COUNTERFEIT PARACETAMOL TABLET ANALYSIS AND ITS DISCRIMINATION USING FOURIER TRANSFORM INFRARED SPECTROSCOPY COUPLED WITH CHEMOMETRICS TECHNIQUES

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This dissertation is especially dedicated to my late mother
Rosnah binti Bandu, father and siblings

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ABSTRACT

Paracetamol tablet is a well-known over the counter medicine and is widely available for consumers. For that reason, the originality of paracetamol tablets sold in the market is questionable. Even though pharmaceutical measures for ensuring that the manufactured medicines would comply fully with the standards were taken, cases involving counterfeit paracetamol products have been increasingly reported throughout the world. Hence, this present cross-sectional research which analysed BRAND X 500 mg paracetamol tablets sampled from varying outlets of different districts in Johor appears important for the relevant authorities to understand the current status of authenticity of such product and also for consumer protection. In this research, while the quality of samples was determined based on their active pharmaceutical ingredient (API) amounts using validated High Performance liquid chromatography (HPLC), their organisation and classification were done by Fourier Transform Infrared Spectroscopy (FTIR) coupled with Principal Component Analysis (PCA) and Linear Discriminant Analysis (LDA). Quality examination of the samples indicated a variability in qualities; (1) in-range (475-525 mg), (2) lower than range (324-466 mg) and (3) higher than range (532-598 mg). These indications were made according to British Pharmacopoeia (2013) which stated that preparation of paracetamol products must have 95-105% of paracetamol content. Despite being categorically different in the amounts of paracetamol contents as well as districts and outlets, PCA and LDA showed that all the samples were convoluted into a single group, which supports the idea that all BRAND X 500 mg paracetamol tablet samples in this present research may originate from a common source/manufacturer. However, discrimination between the lower than range and the higher than range samples by PCA and LDA (accountable for 91% of variances and 93% correct classification respectively) had resulted in successful separation between them. Therefore, analysis of BRAND X 500 mg paracetamol tablet samples and their discrimination prove to be significant for providing empirically robust scientific evidence for the relevant authorities to prevent increasing flooding of its counterfeit products especially in Malaysia.

ABSTRAK

Tablet parasetamol merupakan ubat terkenal yang boleh dibeli tanpa nasihat doktor di kebanyakkan kedai, oleh kerana kewujudannya yang meluas dan mudah didapati oleh pengguna menyebabkan keasliannnya dipersoalkan. Walaupun tindakan farmaseutikal untuk memastikan ubat yang dihasilkan mematuhi–standard yang di tetapkan telah diambil, kes-kes berkaitan pemalsuan produk-produk parasetamol dilaporkan semakin meningkat diseluruh dunia. Justeru itu, kajian keratan lintang ini yang dijalankan untuk menganalisis tablet parasetamol 500 mg JENAMA X yang disampel daripada pelbagai jenis kedai dan daerah yang berbeza di Johor adalah penting bagi pihak berkuasa yang berkaitan memahami status terkini keaslian produk tersebut dan juga untuk perlindungan pengguna. Dalam kajian ini, sementara kualiti sampel ditentukan berdasarkan kandungan farmaseutikal aktif (API) menggunakan kromatografi cecair berprestasi tinggi (HPLC), organisasi dan klasifikasi sampel dilakukan menggunakan spektroskopi transformasian fourier inframerah (FTIR) digandingkan dengan analisis komponen utama (PCA) dan analisis diskriminan linear (LDA). Pemeriksaan kualiti sampel menunjukkan kepelbagaian dalam kualiti, iaitu (1) dalam kelompok (475-525 mg), (2) rendah berbanding kelompok (324-466 mg) dan tinggi berbanding kelompok (532-598 mg). Indikasi-indikasi tersebut dibuat berpandukan British Pharmacopoeia (2013) yang menyatakan bahawa pembuatan produk parasetamol haruslah mempunyai 95-105% kandungan parasetamol. Walaupun berbeza secara kategori dari segi kandungan parasetamol serta daerah dan kedai, analisis menggunakan PCA dan LDA menunjukkan bahawa kesemua sampel berlingkar menjadi satu kumpulan (sama), seterusnya menyokong pandangan bahawa tablet parasetamol 500 mg JENAMA X yang di sampel dalam kajian ini berkemungkinan berasal daripada sumber/ pengilang yang sama. Namun, diskriminasi antara sampel rendah berbanding kelompok dan sampel tinggi berbanding kelompok menggunakan PCA dan LDA (membawa kepada 91% variasi dan 93% ketepatan klasifikasi secara respektif) berjaya menghasilkan ~~n~~ pemisahan antara dua kelompok tersebut. Oleh itu, analisis sampel 500 mg JENAMA X dan diskriminasinya adalah terbukti penting untuk memberikan bukti saintifik emperik yang kukuh untuk kegunaan pihak berkuasa yang berkaitan bagi mengelakkan peningkatan limpahan produk-produk JENAMA X yang palsu terutamanya di Malaysia.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

