CLASSIFICATION OF HERBAL MEDICINES:

QUALITY AND SAFETY

A thesis submitted in partial fulfilment

of the requirements for the award of

Doctorate in Pharmacy

Alexandra Curmi

Department of Pharmacy

University of Malta

2017

University of Malta
L-Università ta' Malta

UNIVERSITY OF MALTA
FACULTY/INSTITUTE/CENTRE/SCHOOL_____

DECLARATION OF AUTHENTICITY FOR DOCTORAL STUDENTS

Student's I.D. /Code _____

Student's Name & Surname _____

Course _____

Title of Dissertation/Thesis

_____

_____

_____

I hereby declare that I am the legitimate author of this Dissertation/Thesis and that it is my original work.

No portion of this work has been submitted in support of an application for another degree or qualification of this or any other university or institution of higher education.

I hold the University of Malta harmless against any third party claims with regard to copyright violation, breach of confidentiality, defamation and any other third party right infringement.

☐ As a Ph.D. student, as per Regulation 49 of the Doctor of Philosophy Regulations, I accept that my thesis be made publicly available on the University of Malta Institutional Repository.

☐ As a Professional Doctoral student, as per Regulation 54 of the Professional Doctorate Regulations, I accept that my dissertation be made publicly available on the University of Malta Institutional Repository.

☐ As a Doctor of Sacred Theology student, as per Regulation 17 of the Doctor of Sacred Theology Regulations, I accept that my dissertation be made publicly available on the University of Malta Institutional Repository.

☐ As a Doctor of Music student, as per Regulation 24 of the Doctor of Music Regulations, I accept that my dissertation be made publicly available on the University of Malta Institutional Repository.

_____ _____

Signature of Student Date

* *Tick applicable paragraph.*

11.06.2015

To all my dear family,

But most especially to my husband Clifton

And

My two daughters Michela and Katrina.

Acknowledgements

This dissertation would not have been completed without the consistent support and guidance of Professor Lilian Azzopardi, Head of Department of Pharmacy my academic supervisor who supported me throughout the entire duration of the project.

My sincere gratitude and appreciation also goes to my advisor, Professor Everaldo Attard, Associate Professor Agricultural Chemistry and Pharmacognosy at the Institute of Earth Systems for his valuable advice and continuous support throughout and Co-supervisor Dr Janis Vella from the Pharmacy Department.

My thanks also goes to Helen Vella from the Medicines Authority and Ms. Lara Pace statistical analyst and visiting Lecturer at the Department of Statistics, University of Malta for helping me with the statistics.

Finally, I extend my thanks to my family namely my husband Clifton Curmi who patiently accompanied me throughout this project.

Abstract

Classification of herbal medicines: Quality and Safety

The use of herbal medicines is on the increase. One of the possible reasons for the vast use of herbals may be due to the misconception that herbals are ‘natural’ and hence automatically safe.

The aims of this research were to evaluate knowledge and confidence of pharmacists and health shop employees with regards to use of herbal medicines, to evaluate perception and attitudes of patients towards herbals and to analyse classifications of herbals within the EU from a regulatory aspect.

A questionnaire was disseminated to 107 pharmacists and 14 health shop employees to determine knowledge and perception on herbal products and classification of herbal medicines. Another questionnaire was disseminated to 150 members of the general public, to determine their perception and attitudes towards the use of herbal products. A review on how herbal medicines are regulated within the EU was carried out.

Pharmacists’ attained a mean knowledge score of 27 out of 56, while health shop employees obtained a mean knowledge score of 28 out of a maximum score of 56. Fifty six percent of the public interviewed co-administer herbal and conventional medicines and 65% prefer to seek advice about herbals from the pharmacist. There are still loopholes which need to be addressed from a regulatory aspect despite efforts to regularise herbal medicines.

The results indicate the need to empower pharmacists and health shop employees with scientific information about herbal medicines to help improve their knowledge. Co-administration of herbal medicines with conventional medicines may jeopardise patient safety and such instances require a higher level of pharmacist intervention.

Keywords: herbal medicines, legislation, safety, knowledge, pharmacists, health shop employees.

TABLE OF CONTENTS

.

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

DSHEA	Dietary Supplement Health and Education Act of 1994
EMA	European Medicines Agency
FDA	Food and Drug Administration
GACP	Good Agricultural Collection Practice
GMP	Good Manufacturing Practice
HMP	Herbal Medicinal Product
HMPC	Committee on Herbal Medicinal Products
MA	Marketing Authorization
MCAST	Malta College of Arts Science and Technology
MCCAA	Malta Competition and Consumer Affairs Authority
PAH's	Polycyclic Aromatic Hydrocarbons
PAs	Pyrrolizidine Alkaloids
QDG	Quality Drafting Group
THMP	Traditional Herbal Medicinal Product
THR	Traditional Herbal Registration
TUR	Traditional Use Registration
UNECE	United Nations Economic Commission for Europe
WEU	Well Established Use
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background: History of Herbal Medicinal Products

Plants and plant-derived preparations have been used for their medicinal properties for centuries. The earliest documented is in 1550 BC by ancient Egyptians reporting the use of saw palmetto for urinary symptoms (Wilt et al, 1998) and Hippocrates in the 5th century BC stating the use of St. John's wort for mood ailments (Blumenthal et al, 2003).

Herbal medicines were at a time, the only form of remedy to treat ailments. Due to the fact that there was insufficient information about why illnesses developed and which plants were used to cure these illnesses, medicinal plant use was based on experience. Eventually, the reason why medicinal plants helped to treat certain diseases became understood and the use of herbal medicinal plants became based on explicatory facts (Petrovska, 2012). About 100 years ago, synthetic drugs took over, rendering the use of herbal medicine almost extinct in the UK and the USA, and less in India, China and Germany (Spiteri et al, 2013). Today traditional medicine is becoming popular again. According to Global Industry Analysts the herbal supplements and remedies market is predicted to exceed $105 billion by 2017, with Europe occupying the largest market share (Global Industry Analysts Inc, 2015).

The increase in use of herbal products could be attributed to various factors, as highlighted in Table 1.1.

Table 1.1 Factors contributing to increase in use of herbal products (Adapted from Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Frontiers in Pharmacology. 2014;(4):1-10).

Public Interest	**Drug Related Issues**	**Other Factors**
Interest in alternative medicines Increase in self-medication Willingness to choose complementary alternative methods Increase in preventative healthcare Aging population and increase in herbal consumption	High cost of conventional medicines Undesirable side effects caused by conventional medicines Lack of responsiveness of conventional medicines to chronic disease states	Various marketing strategies of manufacturing companies and the media

In Malta, like in other EU member states, the last decade has been characterised by an increased interest and demand for herbal products. Such an interest resulted in increased queries from patients about the use of herbal products prompting a debatable question of whether people handling herbal products including pharmacist and health shop employees are prepared and knowledgeable enough to answer such queries and hence give the right advice and ensure patient safety (Spiteri et al, 2013).

1.2 Historical overview of EU regulation

A contributing factor to why the use of herbal products increased could be attributed to the misconception that since these products are ‘natural’ they are automatically ‘safer’ than conventional medicines. The increase in use of herbal products has been accompanied by an increase in the number of adverse events and herb–drug interactions

being reported (Shaw et al, 2012). Herbal products have been reported to cause adverse events of different severities including some resulting in serious medicinal problems, and even death (Ekor, 2014). This was evidenced by reports of poisonings following the consumption of herbal products (Cosyns et al, 1994; Vanherweghem and Degaute, 1998; Ernst, 2002). After these reports it became evident that the safety and efficacy of all traditional medicines, complementary and alternative medicines, and quality control, were not being tested or evaluated and this caused concerns for both health authorities and the public throughout the world (WHO, 2004).

In an attempt to try to address the situation, health authorities developed legislative measures to try and safeguard the public better. This was done through the development of EU Directive 2004/24/EC, since obligations of EU Directive 2001/83/EC relating to efficacy could not be satisfied by herbal medicinal products. In March 2004, EU Directive 2004/24/EC was adopted. This Directive introduced a new simplified registration called Traditional Herbal Registration which incorporated Traditional Herbal Medicinal Products (THMPs). As the word "traditional" implies, for a herbal medicine or "corresponding" product to fall in this category, evidence of its traditional medicinal use for 30 years must be provided, 15 of which must be in the EU (Fan et al, 2012).

The European Directive 2004/24/EC was given a time frame of 7 years and took full effect on 30th April 2011, allowing manufacturers to come up to date with legal formalities. Once this time frame expired it became illegal for companies to sell manufactured unlicensed herbal medicines within Europe without the appropriate license or a Marketing Authorization (MA) or a Traditional Herbal Registration (THR). The response that the new amended directive 2004/24/EC had across the EU member states was varied between countries. In countries where there was already a functioning

predefined legislation of markets such as Germany, France and Austria, Directive 2004/24/EC helped to enforce these markets, while in countries such as Netherlands and UK whose regulations were more lenient, these became more meticulous.

A harmonised system of regulations was created, allowing more free movement of herbal products within the EU member states. This directive saw the introduction of a new entity - the Committee for Herbal Medicinal Products (HMPC) .

This committee which was established by the European Medicines Agency (EMA), had two tasks (i) to establish community monographs for traditional herbal medicinal products, (ii) to facilitate registration and harmonisation of THMPs by preparing a draft list of herbal substances used medicinally, not considered to be harmful under normal conditions of use (EU Regulation (EC) No 726/2004).

1.3 Classification and definition of herbal products

In the European Union herbal products may be classified as foods, cosmetics or medicines as can be seen in Figure 1.1. This research focussed on products classified as medicines which according to local legislation are available only through community pharmacies and food supplements and cosmetics are available also through health shops.

The EU Directive 2001/83/EC defines a medicine as “any substance or combination of substances presented as having properties for treating or preventing disease in human beings” or “any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis” (EU Directive, 2001).

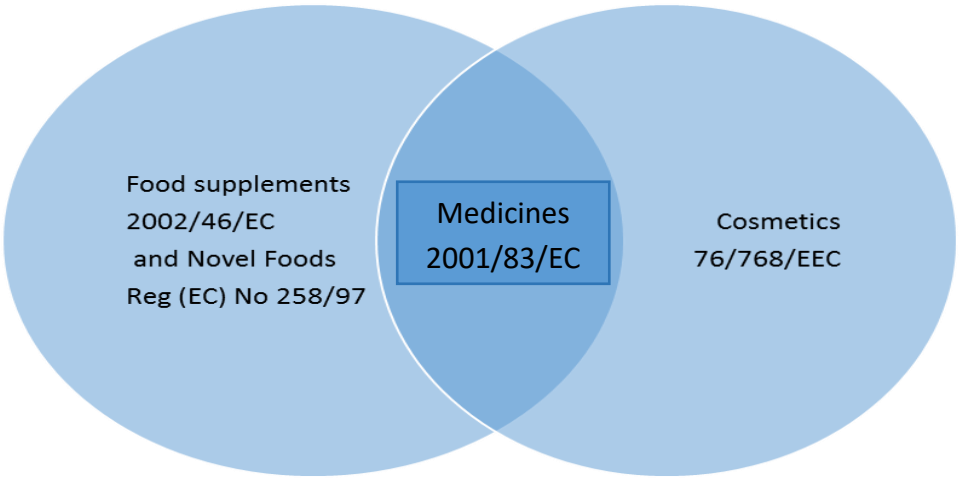


Figure 1.1: Classification of herbal products

Adopted from Attard E. Herbal Medicinal Products. Is your product a herbal medicine? 2010[1]

Food supplements are defined as "foodstuffs, the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect alone or in combination, marketed in dose form, namely in forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop-dispensing bottles and other similar forms of liquids designed to be taken in measured small quantity units" (EU Directive, 2002).

