INVESTIGATION OF ACETAMINOPHEN CONTENT IN OVER-THE-COUNTER MEDICINE SOLD IN JOHOR BAHRU, MALAYSIA

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DEDICATION

This dissertation is dedicated to my parents and siblings after all their endless support and love.

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ABSTRACT

The market of counterfeit medicine is slowly growing making more people to be exposed with these kind products. Counterfeit medicine can bring many adverse effects to health as well as social and economic wise. The purpose of this study is to investigate the content of over-the-counter (OTC) paracetamol that were sold in Johor Bahru area. With the growing market for substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) products including medicinal products, the statuses of these paracetamol tablets sold in market can raise some doubts. For that matter, generic OTC paracetamol 650 mg tablets brand A was chosen to be investigated. The tablets were sampled from three different type of premises namely convenient stores X, pharmacies and traditional medicine stores in four different municipal districts of Majlis Bandaraya Johor Bahru (MBJB): Pulai, Tebrau, Johor Bahru and Pasir Gudang. A few examinations and analyses were conducted to achieve this goal: a) qualitative screening examinations of product packaging (hologram and blister packaging) using Video Spectral Comparator (VSC) instrument to distinguish any SSFFC products, b) chemical profiling the ingredients of the products using Attenuated Total Reflectance – Fourier Transform Infrared (ATR-FTIR) spectroscopy to detect the presence of active pharmaceutical ingredient (API) and c) quantitative analysis of the amount of API using High Performance Liquid Chromatography coupled with Diode-Array Detector (HPLC-DAD) and the method was validated. Visual inspection of the packaging showed that apart from sample PGKU 2, all samples came from genuine source was suggested. The second screening process using ATR-FTIR found that all samples contained API as claimed (within the range of 95-105%). HPLC-DAD findings showed that the content of paracetamol could be divided into three; 1) within the range (625.14 – 671.62 mg), 2) below the range (400.87 – 616.73 mg) and 3) above the range (700.53 – 1147.50 mg). Based on these findings, each of the sample then was classified into three categories of SSFFC, that were substandard, unregistered/unlicensed and falsified. No sample was identified as unregistered/unlicensed. One sample, PGKU 2 was classified as falsified meanwhile the remaining samples were identified as substandard. In conclusion, the output of this study can be used to regulate and pharmaceutical companies and to monitor the SSFFC market.

ABSTRAK

Pasaran bagi bahan ubatan tiruan semakin membesar dan menyebabkan lebih ramai orang terdedah kepada produk ini. Barangan ubatan tiruan boleh memberi banyak kesan buruk dari segi kesihatan serta dari segi ekonomi dan sosial. Tujuan kajian ini dijalankan adalah untuk menyiasat kandungan ubat atas kaunter (OTC) *acetaminophen* atau lebih dikenali umum sebagai *paracetamol*. Dengan perkembangan pasaran bagi barangan tiruan (SSFFC) yang semakin membesar termasuk bahan produk kesihatan telah menimbulkan keraguan dalam status keasliannya. Oleh demikian itu, ubat OTC generik *paracetamol* 650 mg jenama A telah disampel di tiga jenis kedai iaitu kedai serbaneka "X", farmasi dan kedai ubat tradisional di empat daerah Majlis Bandaraya Johor Bahru (MBJB): Pulai, Tebrau, Johor Bahru dan Pasir Gudang. Beberapa pemeriksaan dan analisis telah dijalankan untuk mencapai matlamat kajian: a) pemeriksaan pembungkusan produk (hologram dan pembungkusan blister) menggunakan alat *video spectral comparator* (VSC), b) pemprofilan kimia bahan-bahan produk menggunakan spektroskopi transformasi Fourier inframerah (ATR-FTIR) dan c) kuantitatif analisis kandungan bahan aktif farmaseutikal (API) menggunakan kromatografi cecair berprestasi tinggi (HPLC-DAD). Pemeriksaan visual pembungkusan menunjukkan semua sampel adalah asli selain dari sampel PGKU 2. Pemeriksaan kedua menggunakan ATR-FTIR telah menjumpai API seperti yang dinyatakan (dalam lingkungan 95 – 105%). Keputusan HPLC-DAD menunjukkan kandungan paracetamol boleh dikategorikan kepada tiga; 1) dalam lingkungan (625.14 – 671.62 mg), 2) bawah lingkungan (400.87 – 616.73 mg) dan 3) atas lingkungan (700.53 – 1174.50 mg). Berdasarkan keputusan semua analisis, setiap sampel akan diklasifikasi kepada tiga kategori; substandard, tidak berdaftar/tidak berlesen dan palsu. Tiada sampel yang dikenali sebagai tidak berdaftar/tidak berlesen. Satu sampel, PGKU 2 dikenali sebagai palsu dan selebihnya dikenali sebagai substandard. Kesimpulannya, keputusan yang diperoleh dari analisis ini dapat membantu pihak berkuasa untuk mengawal selia syarikat farmaseutikal dan memantau pasaran SSFFC.