4-AP	-	4-aminophenol
API	-	Active pharmaceutical ingredient
ATR-FTIR	-	Attenuated Reflectance - Fourier Transform Infrared
BQ	-	Benzoquinone
DF	-	Discriminat Function
DNA	-	Deoxyribonucleic acid
e.g.	-	Exempli gratia (for example)
HPLC-UV	-	High Performance Liquid Chromatography-Ultraviolet
HQ	-	Hydroquinone
LDA	-	Linear Discriminant Analysis
mg	-	Miligram
mg/kg	-	Miligram per kilogarm
mL	-	Mililitre
NIR	-	Near Infrared Spectroscopy
OTC	-	Over the counter
p	-	Para
PC	-	Principal Component
PCA	-	Principal Component Analysis
		Spectroscopy
UK	-	United Kingdom
USA	-	United States of America
		Visible
viz.	-	Videlicet (namely)
WHO	-	World Health Organisation

LIST OF ABBREVIATIONS

µg/mL	-	Microgram per mililitre
µL	-	Microlitre
µm	-	Micrometre
cm^{-1}	-	Centimetre per unit distance/metre
DTGS	-	Deuterated triglycine sulphate
kg	-	Kilogram
km	-	Kilometre
LOD	-	Limit of detection
LOD	-	Limit of quantification
mg	-	Miligram
MIR	-	Mid Infrared RegioN
mm	-	Milimetre
n	-	Number of samples
nm	-	Nanometre
Psi	-	Pound-force per square inch
R^2	-	Coefficient of determination
RSD	-	Relative Standard Deviations
S/N	-	Signal-to-noise ratio
ZnSe	-	Zinc selenide

LIST OF SYMBOLS

%	-	Percentage
>	-	More than
®	-	Registered trademark

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Background of Study

During the past few decades, the production and distribution of pharmaceutical products have increased tremendously, in tandem with the ever-growing human population throughout the world (Tannoury and Attieh, 2017). Among others, antipyretic medications like paracetamol and ibuprofen have been made available over the counter for maintaining human health and well-being (Lau *et al.*, 2016). Such medications must be of standard quality, safe and effective (Custer *et al.*, 2015). While stringent pharmaceutical measures for ensuring that the manufactured medicines would comply fully with the prevailing standards, instances wherein counterfeit medicines are recovered in the market has been gaining notoriety (Degardin *et al.*, 2015). Review of literature reveals varying definitions for counterfeit drugs, with the one provided by the World Health Organisation (WHO) acquires popularity among clinicians (Jackson *et al.*, 2010). The same authors indicated that the WHO defines "counterfeit medicines as those that are deliberately and fraudulently mislabelled with respect to identity or source; their quality is unpredictable as they may contain the wrong amount of active ingredients or no active ingredients". The use of counterfeit medicines has been advocated as the probable culprit for a number of clinical conditions such as liver and kidney failures, especially when their concentrations exceeded that of the prescribed therapeutic ranges (Nor Aripin and Choonara, 2009). On the other hand, insufficient amount of active ingredients in counterfeit medicines

may result in ineffective treatment (Majid, 2008). In this context, it has been argued that such counterfeit medicines are "manufactured in clandestine laboratories with no possibility of control" (Nayyar *et al.*, 2012) although the truth remains unclear.