A cosmetic is defined as any substance or preparation intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing

[1] Personal communication by Attard E. 2010: Herbal Medicinal Products, Is your product a Herbal Medicine? The Palace Sliema, April 2010.

their appearance and/or correcting body odours and/or protecting them or keeping them in good condition (EU Directive, 76/768/EEC).

This classification on whether to include a product as being a food supplement, a medicine or a cosmetic depends on:

- The mode of action
- The impact on physiological processes
- The mode of administration

Studies investigating mode of action of herbal products and their preparations have revealed that herbals are composed of various active biological components some of which show therapeutic activities (such as amino acids, alkaloids and cardiac glycosides) while others exert physiological activities (such as vitamins, minerals and other nutrients) (Silano et al, 2011).

While the subdivision of herbal products into cosmetics, foods and medicines can seem simplistic, difficulties may present when classifying a product as a food or medicine because these botanicals exist naturally as heterogenic species (i.e. made up of different biologically active compounds) and this makes identification of specific individual parts within the same species a hard task. The way that medical, governmental, national authorities and influences of society have all contributed to the way these products are being used differently throughout the world.

Figure 1.2 is a decision tree which helps applicants decide whether products fall within the definition of herbal medicinal products or traditional herbal medicinal products.

A herbal medicinal product (HMP) is defined as "any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations" (EU Directive, 2001).

Herbal medicines can be placed on the market using one of the following methods:

1) Full Marketing Authorisation

2) Well-established use herbals (WEU)

3) Traditional Herbal Medicinal Products (THMPS)

Within the herbal products classified as medicines, EU Directive 2001/83/EC also distinguishes between herbal substances and herbal preparations as seen in Table 1.2.

Table 1.2: Definitions of herbal substances and herbal preparations

Herbal substances
All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).
Herbal preparations
Preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates

Adopted from EU Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal. 2001; 311:67–128.

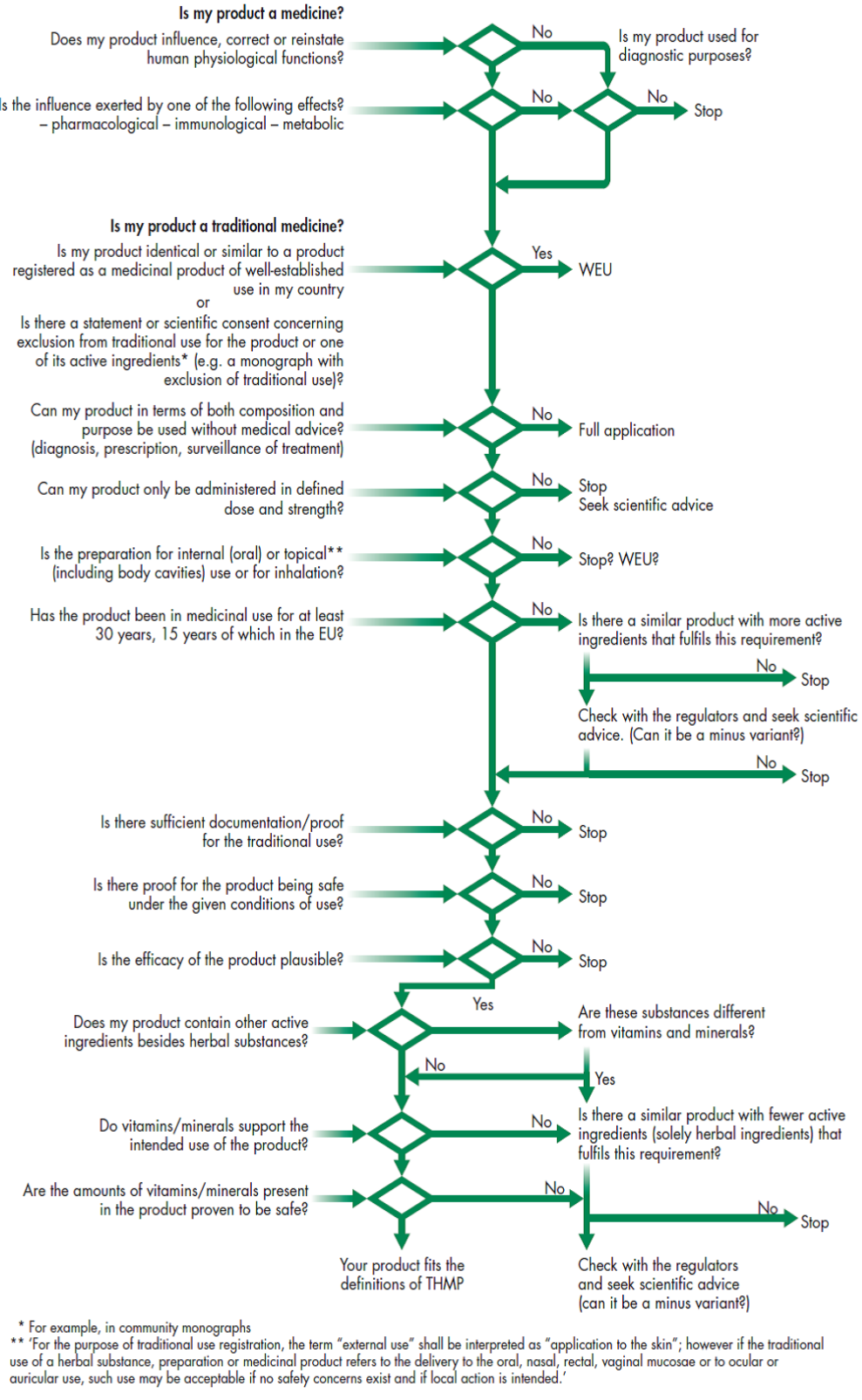


Figure 1.2: Decision tree assisting whether a herbal product is classified as a medicine Adopted from Brendler T, Philips L. A practical guide to licensing herbal medicinal products. 1st ed. London: Pharmaceutical Press; 2009.

1.3.1 Full Marketing Authorisation

Application through Full Marketing Authorization is referred to in article 8(3) of Directive 2001/83/EC. While this is the normal procedure utilised by new medicinal products (including new chemical entities), to be placed on the market, it is not a common pathway utilised by manufacturers to register herbal medicinal products under. The reason is that this type of application must provide quality related documentation including pharmaceutical tests, non-clinical (toxicological and pharmaceutical studies), efficacy documentation through clinical trials that comply with the relevant guidelines of the therapeutic area being treated, and substantial safety data that comply with the necessary guidelines, showing a highly favourable benefit to risk ratio (Brendler and Philips, 2009). There are various levels of evidence as can be defined by the 'Final Concept Paper on the Implementation of Different Levels of scientific Evidence in Core Data for Herbal Medicinal Drugs' (EMA, 2004). The highest level of evidence is represented by Grade A (Evidence 1a, 1b) which requests a minimum of one randomized clinical trial as part of the literature of the product. Grade B (Evidence IIa, IIb, and III) does not necessitate a randomized clinical trial but proof of evidence is based on well executed clinical studies. Grade C Evidence (IV) proof of efficacy is based on evidence that is provided by an expert panel and/ or competent authorities with no requirements of any studies. A Full Marketing Authorisation necessitates a complete dossier and development procedure accompanied by various levels of evidence. Based on the efficacy, strong health claims can be adopted resulting in more available options regarding marketing and advertising issues. Such a system of registration is offset by high costs incurred in development and registration of the product (Brendler and Philips, 2009).

1.3.2 Traditional Herbal Medicinal Product

Another method of placing a herbal medicinal product on the market is the Traditional Herbal Medicinal Product (THMP). This category of registration includes all herbal products that cannot satisfy the efficacy requirements for marketing authorization, but are supported by a long tradition of medicine use. This method is based on the main criteria of showing 30 years of traditional use of the product in question. In this regard, the Committee on Herbal Medicinal Products (HMPC), which was set up in 2004, plays a vital role in the determination of THMP status. One of the roles of the HMPC is to establish valid herbal monographs and profiles of herbal medicinal products claiming THMP. In 2006, a working group was set up to assist the HMPC in establishing monographs. This was called the Working Party on Community Monographs and Community List, and besides the previous responsibilities, this working group had additional tasks such as providing guidance to WEU and THMP systems of application, besides also dealing with issues related to safety. The criteria for applying for a THMP requires demonstration of traditional use of the herbal product for a period of 30 years with at least 15 years within the EU. EU Directive 2004/24/EC states that demonstration of traditional use can be applied for the herbal medicine in question or 'corresponding' product meaning that this can apply to products having same active ingredient, same (or similar) use, administration and strength.

THMP's are available as either (i) mono-products meaning that they contain a single substance or preparation or (ii) combinations meaning containing a number of active substances. When it comes to combinations containing different active substances, only THMP with mono-products or combination products with few active ingredients is required and are generally accepted. Plausibility and efficacy can be enhanced by

minimizing the quantity of active substances present in herbal combinations. This practice is known as minus variants (Brendler and Philips, 2009).

Table 1.3: Characteristics for an HMP to be marketed as a THMP.

Use	Without medical supervision For diagnostic purposes For prescriptions or monitoring treatment
Mode of administration	Oral route External route Inhaled route
Time frame	Must have been used for at least 30 years or more, 15 of which must have been in the EU.
Other data necessary	Other evidence that the product is safe to be used under the specified conditions and Efficacy evidence to show its long standing use.

Efficacy of products placed as THMP is not required but is based on traditional use. This should be accompanied by information related to safety and quality issues including manufacturing, analytical and stability data. The THMP system allows for reference to be made to corresponding or community monographs. Compared to full marketing authorization, the THMP system is less expensive but it does not allow strong health claims but only general ones (Brendler and Philips, 2009).

1.3.3 Well established use

One of the common pathways that HMPs are regularised by in the EU, is the well-established medicinal use. This type of authorisation is referred to in article 10a of EU

Directive 2001/83/EC. This article defines what the term ‘well-established medicinal use’ is in pharmaceutical legislation and implies that ‘old’ medicinal products and herbal medicinal products that have extensively been used clinically within the European Union can be regularised in this category (Claeson, 2014).

There are various factors which must be considered to determine whether a product can be classified under the system of Well Established Use (WEU). EU Directive 2003/63/EC defines WEU and provides guidance regarding requirements for WEU category (EU Directive, 2003). Criteria which determine whether a product can be classified as a WEU herbal product are seen in Table 1.4.

Table 1.4: Characteristics for an HMP to be marketed as a WEU

Quantitative issues of the utility of the substance
Level of scientific interest
At least 10 years use from first and systematic use as a medicinal product
Issue of coherence of scientific data

Another criteria requested for use of WEU is that of providing evidence related to efficacy issues through bibliography. This should include safety issues, literature review and studies including epidemiological studies. Any documentation containing both favourable and non-favourable should be included. Reference to other products containing the same ingredients is considered to be an important issue in WEU system. It may be concluded that for WEU registration, a full dossier is necessary, backed by bibliographic data. Similar to THMP reference to similar products and community monographs can be made including the practice of minus variants. Stronger health

claims can be made based on proven efficacy compared to THMP, and this allows wider marketing options. WEU registration and development is more expensive compared to THMP.

Table 1.5: Types of applications for a herbal medicinal product to reach the market in the EU.