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LIST OF ABBREVIATIONS

API	-	Active Pharmaceutical Ingredient
ATR-FTIR	-	Attenuated Total Reflectance Fourier Transform Infrared
CDCR	-	Control of Drugs and Cosmetic Regulation
DCA	-	Drug Control Authorities
HCA	-	Hierarchical Cluster Analysis
HPLC	-	High Performance Liquid Chromatography
ICH	-	International Conference on Harmonization
LOD	-	Limit of Detection
LOQ	-	Limit of Quantification
MBJB	-	Majlis Bandaraya Johor Bahru
MOH	-	Ministry of Health
NPCB	-	National Pharmaceutical Control Bureau
NRRA	-	National or Regional Regulatory Authority
OTC	-	Over The Counter
OVD	-	Optically Variable Device
PCA	-	Principle Components Analysis
R&D	-	Research and Development
SSFFC	-	Substandard/Spurious/Falsely-labelled/Falsified/Counterfeit
USP	-	United States Pharmacopoeia
UTM	-	Universiti Teknologi Malaysia
VSC	-	Video Spectral Comparator
WHO	-	World Health Organization

LIST OF SYMBOLS

k	-	Retention factor
t_0	-	Dead time
t_r	-	Retention time of analyte
σ	-	Standard deviation of the y-intercepts of regression lines
S	-	Slope of the calibration curve

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CHAPTER 1

INTRODUCTION

1.1 Problem Background

One of the most common over-the-counter (OTC) medicine that can be obtained in Malaysia is acetaminophen or commonly known as paracetamol. It is often prescribed to treat fever, mild pain relief, muscular aches, migraine headache and osteoarthritis. A survey conducted in Penang, Malaysia showed that 75% of consumers used it for headache, and 72% of them used it for fever (Chong, Tan, & Chooi, 2017).

Since paracetamol is a cheap OTC drug that is easily obtained, it is prone to be counterfeited. Counterfeiting medicines are a serious crime. Currently there is no universally accepted definition of counterfeit medicines. World Health Organization (WHO) is currently using the term 'substandard/spurious/falsely-labelled/falsified/counterfeit' or abbreviated as SSFFC for medical products, and these products are categorized into three sub-groups; substandard, unregistered and falsified (World Health Organization). On the other hand, counterfeit medicine defined by U.S Food & Drug Administration (FDA) is fake medicine that may be contaminated or contain none or wrong active ingredient, or could have the correct active ingredient but at the wrong dose (U.S Food & Drug). Pharmaceutical Security Institute in 2011 reported that Asia has 40% pharmaceutical crime reported (Stevens & Mydin, 2013). According to a report by Ministry of Health (MOH) Malaysia, 5.2% of medicines sold over-the-counter are fake medicine (Zulkifli *et al*., 2016). Fake medicines possess many risky problems that can affect an individual's health. It may contain harmful toxic contaminants such as heavy metals (arsenic or lead) which are carcinogenic and toxic to human bodies (Stevens & Mydin, 2013). In 1995, a large number of children was admitted to hospital due to renal failure in Bangladesh due to paracetamol elixir containing diethylene glycol

(Hanif et al., 1995). The prices of fake medicines are usually lower than the standard pricing, hence consumers are more likely to purchase the fake medicines causing a substantial loss percentage for the pharmaceutical industry (Blackstone, Fuhr, & Pociask, 2014).