Paracetamol (acetaminophen, N-acetyl-p-amino-phenol, $C_8H_9NO_2$) has been regarded as the first line therapy for mild acute or chronic pain that is not relieved by non-pharmacological approaches like reassurance, rest, ice or heat pack (Belal *et al.*, 2009), and highly demanded by public as the practice of self-medication becomes common (*British Pharmacopoeia*, 2012). It is available in various forms ranging from tablets, capsules, oral solution, oral suspension, and suppositories (Wilson *et al.*, 2011). The recommended dosage of paracetamol for adults ranges between 500 mg to 1000 mg for every 4 to 6 hours, up to a total daily dose of 4000 mg. As for children, the recommended dosage is 15 mg/kg at every 4 to 6 hours, up to a total daily dose of 2400 mg (Pasero and Stannard, 2012). In this context, British Pharmacopoeia (2012) prescribed that a preparation should contain 95-105% of the stated amount of paracetamol for it to exert its effectiveness. Being one of the widely available non-prescription medicine, paracetamol has been reported as the most common drug used for self-poisoning in the United Kingdom as well as in many other countries (Simkin *et al.*, 2012) including Malaysia (Fathelrahman *et al.*, 2008). Hepatic injury has been reported as the principal toxic effect of an extensive paracetamol misuse and overdose (Tan *et al*., 2015).

Interestingly, the number of cases involving counterfeited paracetamol has been increasingly reported in the literature. For example, GlaxoSmithKline in Kenya had discovered knock-offs of its best painkillers Panadol extra in the market (Business Daily, July 31, 2009), the death of 109 children in Nigeria upon receiving counterfeit paracetamol (Majid, 2008), as well as undetectable amount of paracetamol in paracetamol syrup in Pakistan (Ahmed, 2011). While there is no specific scientific report on counterfeit paracetamol in Malaysia, the Sarawak State Health Department indicated that Panadol is one of "the commonly faked brands in the market" (Borneo Post online, May 20, 2015). Therefore, specific empirical study focusing on this aspect in Malaysia merits public health consideration.