Type of Application	Source of legislation	Main Characteristics
'**Full Marketing Authorisation'**	Directive 2001/83/EC Article 8 (3)	New Medicinal Product /Single Entity Quality Documentation Non-Clinical Studies Clinical trials Efficacy shown through results of clinical trials Adequate safety data
'Well-established use' marketing authorisation	Directive 2004/24/EC Article 10 (a)	Medicinal products for which there is an extensive clinical Experience Quality Documentation Based on clinical experience and scientific data available No new data from clinical trials No limits for therapeutic indications
'Traditional use' marketing authorisation	Directive 2004/24/EC Article 16 (a)	Simplified Registration (Efficacy requirements not satisfied) Quality Documentation Efficacy is based on long standing use and experience Therapeutic indications that are considered safe and can be utilised without physician supervision

Adapted from EU Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal. 2001;311:67–128.

1.4 Ensuring Quality of Herbal Medicinal Products

In the European Union an elaborate regulatory framework exists to regulate herbal medicinal products. This elaborate system bases itself on the fact that for a medicinal product to be placed on the market it needs a marketing authorisation that must be granted by the responsible authorities. The requisites and actions needed to acquire this marketing authorisation are all arranged in regulations, EU Directives and scientific guidelines (European Commission, 2015).

The EU regulatory structure describes in a very detailed manner the necessary requirements to satisfy quality standards for medicinal products. The regulatory structure recognises that herbal medicinal products are unique in their composition and accommodates specific requirements for these products, by outlining that the quality standards required are independent of their legal status (Kroes, 2014).

The foundations that lay down the laws ensuring the quality of medicinal products is defined in 2 directives of Volume 1 of the EU legislation. These are EU Directive 2001/83/EC and EU Directive 2003/63/EC.

1.4.1 EU Directive 2001/83/EC

The first directive 2001/83/EC lays down the essential key requirements and legal definitions of herbal entities, which include herbal substances, herbal preparations and herbal medicinal products, definitions of which can be seen in Table 1.2. These definitions provided new essential standards of quality for HMP, which previously could not be defined because of the complex way in which these products exist in

nature. Different methods and ways were needed to be implemented to safeguard the quality of herbal products (Kroes, 2014).

EU Directive (2001/83/EC) continues to appoint the role of the European Pharmacopoeia and states that all monographs and substances written within it are legally binding. In the event that no monograph is available for a particular substance, an EU member state can make use of its own national pharmacopoeia, provided it is available. This same directive also states that all medicinal products, including HMP must comply fully with the principles and guidelines of good manufacturing practices (GMP) and that these guidelines must be applied to both the finished herbal medicinal product as well as the active substances. To comply with the new amended part of Article 46(f) of the directive 2001/83/EC, the marketing authorisation holders must ensure that the starting materials or active substances utilised are manufactured according to the GMP guidelines for starting materials and distributed according to distribution practices for active substances. This is ensured, by a submitted "QP declaration" by a Qualified Person, ensuring traceability for the active substance along the supply chain (Kroes, 2014)

1.4.2 EU Directive 2003/63/EC

The second directive to ensure the quality of medicinal products is EU Directive 2003/63/EC. This directive which is an amendment of directive 2001/83/EC, states that since there is a difference between herbals and conventional medicines, specific requirements are required when it comes to addressing the quality standards of a herbal medicine in an application dossier. It is necessary to have more detailed information pertaining to the herbal product, with clear specifications with regards to the herbal

substances and preparations involved and other details such as: the name, address and responsibility of the supplier, the processes involved for all the plant production including the geographical source and all the other steps involved such as drying and storage conditions. When a HMP application dossier is being submitted, the dossier should contain detailed information of all scientific methods used to test these substances and preparations, together with results of batch analyses, analytical validation and good justifications for the specifications on reference standards used (Kroes, 2014). Quality requirements for HMP are written as scientific guidelines which in the EU have no actual legal force. These guidelines are considered to be a harmonised "agreed community position" and in the event that these guidelines are not abided, appropriate justification is necessary (EMA, 2009a).

The committee responsible for preparing the scientific guidelines for the development of herbal medicinal products for the EMA, is called the Committee on Herbal medicinal products (HMPC). This was created by Regulation EC no 726/2004 and EU Directive 2004/24/EC (EU Regulation (EC) No 726/2004; EU Directive, 2004). The Quality Drafting Group (QDG) has created and revised guidelines pertaining to herbal medicinal products. For example "The guideline on quality of herbal medicinal products/ traditional herbal medicinal products" (EMA, 2011a) provides guidelines of what type of information should be included in the application dossier and it gives important definitions to terms such as genuine (native) herbal preparations, drugs used to extract ratios and markers, considered essential in this stage. It specifies important factors that should be included in the assessment of quality control e.g. chromatographic fingerprint analysis and not just markers and constituents with known therapeutic activity (Kroes, 2014).

In another EMA guideline entitled: “The quality of combination herbal medicinal products/ traditional herbal medicinal products (EMA, 2011b), ways on how to deal with identification and assays of herbal substances and preparations in herbal medicinal products due to their complex nature are addressed. Attention should be paid to the validation and design involved in the manufacturing process; giving accurate documentation of every important step involved supplemented with more tests identifying and quantifying the final product (EMA, 2008b).

1.5 Ensuring Efficacy of Herbal Medicinal Products

EU Directive 2001/83/EC highlights the efficacy requirements of herbal medicinal products for use in humans within the EU. This Directive was amended to allow herbal medicinal products to be registered on the basis of traditional use. The way Herbal Medicinal products are subdivided into different categories depends on the type of efficacy documentation provided. The applicant must submit documentation in a Common Technical Document format, (as for conventional medicines) part of which is made up of the efficacy documentation. The requirements for efficacy documentation varies between the three types of application as discussed in Section 1.3.

When a herbal medicine is being assessed, there may be several studies with different outcomes to be considered, in this case a meta-analysis of all the results is usually resorted to. Although all clinical data is expected to be documented, it is the ‘wide spread medicinal use’ of the product that demonstrates efficacy of the product. After assessing all the evidence available, it may be concluded whether a herbal substance has ‘recognised efficacy’ (EMA, 2016a). The definition of ‘recognised efficacy’ as applied for herbal medicinal products which are assessed as part of the requirements for

application of ‘well-established use’ , remains a debatable issue due to lack of standardization. This is evident in cases where one product is legislated under a well-established use in one country but legislated under traditional herbal product in another even though applying for the same clinical indication (Claeson, 2014).

Attempts have been made by the HMPC, to formulate a standard template to be able to see whether a substance fulfils the well-established medicinal use category, but this was not successful. A guideline entitled: “Guideline on the assessment of clinical safety and efficacy” to try and address the situation was setup (EMA, 2016a). Within this guideline, it is stated that documentation showing medicinal usage of at least 10 years is a prerequisite and it describes main factors that should be incorporated in the efficacy documentation.

Table 1.6: Essential factors to incorporate when presenting efficacy documentation

A complete review and assessment of any relevant clinical information with respect to the herbal medicinal product or substance being investigated
Evidence that the studies performed have been carried out on a substantial amount of patients for the specified indication and were efficacious
At least one controlled clinical post marketing trial or epidemiological study of substantial quality is required to proof efficacy

Adopted from EMA, 2016a. Guideline on the assessment of clinical safety and efficacy in the preparation of European Union herbal monographs for well-established and traditional herbal medicinal products EMA/HMPC/104613/2005 Rev. 1. London.

It is evident, that despite developments in terms of legislative requirements, the issue of efficacy in herbal medicinal products and how this can be assessed and documented in a harmonized way remains debatable, leaving room for further development on how to ensure efficacy of herbal medicinal products.

1.6 Ensuring Safety of Herbal Medicinal Products

The definition of drug safety implies "the possibility or probability of not causing harm when used under the specified indications for use" (Moreira et al, 2014). Safety is a fundamental principle in the provision of herbal medicines and herbal products for health care, and a critical component of quality control (WHO, 2004).

In the past couple of years, there has been an increased discussion of ways to improve the assessment of safety in herbals. Guidance papers describing how to improve the safety and toxicity testing of HMPS, have been published by: International Life Sciences Institute in 2003, the Union of Pure and Applied Chemistry in 2004, the European Medicines Agency (EMEA in 2007 and 2009) and the European Food Safety Authority (EFSA, 2009). There are international regulatory systems specifying different testing requirements for safety and toxicity for HMPs but not a harmonised system used internationally (Jordan et al, 2010).

A harmonised system cannot exist if different countries classify herbals differently. In the European Union the THMPs Directive 2004/24/EC classifies HMPs under the 'well-established use' or 'traditional herbal medicines' which does not require the same safety requirements as to synthetic drugs and besides having a committee evaluating the safety parameters its main concept allows, that 'long term us' period to suffice as good evidence of safety (Sahoo et al, 2010).

The FDA does not classify herbals as medicinal entities or as conventional foods but as dietary supplements and under the Dietary Supplement Health and Education Act of 1994 (DSHEA) it is up to the manufacturer to ensure that safety evaluation is guaranteed. Requirements such as limited toxicity testing and long term use are allowed as good evidence of safety (Jordan et al, 2010).

In an article written by Sackett et al, 1996 the authors state that Evidence Based Medicine (EBM) is "the use of current best evidence to make decisions about the care of individual patients and that the first source of evidence to establish the safety and efficacy of a therapeutic intervention is through controlled and randomised clinical trials and unbiased systematic reviews" (Sackett et al, 1996). This means that evidence of clinical efficacy and safety cannot be based on pharmacological actions studied in animal and in vitro experiments and or expert opinion. It must be shown by means of well-designed phase III studies or particularly by phase II trials (Moreira et al, 2014).

In 2006, the HMPC issued a new guideline entitled: "Guideline on non-clinical documentation for herbal medicinal products in applications for marketing authorisation (bibliographical and mixed applications) and in applications for simplified registration" (EMA, 2006a). The purpose of this guideline was not intended to diminish the requirements set out by EU Directive 2001/83/EC and EU Directive 2004/24/EC, but as an added means to help prepare and evaluate applications for HMPs which had been used over a long time span. Presumptions are made that since herbal medicinal products have been used for long periods, there is sufficient accessible bibliographical evidence to proof the non-clinical safety of these products from scientific public literature, handbooks and monographs, but when a HMP is being evaluated, it is the animal studies performed that should be thoroughly examined. Since if when examined

tests performed show unfavourable benefit/risk results, then marketing authorization is denied. Alternatively, if epidemiological studies and results demonstrate wide spread use in humans, then no further tests are required (EMA, 2006a; Wiesner, 2014).

The same guideline declares that should a herbal product have satisfactory evidence showing clinical experience including tests on organ toxicity, single and repeated dose toxicity, immunotoxicity and local tolerance, no further testing of traditional herbal preparation is required. The same applies to pharmacological and pharmacokinetic safety tests, provided that no suspicious risk is foreseen (Wiesner, 2014).

A clinical safety assessment will involve assessing all the documented clinical experience in its long standing use and particular attention will be paid to detect 3 parameters namely: toxicity to reproduction, genotoxicity and carcinogenicity which are normally difficult to identify clinically (Wiesner, 2014).

1.6.1 Safety through Pharmacovigilance

Pharmacovigilance is the study of safety of marketed drugs under the practical conditions of clinical usage in large communities. This concept was first developed to assess the safety of pharmaceutical medicines, and can be applied to other medicinal products including herbals (Mann and Andrews, 2002).The goal of pharmacovigilance is to enhance the safety monitoring and detection of drug adverse events which might have might have not been detected or were not recognised during the clinical trial phase (Gromek et al, 2015). With the increase in use of herbal medicines and increased reports of suspected toxicity and adverse events, pharmacovigilance systems are needed for herbal products.

