9 cfu/ml Bifidobacterium animalis	10^9 cfu/ml Bifidobacterium animalis
9	10^9 cfu/ml Saccharomyces boulardii	10^9 cfu/ml Saccharomyces boulardii
10	10^9 cfu/ml Streptococcus thermophillus, Lactobacillus plantarum, Bifidobacterium breve, Bifidobacterium longum	10^9 cfu/ml Streptococcus thermophillus, Lactobacillus plantarum, Bifidobacterium breve, Bifidobacterium longum
11	10^9 cfu/ml Laclobacillıs rhamnosus	10^9 cfu/ml Laclobacillıs rhamnosus
12	1^{09} cfu/ml Saccharomyces boulardii	10^9 cfu/ml Saccharomyces boulardii
13	10^9 cfu/ml, Lactobacillus bulgaricus, Lactobacillus acidophilu, Bifidobacteria Streptococcus thermophillus	10^9 cfu/ml, Lactobacillus bulgaricus, Lactobacillus acidophilus, Bifidobacteria. No production of Streptococcus thermophillus
14	10^9 cfu/ml Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus rhamnosus ve Saccharomyces boulardii	10^9 cfu/ml Bifidobacterium longum. No production of Lactobacillus acidophilus, Lactobacillus rhamnosus and Saccharomyces boulardii
15	10^9 cfu/ml Streptococcus thermophillus Saccharomyces boulardii	10^9 cfu/ml Streptococcus thermophillus. No production of Saccharomyces boulardii
16	10^9 cfu/ml Bifidobacterium animalis	$5x10^4$ cfu/ml Bifidobacterium animalis
17	Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacilluscasei, Bifidobacterium bifidum	No production

DISCUSSION

Probiotics, which have many equivalents and rapid circulation, are currently used in the treatment of many diseases. These products can be purchased from chemists on patient request both with and without a prescription. However, there has been insufficient research in respect of counterfeit probiotics obtained in this way from chemists. It is noticeable that studies have been more focused on the abused illegal drug group of phosphodiesterase inhibitors, which are sexual performance enhancing drugs (11,12). As this group of drugs are sold at a lower price than the originals and because of the indications for use, they are thought to be more vulnerable to exploitation (12). This group of phosphodiesterase type 5 enzyme inhibitors, which is known to be the most common sexual performance stimulant on the black market, is the most commonly abused drug group in the black market for drugs in Europe (13). It has been reported that this group has entered the system through manufacture and distribution by large, well-organized, criminal networks, then placement in the counterfeit drug market by drug wholesalers (14). These types of drugs with a large market share and high consumption are often encountered in judicial processes. There are several studies in literature related to these drugs obtained especially during smuggling and other control operations. In addition, this group of drugs together with other drugs open to abuse are frequently audited.

Studies, announcements and reports published about drugs obtained, particularly in judicial processes, have attempted to raise awareness on the subject of counterfeit drugs. However, there have been insufficient checks and studies on the subject of drugs not in this group which are sold in chemists.

On the internet website of the Turkish Drugs and Medical Device Institute, it is emphasized that "it is important to check drugs sold at a lower price than that defined by the Ministry of Health in respect of the information on outer packaging by comparing if possible with a previously purchased drug, and attention must be paid to any change to the use-by date and whether or not there has been any erasure or scratching away of the label or on the box" (15).

In this study, 17 products were obtained from chemists and were checked in respect of date of manufacture and use-by date, holograms and packaging. All the drugs examined were seen to be in the original packaging, original holograms were on the packaging, date of manufacture and use-by date were written, and the serial number. No physical findings were determined which suggested that there would be any problems in using the product.

In counterfeit products, as the active substance content and dose are unknown by the user, this constitutes a danger. Potential side-effects which could develop to the active substances may even lead to death, and different active substances in the content can cause drug-drug interactions. Moreover, diagnosis of patients using drugs with unspecified content is made more difficult and may not always be possible (17). In the current study, the drugs were numbered from 1 to 17, and while the active substances of drug nos 1-12 were determined to be as written on the prospectus, active substances in nos 13-17 were insufficient or absent. Furthermore, in the drug labelled no 17, no micro-organism written in the prospectus was determined in the laboratory tests.

Probiotics are contribute to the flora by improving the bacterial balance in the intestine, and by binding to the receptors through competition, they do not leave room for pathogenic agents and allow them to be excreted with feces. Bacteria used as probiotics must be obtained from the intestinal flora, be viable, resistant to stomach and bile acids, and have the ability to adapt and colonize intestinal cells. They should also be able to maintain their effects when taken with antibiotics. Nutritional sources of probiotics are fermented yogurts using Lactobacilli, Bifidobacteria, Enterococci and Streptococci, cheese, pickles, bread, beer, wine, kumiss and kefir (9,16). In the current study, active ingredients 13-17 were insufficient or absent. In addition, no microorganism written in the package insert was detected in the laboratory tests of the drug labeled 17. These, in turn, may prolong the treatment process or cause worse outcomes.

The Turkish Drugs and Medical Device Institute has also stated that patients must obtain drugs frrom chemists, and as the sale of drugs over the internet is illegal, when drug sales are encountered on internet sites or from different sources, this must be communicated to the Ministry of Health, and drugs must not be purchased from those sites (15). However, this group of drugs can be easily obtained from internet sites. The sale of drugs from these sites must be regulated and even restricted by the relevant authorities.

When drugs prescribed for a patient at what is thought to be a sufficient dose of active substance in the content are perceived by the patient not to be of benefit, the patient may try other treatment methods. In this way, the treatment process will be prolonged and the healthcare costs will increase.

Although not easy, frequent checks should be made of products which are sold by chemists but controlled by the Ministry of Food, Agriculture and Livestock. During these checks, samples of the products should be taken and examinations made by sending them to the correct laboratories.

CONCLUSION

It is also necessary to make more detailed checks of the products sold by chemists by collecting them under one body. Checks should be made not only of products which can be abused, but of all drugs, both those obtained with prescription or without. In these checks, detailed examinations must be made and the active substances of the drugs must be examined.

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