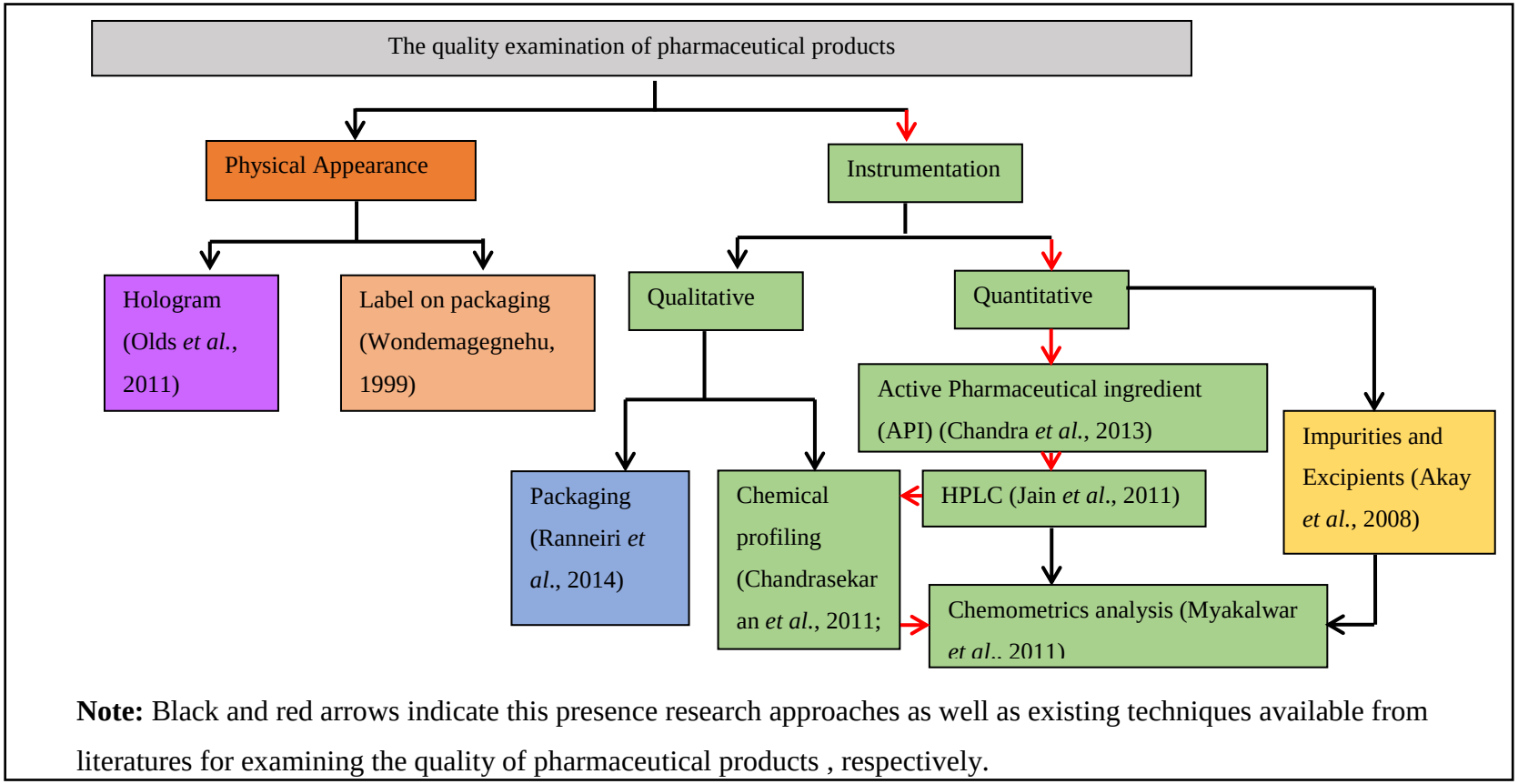
In addition to possible ineffectiveness of these substandard paracetamol products to confer the desired pharmacological effects, the possibility that they contain higher amount of impurities e.g. 4-aminophenol (4-AP) (Akay *et al.*, 2008) cannot be ruled out. Apart from being nephrotoxic and teratogenic (Calinescu *et al.*, 2012) 4-AP may undergo further degradation to form the genotoxic and carcinogenic benzoquinone (BQ) (Das *et al.*, 2010) and hydroquinone (HQ) (DeCaprio, 1999). Exposure towards HQ has been associated with chromosomal aberrations, abnormal mitoses, formation of micronuclei, aneuploidy, deoxyribonucleic acid (DNA) strand breakage, and sister chromatid exchange (Hebeda *et al.*, 2012). Moreover, liver and stomach neoplasia as well as mononuclear cell leukaemia have also been attributed to the long term exposure of HQ (DeCaprio, 1999). Apart from health implications, counterfeit paracetamol may lead to substantial economic loss (Degardin *et al.*, 2014) and violation of consumer rights (Deisingh, 2004).