In 2001, the WHO Uppsala Monitoring Centre launched a surveillance project to try and generate more qualitative adverse drug reactions reporting for traditional medicines especially those associated with herbal and other traditional medicines. After a decade, this project generated over 4 million reports, 21,000 of which were related to herbal medicines (Shaw et al, 2012). In 2004, the World Health Organisation (WHO) recognised the increase in use of herbal medicines worldwide and developed guidelines within the already existing pharmacovigilance framework to help monitor herbal safety. These guidelines were entitled "WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems" (WHO, 2004).

1.6.2 Challenges of herbal pharmacovigilance

In the EU, herbal medicines sold to the public originate from various countries, including China, India, America, Africa and Europe. Since active ingredients all come from different geographical locations, a great diversity in the type of herbal species available is likely. A study by Shaw et al, 2012 examines factors that contribute to make the challenge of monitoring the safety of herbal medicines a difficult one (Shaw et al, 2012). The first and most important factor is an appropriate naming system. There is still confusion about which naming system to use when referring to a herbal product that is the botanical name, pharmaceutical name or the herbal drug name and this indirectly also leads to problems in terms of the validation of the botanical identity of herbal ingredients (Shaw et al, 2012).The natural state that these herbal medicines exist as, is another challenge that has to be considered when monitoring the safety of these products. Herbal medicines, are made up of chemically rich multi- components and not individual isolated compounds, as synthetic medicines. This chemical profile that makes

them unique, could be altered if any variation occurs to factors such as a change in geographical origin, genotype, harvesting time and storage and many others (Shaw et al, 2012).

Another challenge, could be the way in which national regulation authorities classify and regulate herbal medicines. Herbal use has developed differently and has diversified from one country to another. This can be seen in the US, where herbal products are classified as dietary supplements and not medicines, while in the EU herbals can be marketed as herbal medicines (if they are found to possess 'properties for treating or preventing a disease in human beings'), or food substances if the product ('cannot claim to treat or prevent disease or contain a pharmacologically active substance'). Examples can be seen in Table 1.7.

In the EU for a herbal medicine to be placed on the market as a medicine it must satisfy 2 Directives, (Directive 2001/83/EC, and 2004/24/EC) and needs to be classified as a 'well-established use' or 'traditional herbal medicine' and must satisfy legal requirements of safety and quality. While if it is to be classified as a food supplement, the same legal responsibilities in terms of quality do not apply (Shaw et al, 2012).

The first and main directive that contains all the basic requirements to assess the safety parameter of medicinal and herbal products is Directive 2001/83/EC.

Table 1.7: Regulatory status of five plant based herbal (medical) products in five different representative systems

	UK	Australia	Russia	USA	Germany
Ginkgo	Food supplement/ traditional Medicine	Listed medicine*	Food supplement	Dietary supplement	Medicine
Echinacea	Medicine/ traditional medicine/food supplement	Listed medicine*	Medicine	Dietary supplement	Medicine
Cimicifuga	Traditional medicine	Listed medicine*	Medicine/ food supplement	Dietary supplement	Medicine
Siberian ginseng	Food supplement	Listed medicine*	Medicine	Dietary Supplement	Medicine /food supplement

*A medicine with generally lower claims and a good safety record.

Adapted from Heinrich M, 2015. Quality and safety of herbal medical products: regulation and the need for quality assurance along the value chains. British Journal of Clinical Pharmacology. 2015; 80(1):62-66.

This directive specifies the primary and secondary pharmacodynamic tests that importantly assess the safety aspects of all medicinal entities, and other safety parameter tests such as pharmacology, pharmacokinetics, single dose and repeat dose toxicity, genotoxicity, carcinogenicity, reproductive and development toxicity, which are required to obtain a marketing authorisation (Wiesner, 2014).

In 2006, to help enhance the applicant process when applying for a marketing authorisation for herbal medicinal products, the HMPC issued a guideline on non-

clinical documentation for herbal medicinal products (EMA, 2006a). This guideline was not meant to diminish the already set specifications set in Directive 2001/83/EC or its amendment but as additional help to it. The scope was to address the minimum specifications required in terms of non-clinical data for well-established use HMPs or 'Bibliographical application' and in the event that the minimum specifications are not satisfied, to address the new and additional clinical tests required to evaluate the safety of the herbal product and thus apply for a 'mixed application'.

This guideline also gave instructions on which non-clinical safety aspects were required in the expert report for THMPs or simplified registration (EMA, 2006a).The same guideline stated that should there be satisfactory and well-documented evidence of the clinical use in humans, then routine compulsory tests requested for synthetic drugs such as organ toxicity, single dose and repeated dose toxicity, immunotoxicity, local tolerance test are no longer required. The same applies to safety parameters of pharmacology and pharmacokinetics, if no risk is suspected. In the expert report it is stated that the evaluation of all safety aspects must be assessed and justification on why the herbal product was acknowledged as safe for use is required. It is custom that the non-clinical evaluation of THMPs and HMPs is obtained from the overall evidence gathered from their long standing traditional use.

During the evaluation process what is assessed are the possible effects that in normal clinical use are hard to identify. The tests usually include toxicity to reproduction, genotoxicity and carcinogenicity (EMA, 2006a).

1.7 Toxicity of herbal products

Although herbal medicine use has increased, there are still concerns about their use and safety. The main issues relating to safety are the lack of standardisation of active components, a common scenario in herbal medicines considering that no more than ten percent of products in the global market are standardised (Ifeoma and Oluwakanyinsola, 2013). This poses an increased risk of toxicity and a threat on patients' health and safety. There is little or no information related to toxicity issues of herbal products. Another problem associated with toxicity is that some countries like the US do not apply regulatory standards of efficacy and safety for herbal medicines as for synthetic drugs, and the parameters of safety and use cannot be guaranteed (Ifeoma and Oluwakanyinsola, 2013). One of the parameters that can be implemented to determine the lack of safety of these products is toxicity testing, which can identify any risks associated with the consumption of herbals including potential adverse effects (Ifeoma and Oluwakanyinsola, 2013). When plants face adverse conditions such as severe drought, they enact a natural defence mechanism to counteract this adversity and as a result produce toxic secondary metabolites. This can be seen by medicinally relevant plant species such as *Digitalis purpurea* and *Atropa belladonna.* Once these toxic metabolites are produced they cannot be distinguished from therapeutic substances. Toxicology related assessment of herbals is needed primarily to evaluate adverse effects caused by herbals. Such assessment is useful to identify levels at which such adverse effects can occur. The type of adverse effect and its significance are two important parameters which can be considered in the safety evaluation profile of herbals. Toxicity related tests are useful to identify risks associated with use of herbals particularly in specific populations. Another important aspect of toxicity testing is to determine the

presence of toxic compounds which can be utilised in both the pre-clinical and post clinical stage. Once toxic testing is done, compounds identified to be toxic can be modified through structural adjustment (through reduction processes or chemical group alteration) to ultimately produce safer and more tolerable herbals (Ifeoma and Oluwakanyinsola, 2013).

1.7.1 Reproductive and developmental toxicity

An important aspect of safety assessment of chemicals (industrial and agricultural chemicals and pharmaceuticals) is determining their potential reproductive and developmental toxicity.

The United Nations Economic Commission for Europe (UNECE) defines reproductive toxicity as "adverse effects [of chemicals] on sexual function and fertility in adult males and females" and developmental toxicity in the offspring as "adverse effects induced during pregnancy, or as a result of parental exposure" (UNECE, 2011). According to an article by McKenna and McIntyre in 2006, pregnant women have resorted to using herbal medicines during their pregnancy as being natural, they were perceived as being safer to synthetic drugs. There is scarce information on herbals consumed during pregnancy (Marcus and Snodgrass, 2005).

A study carried out recently by Pallivalapila et al, 2015 concluded that two thirds of respondents (61.4%) stated that they had used some form of complementary and alternative medicine during the third trimester (Pallivalapila et al, 2015). This increase in popular use of herbal medicines raises issues of great concern during this phase of pregnancy for both the foetus and the mother, since herbal products could be teratogenic

(Pallivalapila et al, 2015). This can be seen in a multicentre study carried out by Facchinetti et al, 2012 on the unfavourable effects that the consumption of herbals during pregnancy had, both on the gestation period and the birth weight (Facchinetti et al, 2012). Herbal medicinal products should be evaluated further with respect to safety at all stages of both the reproductive and developmental phase (Yimam et al, 2015). The EMEA guideline, states that tests investigating effect of traditional herbal medicinal products on fertility are not required, unless literature reports indicate any hormonal influence or there are traditional uses with claims to regulate fertility. In such cases embryo-foetal and peri-post natal investigations are required (EMA, 2006a).

1.7.2 Carcinogenicity

Carcinogenicity testing is another test that can be carried out to determine whether HMPs contain carcinogenic substances. Maurici et al, 2005 defined carcinogenic as substances capable of inducing tumours and the prevalence and malignancy of these tumours (Mulware, 2012).

Carcinogenic studies or rodent carcinogenicity bioassays are performed on rats and mice and involve costly and timely clinical safety studies. For conventional drugs, carcinogenicity testing is obligatory and must be carried out during the research and development phase by means of in-vitro and in-vivo short term genotoxicity testing and long term rodent carcinogenicity assays. It is possible to refrain from submitting long term carcinogenic studies if negative results from the genotoxic tests are obtained and the drug's length of use is continuous for 3 months or intermittent for less than six months (Moreira et al, 2014).

With regards to HMPs, long term carcinogenic studies and genotoxic studies were not carried out for long periods of time but were carried out in a short time span. It is unlikely that any potential carcinogenic substances could have been revealed. A good way to reveal carcinogenic effects of THMPs would be through observational and epidemiological studies. Few of these have ever been carried out (Moreira et al, 2014).

In the same article written by Moreira et al, 2014 traditionally used herbal medicinal plants and their active ingredients which are suspected to be carcinogenic both to human and rodents are mentioned (Moreira et al, 2014).The author declares that since a majority of herbal products have not been tested for carcinogenicity, there are more products than those listed in table 1.8 which illustrates examples of traditional herbal medicines with potential carcinogenic effects. Although these plants have been used for years, there is still not enough evidence to demonstrate safety. Long standing use does not necessarily justify safety of the product (Moreira et al, 2014).

Table 1.8: Examples of traditional herbal medicines and/or their constituents with suspected carcinogenic effects

Plant species	**Active component**	**Traditional use**	**Humans or Animals**	**Findings**	**Article**
Aristolochia	Aristolochic acid (AA)	Chinese traditional medicine; arthritis, rheumatism etc.	Humans	Nephrotoxic upper tract urothelial carcinoma	Chen at al, 2013 Hollstein et al, 2013 Wu and Wang, 2013
Symphytum officinale L,(comfrey)	Pyrrolizidine alkaloids	Traditional medicine in Africa, China etc.	Human and Rodents	Hepatotoxicity, hepatic venous occlusive disease, liver cancer, genotoxicity	Chen et al, 2010 Mei et al, 2011 Roeder and Wiedenfeld , 2011;2013
Gingko biloba L	Leaf extract	Chinese traditional medicine; Widespread use worldwide	Human and Rodents	Dose related increase in liver tumours including hepatocellular carcinoma Evidence of carcinogenic potential in thyroid gland	Hoenerhoff et al, 2013 NTP, 2013
Senna alata L.	Sennosides	Traditional medicine (Africa, Nigeria, Ghana and Guinea)	Rodents in Vitro	Mutagenic to S. thyphimurium TA98 and TA 1537	Hong and Lyu, 2011
Sassafras albidum	Sassafras oil; safrole	Traditional medicine, Native Americans and British	Humans and Rodents	Oral squamous carcinoma (humans) dna adduct formation and potent rodent carcinogen	Amarasinghe et al, 2010; Chen at al, 1999; Hsieh et al, 2001; Kapadia et al, 1978.