Several technologies are being used to combat these problems. It includes as the usage of visible markers or holograms, barcodes, 2D datamatrix code and radiofrequency identifications (Hall, 2012). In 2005, Malaysia introduced Meditag™ program that requires all Drug Control Authorities (DCA) registered products to bear holographic security device (Zulkifli *et al.*, 2016). On the other hand, several techniques have been used to determine paracetamol content in pharmaceutical formulations or biological samples. For examples; Fourier transform infrared spectroscopy (FTIR) with the result of percentage recovery between 98% to 99% in solid paracetamol samples (Mallah *et al.*, 2015) and UV-Vis spectrophotometry with percentage recovery between 101.67% to 102.43% in paracetamol and nabumethone combined tablet samples (Rote *et al.*, 2012). Altun (2002) performed analysis of paracetamol using high performance liquid chromatography (HPLC) with percentage recovery of 101.62% in a mixture of paracetamol, caffeine and dipyrone samples, while Calinescu *et al.* (2012) obtained recovery results in the range 99.6% to 102.8% in paracetamol and its impurities samples using the same instrument.

This present study, a few examinations were conducted to investigate the status of OTC paracetamol tablets Brand A that were sold in four municipal districts of Majlis Bandaraya Johor Bahru (MBJB); Pulai, Tebrau, Johor Bahru and Pasir Gudang. With the ever-growing population people living in MBJB areas, more people are exposed with the risk of getting SSFFC products on their hands.

1.2 Problem Statement

Amount of SSFFC medical products are on the rise on the market despite many efforts being done by the authorities to combat it. Falsified or substandard medicines can bring many adverse health effects towards its consumers, as well as

economic effects (Aminu & Gwarzo, 2017; Burki, 2010; Newton *et al.,* 2010). Due to its lower prices as compared to its genuine products, the public tend to choose the fake instead (Dégardin *et al.*, 2014). Lacked information on qualitative and quantitative analyses regarding these SSFFC medicines making the public to be less aware of these rising problems. Up until 2018, there is no study have been done on the status of Brand A whether in Johor Bahru or Malaysia. This study will help to provide more information on the status of paracetamol tablets and to bring more awareness towards the public.

1.3 Research Goals

1.3.1 Research Objectives

The aim of the study is to investigate on the content of over the counter (OTC) paracetamol that were sold in Johor Bahru, Malaysia. The objectives of the research are:

(a) To qualitatively screen packaging and the tablet of paracetamol 650 mg Brand A using Video Spectral Comparator instrument for distinguishing any possible SSFFC products

(b) To qualitatively screen the active and non-active ingredients of paracetamol 650 mg Brand A by using Attenuated Total Reflectance – Fourier Transform Infrared Spectroscopy instrument.

(c) To quantitatively determine the amount of active ingredient (acetaminophen) in paracetamol 650 mg Brand A using High Performance Liquid Chromatography coupled with Diode-Array Detector.

1.4 Scopes of study

This present research is involving paracetamol 650 mg tablet brand A acquired from different type of premises namely convenient stores X, pharmacies and traditional medicine stores. Four municipal districts of MBJB were chosen as sampling locations. This study was conducted from September until December 2018. Regardless multiple contacts were made concerning getting direct samples manufacturers of paracetamol 650 mg Brand A, no response was given. Screening of the sample packaging was done using Video Spectral Comparator (VSC) to check for its authenticity. Chemical profiling of the sample was also done using Attenuated Total Reflectance – Fourier Transform Infrared Spectroscopy (ATR-FTIR). Paracetamol content in the sample also was analyzed and quantitated by using High Performance Liquid Chromatography coupled with Diode-Array Detector (HPLC-DAD). At the end of this study, the samples were classified into three different categories as described by World Health Organization (WHO); substandard, unregistered/unlicensed and falsified.

1.5 Significance of study

Findings that were obtained from this study can be used as a useful data for related authorities to regulate pharmaceutical companies and manufacturers to meet the quality and standards that have been set up. The data also can be used by the authorities to monitor the counterfeit market of medicinal products.

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