1.2 Problem Statements

Studies on the quality of paracetamol tablets sold by retail pharmacies and/or supermarket in Malaysia were last reported in 2011, indicating variability in their quality (assessed by Near Infrared Spectroscopy (NIR)) (Said *et al.*, 2011) as well as physical characteristics (*viz*. weight, hardness, friability, disintegration and dissolution) (Chandrasekaran *et al.*, 2011). In addition to the seven years elapsed, specific research focusing on the concentration of its active pharmaceutical ingredient (API) which is paracetamol, in the popularly marketed 500 mg tablets, especially those of blister packaging, sold by various types of outlets (e.g. established pharmacy, convenience store and petrol station, as well as local grocery shops) at different locations within Malaysia remains unreported, so far. The only available reliable source of literature being the scarce press statement by the local authority such as that reported by Borneo Post Online (May 20, 2015). Moreover, because in Malaysia the 500 mg paracetamol tablets are commonly sold as loose blister packaging (that does not have hologram attached to it), the authenticity of this pharmaceutical product can be questionable. Such a lack of information may deprive public confidence on the

safety and effectiveness of consuming the 500 mg paracetamol tablets, accentuating the needs to undertake this empirical study to address such pertinent issue.

In this regard, having the ability to differentiate the authentic and counterfeit 500 mg paracetamol tablets appears imperative for consumer protection. Despite being one of the popular over the counter medicine, review of literature reveals only two specific studies focusing on the use of chemometric techniques for differentiating paracetamol products from different manufacturers (Khanmohammadi *et al*., 2010; Said *et al*., 2011); one of which differentiated paracetamol products between Malaysia and the United Kingdom (Said *et al*., 2011). While developing a database to differentiate paracetamol products, Said *et al*. (2011) indicated substantial variability in the quality of the tablets purchased from the Malaysian pharmacy and supermarkets. Considering (1) such indication, and (2) because assuming that the current quality of paracetamol in Malaysia would remain the same can be misleading, providing empirically robust scientific evidence using principal component analysis (PCA) and linear discriminant analysis (LDA) for differentiating the genuine and counterfeit 500 mg paracetamol tablets from different districts in Johor, Malaysia attempted here, acquires forensic significance. Figure 1.1 represent the conceptual frameworks of this present research.



Note: Black and red arrows indicate this presence research approaches as well as existing techniques available from literatures for examining the quality of pharmaceutical products , respectively.

Figure 1.1 The conceptual framework of this present research

1.3 Objective of Study

The objectives of this present cross-sectional research conducted in the ten districts of Johor, Malaysia were:

1. To determine the concentrations of paracetamol in BRAND X 500 mg paracetamol tablets sampled from the different outlets.
2. To examine the quality of BRAND X 500 mg paracetamol tablets according to their paracetamol contents.
3. To study the organisation and classification of BRAND X 500 mg paracetamol tablets among the different outlets and districts.

1.4 Scope of Study

This cross-sectional present research was conducted during January to February 2017, involving BRAND X 500 mg paracetamol tablets (blister packaging) purchased from the different outlets (established Pharmacy A, Petrol Station A and Convenience Store A as well as Local Grocery Shops A-C) in all the ten districts of Johor, Malaysia. The districts were Johor Bahru, Mersing, Segamat, Pontian, Kota Tinggi, Kulai, Tangkak, Kluang, Muar and Batu Pahat. Since, our attempts to obtain directly the genuine BRAND X 500 mg paracetamol tablet samples were ignored by the manufacturer, direct comparison with those purchased from the different outlets could not be made. The concentration of paracetamol in the tablets was analysed using the High Performance Liquid Chromatography (HPLC) with Ultraviolet Visible (UV) detector, following method validation. Parameters standardised during method validation included linearity and sensitivity as well as repeatability and reproducibility of the procedure. All the samples were then divided into those of containing in-range, lower than range and higher than range paracetamol contents, as prescribed by the British Pharmacopeia (2012). The samples were analysed using Attenuated Reflectance - Fourier Transform Infrared Spectroscopy (ATR-FTIR) for obtaining

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