Adapted from Moreira D, Teixeira S, Monteiro M, De-Oliveira A, Paumgartten F. Traditional use and safety of herbal medicines. Revista Brasileira de Farmacognosia. 2014; 24(4): 502-503.

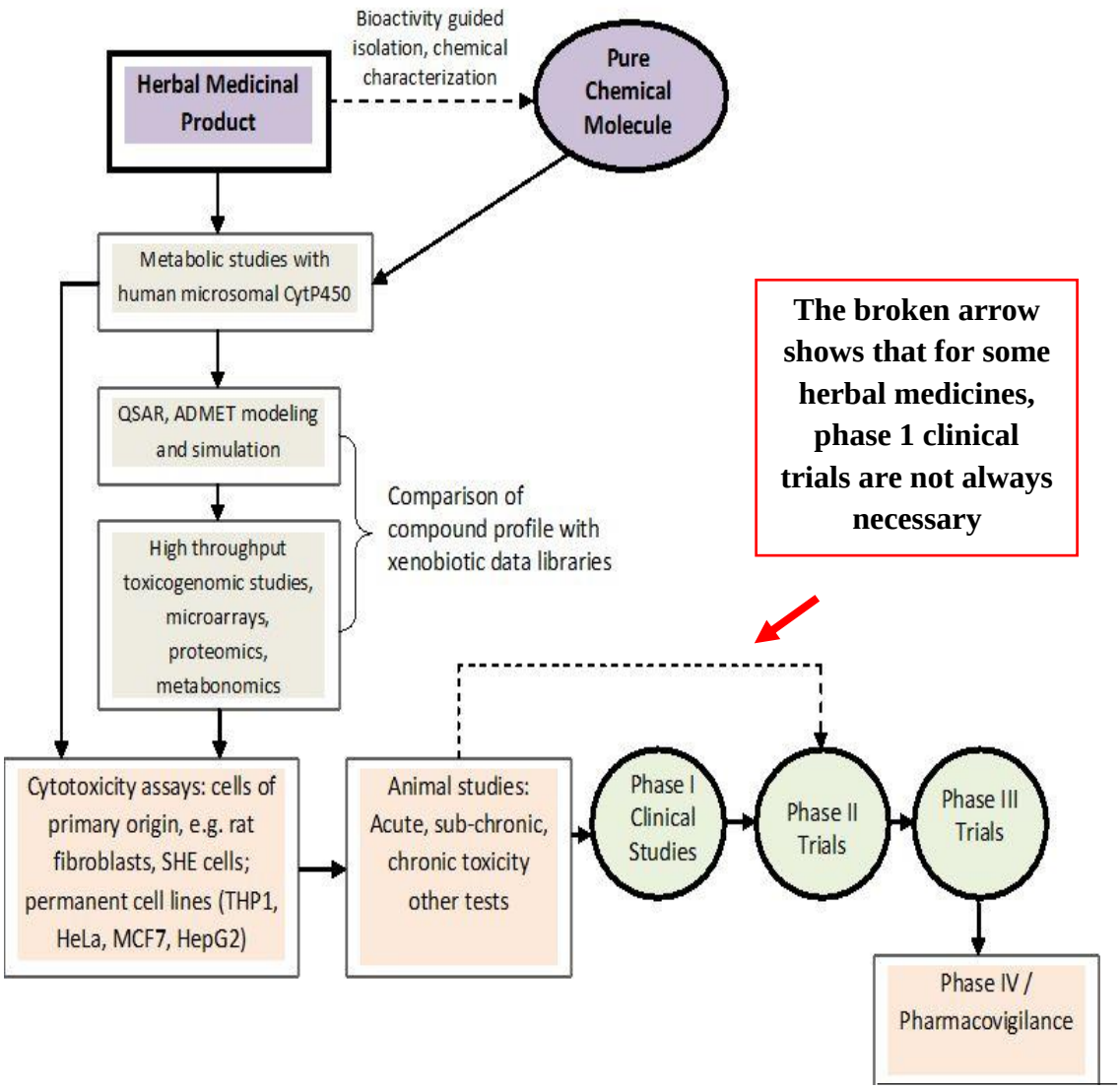


Figure 1.3: Schematic processes involved in evaluating and establishing the toxicity of medicinal herbs

Adapted from Ifeoma O, Oluwakanyinsola S. Screening of Herbal Medicines for Potential Toxicities. New Insights into Toxicity and Drug Testing [Internet]. 1st ed. 2013. Available from: https://www.intechopen.com/books/new-insights-into-toxicity-and-drug-testing/screening-of-herbal-medicines-for-potential-toxicities

1.7.3 Genotoxicity

Genotoxicity tests unlike other toxicity tests are difficult to interpret. Genotoxicity tests are performed to identify compounds that are hazardous with respect to DNA in terms of damage and fixation. Gene mutations, structural chromosomal aberration, recombination and numerical changes are possible effects that can occur to DNA. Once these changes affect DNA they are responsible for inheritable effects on future generations (Jena et al, 2002).Studies have shown that there are some commonly used medicinal plants that are genotoxic (Marques et al, 2003; Ananthi et al, 2010; Melo-Reis et al, 2011; Regner et al, 2011; Shin et al, 2011; Sponchiado et al, 2016). There are studies which identify medicinal plants as genotoxic. These include *Cochlospermum regium Pilg* (Castro et al, 2004; Andrade et al, 2008) and *Ocotea duckei* Vattimo (Marques et al, 2003), and *Copaifera langsdorfii Desfon* (Chen-Chen and Sena, 2002). The assessment of genotoxic issues throughout the evaluation phase of herbal products to identify any mutagenic properties are useful for safety reasons and could have an impact on economic issues (Di Stasi et al, 2002;Melo-Reis et al, 2011). Procedures and methods have been identified to evaluate compounds that could be genotoxic and carcinogenic. These have even been applied to areas related to food additives, pesticides, industrial and environmental chemicals and medicinal plants (Sponchiado et al, 2016).

The EMA guideline on non-clinical documentation for herbal medicinal products in applications for all marketing authorisations declared that it was not necessary to carry out investigations to determine the genotoxic potential of THMPs. If the literature information pertaining to the THMP was not sufficient, further tests must be performed (EMA, 2006a). In 2008, to assist further applicants when applying for a marketing

authorisation, HMPC published again another guideline entitled: “Guideline on the assessment of genotoxicity of herbal substances and preparations” (EMA, 2008c). The main scope of this guideline was to advise applicants on what procedures to use to assess the genotoxic potential of HMP and how to interpret the results of genotoxicity data. This guideline indicated that if the AMES-test is carried out in agreement with ICH guidelines and a negative result is obtained no further investigations are required. If the test results come positive then additional tests are required which involve the mouse lymphoma assay/ mammalian cell assay and rodent micronucleus test/ other in – vivo tests. If a HMP being examined gives positive AMES tests as a result of constituents which cannot be explained or particular constituents which have an already well-established safety profile e.g. as in the case of quercetin, further investigations involving in-vivo tests must be performed (EMA, 2008c)

Ten years later after the first guideline entitled: “Guideline on non-clinical documentation for herbal medicinal products in applications for marketing authorisation (bibliographic and mixed applications) and in applications for simplified registration” (EMA, 2006a), EMA concluded that widespread experience had been obtained from this guideline and that an update was necessary. In July 2016 a concept paper was created to revise the “Guideline on non-clinical documentation for herbal medicinal products in applications for marketing authorisation and in applications for simplified registration” (EMA, 2016e). The purpose of which was to revise the document with respect to new standards and advanced practices that had taken place in that time frame, and to discuss 3 main concerns:

1) With respect to the main guideline (EMEA/HMPC/32116/2005) there are two important guidelines "(EMEA/HMPC/107079/2007) and (EMEA/HMPC/67644/2009)" which need to be included with it.
2) These two guidelines only address the main procedures that should be utilised to analyse herbal products and material selection and that since plants consist of multicomponent species, there are still issues with regards to the best test methods to use and how to evaluate them.
3) Since the new enacted guideline ICH S2 (R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use (EMA, 2008e) it was revealed that genotoxicity testing should incorporate two in-vivo tests as indicated by the ICH guideline. Further deliberation should be included on the guideline on the limits of genotoxic impurities (EMA, 2006c, EMA, 2008e).

It is evident that determining safety parameters particularly toxicity issues is a challenge that needs to be addressed further. Such a challenge involves identification of approaches or methods of testing so as to provide better regulations that will further enhance patient safety.

1.7.4 Contaminants

Adulteration in herbal medicines may be due to a number of causes such as the replacement or wrongly identified ingredients with plants that are toxic, containing undeclared contents, taken in the wrong dose, and the use of contaminated products with mycotoxins, heavy metals, and microbial metabolites which could all be dangerous (Kosalec et al, 2009).

The way herbals are cultivated and the environment they are grown in are all determinant factors which effect the final product (Sahoo et al, 2010). Contaminants

such as radionuclides and metals can occur naturally in the soil and the air, and others are the result of environmental pollutants and factory emissions. Contaminants can be present if a herb is grown organically (Kosalec et al, 2009).

Contaminants can be subdivided further into biological or chemical contaminants. Biological contamination normally consists of microbes and organisms, whilst chemical contaminants consist of mycotoxins, toxic heavy metal elements and pesticides.

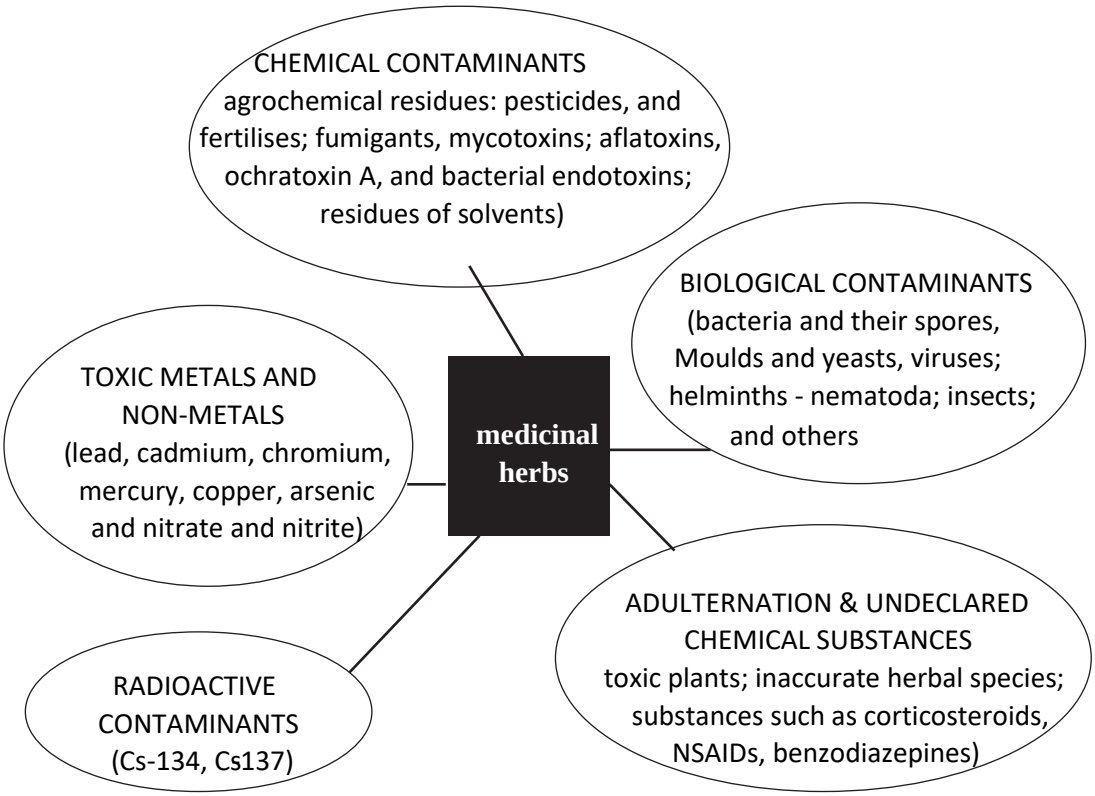


Figure 1.4: The most common contaminants of medicinal herbs

Adopted from Kosalec I, Cvek J, Tomić S. Contaminants of Medicinal Herbs and Herbal Products. Archives of Industrial Hygiene and Toxicology. 2009; 60(4): 485-501).

1.7.4.1 Biological Contamination

Bacteria, their spores, yeasts, fungi and other organisms are contaminants that may be present in all herbal products. This type of contamination can occur during the first stages of manufacturing and packaging of herbal products, when the ground premises or the facilities being utilised are contaminated. Biological contaminants can be introduced if there is contaminated air, bacteria originating from humans, and sometimes manure. To address this possible type of contamination, WHO and European Medicines Agency have adopted guidelines to ensure that quality assurance is maintained and for this reason guidelines addressing Good Agricultural and Collection Practices (GACP) and Good Manufacturing Process (GMP)practices for medicinal plants ensure that contamination is avoided. The guidelines were entitled "Guidelines on quality of herbal medicinal products/traditional herbal medicinal products" (EMA, 2011a), and "WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues" (WHO, 2007). Pharmacopoeia standards have also been adjusted and published with respect to which microbes are allowed and to what limit they are accepted (European Pharmacopoeia, 2016).

The evaluation of microbial contamination in herbal products should be carefully investigated particularly depending on the following

- Route of administration (eye, nose, respiratory system)
- Intended patient (infant, elderly, sick patients)
- Concurrent medications (immunosuppressant and corticosteroids) and
- Concurrent disease
- Characteristics of the product (possible presence of substrates)

This can have an impact on the patient in terms of health and safety. If the bacterial contaminant strain present in the herbal product has resistance to currently used antibiotics this could pose problems. Microbial count is an important factor that should be a quality indicator to assess safety (Kosalec et al, 2009).

To address the situation of safety in terms of quality assurance attempts have been developed by the WHO and other legislating bodies. The WHO started by developing the first guideline entitled "Quality control methods for medicinal plant materials", recommending methods to examine identify, purity, and content of herbal materials to help national laboratories in their assessment (WHO, 1998). In 2003, the WHO established another guideline entitled "Guidelines on good agricultural and collection practices (GACP) for medicinal plants" (WHO, 2003) and in 2007 another guideline entitled "WHO guidelines for assessing the quality of herbal medicines with reference to contaminants and residues" was published (WHO, 2007). The European Union, China and Japan also published their own national guidelines to address proper agricultural and collection practices (Sahoo et al, 2010).

The most common causes of adulteration of herbal products include undeclared potent pharmaceutical substances, substitution or misidentification with toxic plant species, incorrect dosing, interactions with conventional medicines, and use of products contaminated with potentially hazardous substances, such as microbial metabolites (e.g. mycotoxins), radioactive particles, heavy metals, and agrochemical residues (Kosalec et al, 2009; Fan et al, 2012).

1.7.4.2 Chemical contamination

Mycotoxin contamination is another major concern in terms of safety aspect of herbal medicines. This is because mycotoxins are secondary metabolites produced by a wide range of fungi namely *Aspergillus* and *Penicillum* species which can contaminate food and medicinal herbs. The 2 mycotoxins identified in raw medicinal herbs of concern are aflatoxins (AFs) and Ochratoxin A (OTA).

Studies to identify presence of mycotoxin contamination in food, medicinal plants and aromatic herbs, have been conducted and it was evidenced that mycotoxin contamination is a common problem encountered in all parts of the world ranging from places such as USA (D'Ovidio et al, 2006), Spain (Ariño et al, 2007), China (Yang et al, 2010) and India, (Rashidi and Deokule, 2013).

According to the International Agency for Research on Cancer (IARC), the mycotoxin OTA besides being a class 2B carcinogenic compound, has shown to be nephrotoxic, teratogenic, immunotoxic and also nephropathic in humans. Fumonisins B_1 and (FB_1) which are also toxins produced by the *Fusarium* species have also been classified by IARC as being class 2B Carcinogenic (Kosalec et al, 2009). To address the situation the EU has stated acceptable maximum levels for aflatoxin mycotoxins B_1 and total Sum of aflatoxins B_1, B_2, G_1, and G_2 that should be contained in foodstuffs. The European Pharmacopoeia has even established a proper method to determine aflatoxin B_1 levels and stated that the acceptable limit of aflatoxin is 2µg/kg for herbal drugs (European Pharmacopoeia, 2014). The regulatory authority of any member may request the limit for the total sum of mycotoxins of B_1, B_2, G_1, and G_2 to be 4µg/kg per herbal product, but there is no obligation to assess aflatoxin levels for all herbal medicines unless specified by a particular monograph (EMA, 2014).

In May 2015, the HMPC on quality produced a reflection paper, the scope of which was to discuss microbiological quality issues of herbal medicinal products and THMP, and how such issues can be addressed by adopting preventative measures and decontamination processes. The reflection paper highlights the importance to address the issue of determining limits of acceptable levels of contaminants present (bacteria and fungi) in accordance to the European Pharmacopeia. Preventing contamination is considered to be the preferred measure rather than adopting decontamination processes (EMA, 2014).

1.7.4.2.1 Polycyclic aromatic hydrocarbons (PAH's) contamination

The presence of polycyclic aromatic hydrocarbons (PAHs) is another form of contamination in herbal medicinal products. PAH's consist of a large group of semi volatile compounds which are classified as environmental pollutants due to their carcinogenic properties. There are modes of contamination through PAH's mainly through the atmosphere, soil and water. Thermal treatment such as drying or cigarette smoking is another source of contamination with PAH's. PAH's have toxic, mutagenic and carcinogenic properties. PAH's are considered to be of concern in terms of possible adverse effects on human health, possibly causing lung cancer through exposure and inhalation of PAH's (Abdel-Shafy and Mansour, 2016).

In December 2016, the EMEA issued a reflection paper about PAH's in herbal medicines and THMP's, which included different points of view from stakeholders about potential implications that PAH's can have on HMP's and THMP'S. Analytical methods of detection of such contaminants were also discussed in this paper including the definition of maximum threshold for PAH's (EMA, 2016c). The recently amended

regulation EC 1881/2006 replaced by 2015/1933 specified maximum acceptable levels of PAH's in cocoa fibre, banana chips, food supplements and dried herbs. To address the situation some countries within the EU issued national regulations (e.g. Holland) stipulating the maximum acceptable levels of PAHs. The European Pharmacopeia introduced PAH's testing by means of monographs. Although some measures have been taken, it is evident that appropriate measures including proper guidelines need to be issued and implemented to counteract the problem of PAH's contamination (EMA, 2016c).

1.7.4.2.2 Heavy metal contamination

A factor that can be present in herbal medicines and can contribute to their toxic nature are toxic minerals and heavy metals such as mercury, arsenic, lead and cadmium. Toxic metal poisoning in plants can result from soil, water and air and from the accumulation of toxic metals in polluted areas, such as mines and highways and as a result of anthropogenic processes such as synthetic fertilizers, organic manures and during transportation and unhygienic storage (Tripathy et al, 2015).The toxic effects manifested depend on the toxic metal ingested, such as ingestion of lead being manifested as abdominal pain, vomiting, severe anaemia, hemoglobulinuria and the darkening of stools. Mercury poisoning can cause symptoms such as peripheral neuropathy, psychological disturbances and arrhythmias. At later stages, renal impairment and death can result (Shaban et al, 2016). The problem of heavy metal poisonings in medicinal plants has been revealed by studies carried out in India, America, Middle East, Europe and Australia. Heavy metal levels more than the

permitted amounts stated by the WHO have been found in these countries (Baye and Hymete, 2009; Okatch et al, 2012 and Dghaim et al, 2015).

To address the problem of contaminants in herbal medicines the WHO issued a report entitled “WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues”. The aim of these guidelines issued in 2007, was to provide guidance in terms of ensuring quality specifically related to contaminants and residues, and to include analytical and practical techniques on how to assess quality of finished herbal products (WHO, 2007). In 2008, the EMA issued their own set of guidelines entitled “Guideline on the specification limits for residues of metal catalysts or metal reagents”. The purpose of which was to recommend acceptable maximum limits for residues of metal catalysts or metal reagents in drug products (EMA, 2008d).

Presence of toxic heavy metals along the food chain is a concern, despite the introduction of measures to counteract it. This presence entails precautionary and legislative measures that need to be enacted, identification of locations to cultivate herbal preparations used for the development of herbal drugs should be far from urban roads, rail stations and highways since these may aggravate the problem due to the possibility of causing higher heavy metal toxicity, impacting the atmosphere, soil and water which are all components utilised by herbal products.

1.7.4.2.3 Pyrrolizidine alkaloids (PAs) contamination

The presence of pyrrolizidine alkaloids (PAs) in plants is another important factor that could pose a threat to humans when ingested. This is because Pyrrolizidine alkaloids (PAs) containing a 1, 2-double bond in their basic moiety (necine) have been found to

be hepatotoxic, carcinogenic, genotoxic, teratogenic and sometimes pneumotoxic (Wiedenfeld, 2011). Pyrrolizidine alkaloids consist of around 300 chemicals found in commonly used plants. Toxicity occurs when toxic pyrroles form in the hepatic P-450 metabolic pathway, which causes obstruction to the hepatic venous system resulting in venous occlusive disease (Dharmananda, 2001). The presence of PAs in several plants used in herbal medicines has been identified recently and has raised great interest on the implications it has on health. The U.S. Food and Drug Administration (FDA) and Centres for Disease Control (CDC) prepared bulletins on PA contamination. The HMPC issued a public statement in May 2016 about contamination of herbal products with pyrrolizidine alkaloid, and made recommendations to ensure quality of herbal products (EMA, 2016b).

Analytical tests can identify minimum levels of PAs in food or herbal products. Regulatory issues related to contamination with PAs need to be tackled through identification and establishment of regulatory standards. Establishment of an official analytical method for PA detection is considered to be of high priority (EMA, 2016b).

1.8 Aims of the study

The aims of this study were:

1. To analyse how HMPs are classified within the EU and to determine whether such a classification safeguards the interests of the patient.
2. To assess the level of knowledge of pharmacists and health shop employees.
3. To identify attitudes and perception of patients in a local community pharmacy setting towards HMPs.

CHAPTER 2

METHODOLOGY

2.1 Analysis of current EU scenario for classification of herbal medicines

A literature review about classification and safety of herbal medicines within the EU was carried out and the following related issues were addressed:

- Legislation
- Quality
- Safety and efficacy
- Pharmacovigilance

This was carried using different search engines namely PubMed and Academic Search Complete. Strengths and weaknesses of EU legislation in relation to the above mentioned issues were identified. The situation in Malta relating to the classification of HMPs was also investigated. This was achieved through individual meetings with competent authorities namely the Malta Competition and Consumer Affairs Authority (MCCAA) and the Malta Medicines Authority.

2.2 Development of Questionnaires

Two questionnaires were developed for two groups of respondents. The aim of the first questionnaire was to determine knowledge and perception on herbal products of pharmacists and health food shop employees. The aim of the second questionnaire was to survey the general public regarding use and general knowledge of herbal products. Ethics approval to carry out the study was attained by the Research Ethics Committee prior to commencement of the research (Appendix A).

2.2.1 Development of Questionnaire to determine knowledge of pharmacists and health shop employees

A questionnaire entitled 'Survey on Classification of Herbal Supplements' was developed based on similar studies (Chang et al, 2000; Alkharfy, 2010; Sweileh et al, 2013 and Coon et al, 2015) and consisted of four sections (Appendix B).

Section 1 of the questionnaire included preliminary data whereby general background information about the respondent was collected. This data included demographic data (age, gender), qualifications and data related to the area of work (working experience, occupation, area of work).

Section 2 of the questionnaire was entitled 'Knowledge assessment' and this part of the questionnaire consisted of seven questions related to use of herbal medicines. This part of the questionnaire assessed knowledge about issues related to use of herbal products such as indications, side-effects and interactions of herbal medicinal products.

Section 3 of the questionnaire was entitled 'Classification of herbal products'. In this section four popular products available on the local market were chosen. The list of ingredients and dose of each product was listed. A picture of the packing of each product was included. In this section of the questionnaire the respondent was asked to classify each product by looking at the information related to the dose and ingredients provided. Respondents classified the products either as a medicinal product, herbal supplement or medicinal/ herbal supplement (borderline). An "I don't know" option was allowed for those respondents who could not answer. Respondents were also asked to state reasons for their choice of classification.

Section 4 of the questionnaire was entitled ‘Attitudes and confidence levels on herbal products’. In this section, the respondents were given seven statements related to attitudes and level of confidence when dealing with general issues involving herbal products. Such issues included the beneficial and placebo effects of herbal products, comparison of herbal products and conventional medicines in terms of side effects and interactions. Other issues addressed in this part of the questionnaire included advice to patients on herbals and evidence of herbal products. The Likert rating scale was adopted as a mode of answering whereby respondents were asked to rate their level of agreement ranging from a score of 1 (strongly agree) to a maximum score of 5 (strongly disagree). This was applied for all of the seven statements provided.

2.2.2 Validation of the pharmacist and health shop employees questionnaire

Following development of the questionnaire, a panel composed of eight members was set up to validate the questionnaire. The members of the panel included four pharmacists, two physicians and two members from the general public.

Following the setup of the validation panel each member of the panel was given a brief overview of the research study. Written and verbal instructions about the validation procedure of the questionnaire were provided to each member by providing a validation tool kit.

The members of the validation panel were asked to validate and assess each section of the questionnaire in terms of:

- Clarity of each question
- Level of agreement of each question

- Appropriateness of questions (to ensure that questions are assessing what they should be assessing)
- Relevance of each question in the questionnaire
- Appropriateness of length of questionnaire

Each member was asked to grade each question by giving a score from 1-5 (where 1 represented the minimum score and 5 the maximum score) in terms of the parameters mentioned above. When a score of 2 or less was assigned for a particular question the member of the panel was asked to state his/her reasons. The validation task was concluded by asking members of the panel for any general remarks.

At the end of the validation task, analysis of the tool kits was done for any recommendations on how the questionnaire could be modified and improved.

The validation panel agreed that no adjustments to the questionnaire were needed.

2.2.3 Method of delivery of the pharmacist and health shop employee Questionnaire

Following development and validation of the questionnaire, the questionnaire was delivered to 200 community pharmacies and 50 health food shop employees, those who consented to participate answered the questionnaire. To help maximize response rate of questionnaire, other methods of delivery were adopted and these were:

- Electronic delivery via the Pharmacy Council who contacted registered pharmacists in Malta.
- Electronic delivery via Pharmacy Academia who contacted past pharmacy students members of this group

All filled up and returned questionnaires were analysed statistically.

2.2.3.1 Statistical analysis

The data collected from all the respondents was entered into Microsoft Excel software and statistical analysis was conducted using IBM SPSS statistics for windows, version 20.0. The Spearman's correlation test was used to analyse whether there was a correlations between working experience and total score obtained by the 2 groups. The Friedman test was used to analyse the attitudes and confidence of pharmacists and health shop employees.

2.2.4 Development of Questionnaire for public survey

A questionnaire entitled 'Public survey on Herbal Products' consisted of three sections and was developed to be answered by the general public both in English and Maltese (Appendix C).

Section 1 of the questionnaire consisted of demographic data including gender, age and level of education.

Section 2 of the questionnaire was entitled 'Herbal product use' and consisted of six questions related to trends in use of herbal products by the general public. This included identifying trends of consumption of herbal products, and issues related to preferred sources of advice and purchase of herbal products by the public.

Section 3 of the questionnaire was entitled 'Perception about herbals' and consisted of two questions related to safety of herbal medicinal products and herbal supplements.

2.2.5 Method of delivery for public survey

The Public survey questionnaire was first reviewed and then distributed in pharmacies over three months and individuals who came in to the pharmacy were selected randomly and invited to complete the questionnaire. Before filling up the questionnaire respondents accepting to participate in the study were asked to sign a consent form available in both Maltese and English languages (See Appendix C).

Data collected from the questionnaire was entered into Microsoft Excel software and descriptive statistics was conducted.

CHAPTER 3

RESULTS

3.1 Reflections on EU legislation of HMPs

Following a thorough review of the way HMPs are regularised within the EU, the following reflections including strengths and weaknesses are highlighted in **Table 3.1.**

Table 3.1: Strengths and weaknesses of EU legislation of HMPs.

Strengths	**Weakness**
HMPs are classified as a subcategory of medicines that like medicines must satisfy safety, quality and efficacy documentation. Classification depends on evidence provided. There is even a distinction between herbal substance and herbal preparation for a given herbal material.	TUR -Efficacy documentation is subjective. No guidelines on how to assess whether data provided of traditional use is sufficient.
There are 2 directives that address HMPs namely: EU Directive 2001/83/EC and EU Directive 2004/24/EC. This makes EU herbal monographs more legally correct with respect to the directive as opposed to national pharmacopoeia and compendia.	For TURs the fact that long standing use is justified to replace clinical trials, does not exclude safety concerns. Competent Authorities should have justified reasons why an HMP is accepted as THMP or WEU.
There is HMPC to investigate issues and emerge with scientific opinions and issue herbal monographs providing valuable information on safe use. There is a clear distinction between THMPS and WEU.	The THMP scheme fails to include other traditional forms of medicine such as Asian, Indian or Chinese traditional medicine. These directives do not cover for animal products with a plant origin such as honey and propolis and exclude all animal products (chondroitin, cod liver oil, shark cartilage. These have no alternative to be marketed as food supplements.
Allows the free movement of HMPs across EU member states.	Registration costs for HMPs vary between EU member states and this limits the number of registered products. Free movement does not imply that a herbal product accepted as WEU in one country, will have the same status in another member state.
Herbal monographs issued provide reference standards that can be utilised by other manufacturing companies and national authorities to facilitate when applying for MA.	Lack of clear classification between HMPs and food supplements has led to lack of harmonization between EU member states of how products are classified into HMPs or Food supplements is still a predominant issue. The scope of the monograph is limited to those products that fall within the definition of the product.
No manufacturer can place unlicensed herbal medicines on the market without a MA.	The introduction of TUR scheme has created a viable and simplified process for manufacturers to place products on the market without needing proper research and reducing costs required for other registration pathways.

3.2 Demographic data of Respondents Questionnaire.

One hundred and twenty one (48%) respondents accepted to participate in the survey. This consisted of 107 pharmacists and 14 health shop employees, as highlighted in figure 3.1.

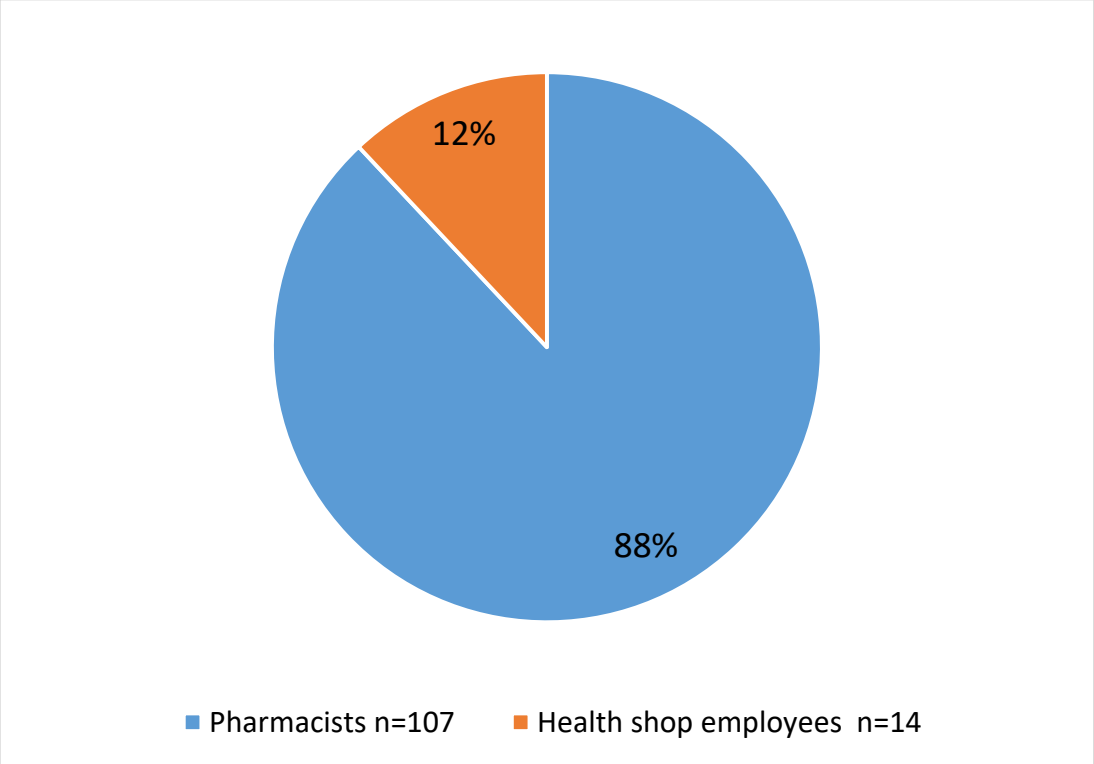


Figure 3.1: Respondents of Questionnaire (N=121).

Tables 3.2 and 3.3 highlight demographic data of participating pharmacists and health shop employees respectively including gender, age, practice setting and years of experience.

Table 3.2: Demographic data of pharmacists (n=107).

Pharmacist Characteristic	n (%)
Gender	
Male	30 (32)
Female	77 (82.39)
Age (years**)**	
Range	18-70
18-30	33 (30.84)
31-50	64 (59.81)
51-70	10 (9.34)
Practice setting	
Community	72 (67.28)
Hospital	5 (4.67)
Industry	3 (2.80)
Medical Representative	11 (10.28)
Others(Academia, Procurement)	16 (14.95)
Number of years of experience	
<10 years	36 (33.6)
10 - 20 years	45 (42)
>20 years	26 (24)

Table 3.3: Demographic data of Health shop employees (n=14)

Health shop employees Characteristics	n (%)
Gender	
Male	1 (7.14)
Female	13 (92.85)
Age (years)	
Range	18-70
18-30	5 (35.71)
31-50	7 (50)
51-70	1 (7.14)
Practice Setting	
Health shop	14 (100)
Number of years of experience	
<10 years	9 (64.2)
Between 10 and 20 years	5 (35.7)
>20 years	0 (0)

3.3 Knowledge Assessment

While pharmacists attained a mean knowledge score of 27.06 out of a possible maximum score of 56, health shop employees obtained a mean knowledge score of 28.15 (Appendix D).

The mean knowledge score obtained for each question found in Appendix E illustrates that pharmacists obtained high scores on questions pertaining to indications of Gingko

biloba and St. John's wort interactions but obtained low scores with regards to Saw palmetto and Black cohosh.

Health shop employees attained high scores on questions related to indications of Gingko biloba, and side effects of Echinacea but obtained low scores in questions pertaining to conventional medicines with interactions and indications of Black cohosh.

Table 3.4 highlights knowledge scores of pharmacists and health shop employees.

Table 3.4: Knowledge Assessment statistics of pharmacists and health shop employees (N= 121)

Group	N	Mean knowledge (out of 56)	Std. Deviation
Pharmacist	107	27.06	8.296
Health shop employees	14	28.15	6.793

3.3.1 Correlation between working experience and total score

The Spearman Correlation test was applied to analyse statistical correlation between working experience and total score attained of both pharmacists' and health shop employees'.

Table 3.5: Correlation between pharmacists' working experience and total score on knowledge

		Working Experience	**Total Score**
Working Experience	Correlation Coefficient	1.000	**-0.141**
	P-value		**0.151**
	Sample size	106	106
Total Score	Correlation Coefficient	**-0.141**	1.000
	P-value	**0.151**	
	Sample size	106	106

Table 3.6: Correlation between health shop employees' working experience and total score on knowledge

		Working Experience	**Total Score**
Working Experience	Correlation Coefficient	1.000	**0.268**
	P-value		**0.354**
	Sample size	14	14
Total Score	Correlation Coefficient	**0.268**	1.000
	P-value	**0.354**	
	Sample size	14	14

There was no statistical significant correlation between the number of years of working experience and knowledge for both groups.

3.4 Classification of herbal products

The responses related to classification of the selected four herbal products by health shop employees and pharmacists are highlighted in Figures 3.2, 3.3, 3.4 and 3.5 respectively.

For Product 1 (which was Altadrine® fat burner caps) 4.67% (n=5) of the pharmacists classified the product as a medicinal product, while 91.59% (n=98) of pharmacists classified the product as a borderline or herbal supplement and 3.73% (n=4) of the pharmacists stated they did not know the answer. In the case of health shop employees none classified the product as a medicinal, 57% (n=8) classified the product as borderline or herbal supplement while 42.86% (n=6) of health shop employees stated they did not know the answer.

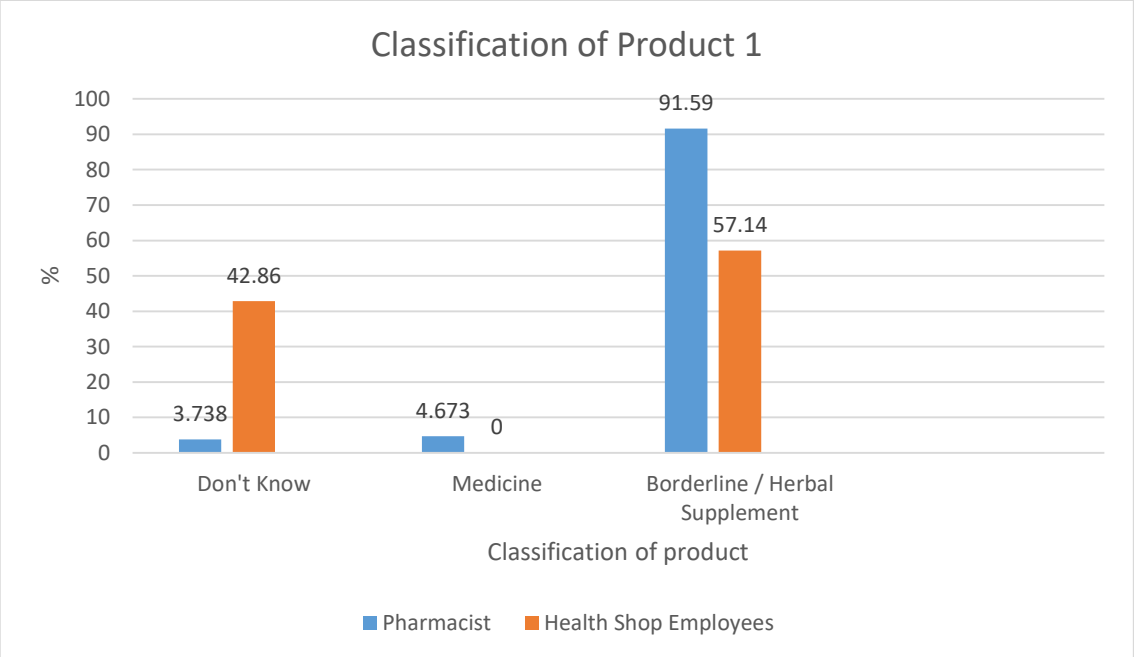


Figure 3.2: Health shop employees and pharmacist response for classification of product 1 (N=121)

For product 2, (which was Yogi® green energy tea). The majority of the pharmacists, 96.26% (n=102) classified the product as a herbal / medicinal supplement product, while 0.935 % (n=1) classified the product as borderline product and 2% (n=3) of the pharmacists stated they didn't know how to classify the product. For this product all health shop employees 100% (n=14) classified this product as medicinal/herbal supplement.

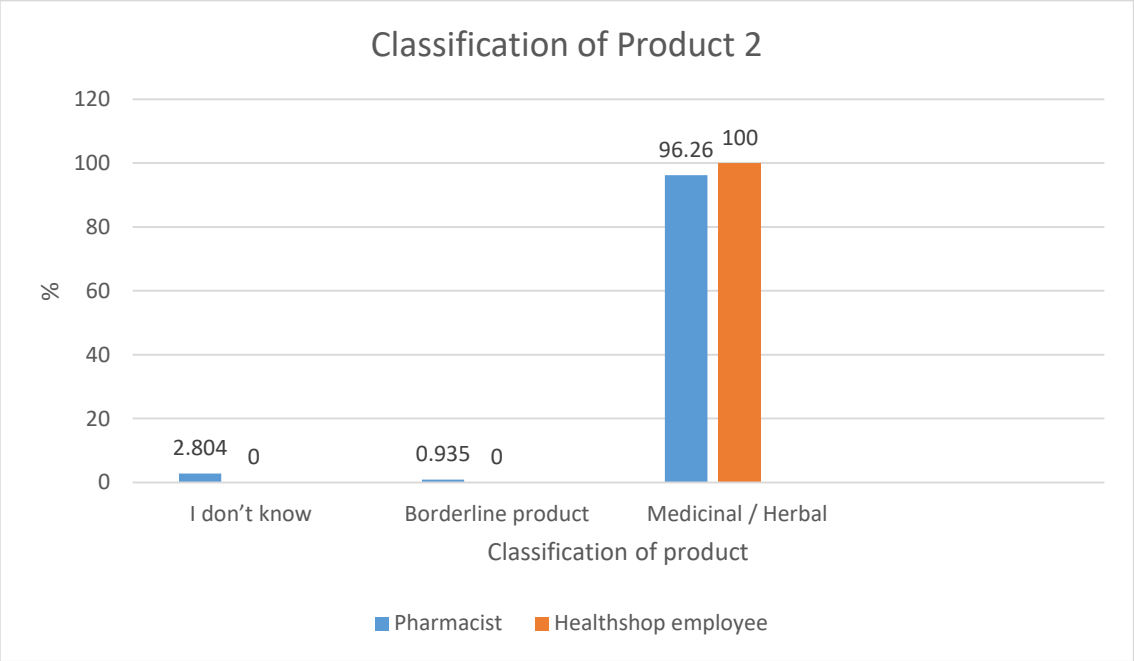


Figure 3.3: Health shop employees and pharmacist response for classification of herbal product 2 (N=121).

For product 3 (which was Fenugreek Arkopharma® caps). Eighty seven percent (n=105) of pharmacists classified the product as medicinal/ herbal supplement, 6.5 % (n=8) classified the product as a borderline product while 6.5% (n=8) gave 'I don't know' response. In the case of health shop employees 85.71% (n=12) classified the product as medicinal/herbal supplement, 14.29% (n=2) classified the product as borderline.

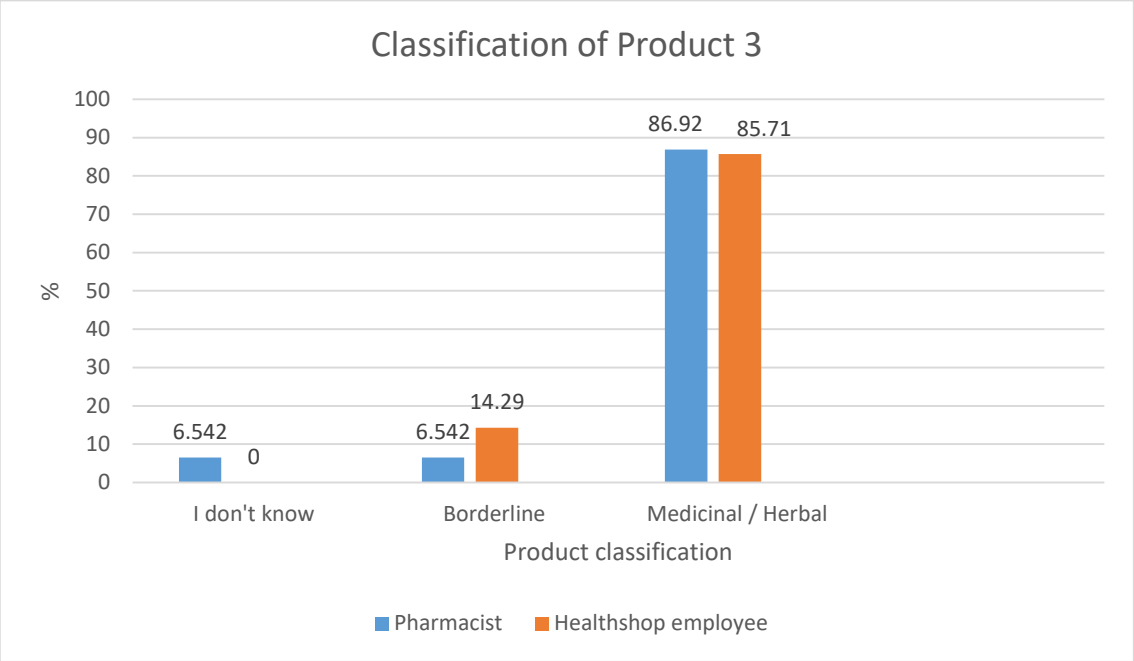


Figure 3.4: Health shop employees and pharmacist response for classification of herbal product 3 (N=121).

For product 4, (which was Vitamins Direct Turmeric Curcuma plus® caps). The majority of the pharmacists 74.77% (n=80) classified the product as medicinal/ herbal, 20.56% (n=22) of pharmacists classified the product as borderline while 4.67% gave an 'I don't know' response. In the case of health shop employees, 71.43% (n=10) classified the product as medicinal/ herbal, while 28.57 % (n=4) opted to choose the 'I don't know' response.

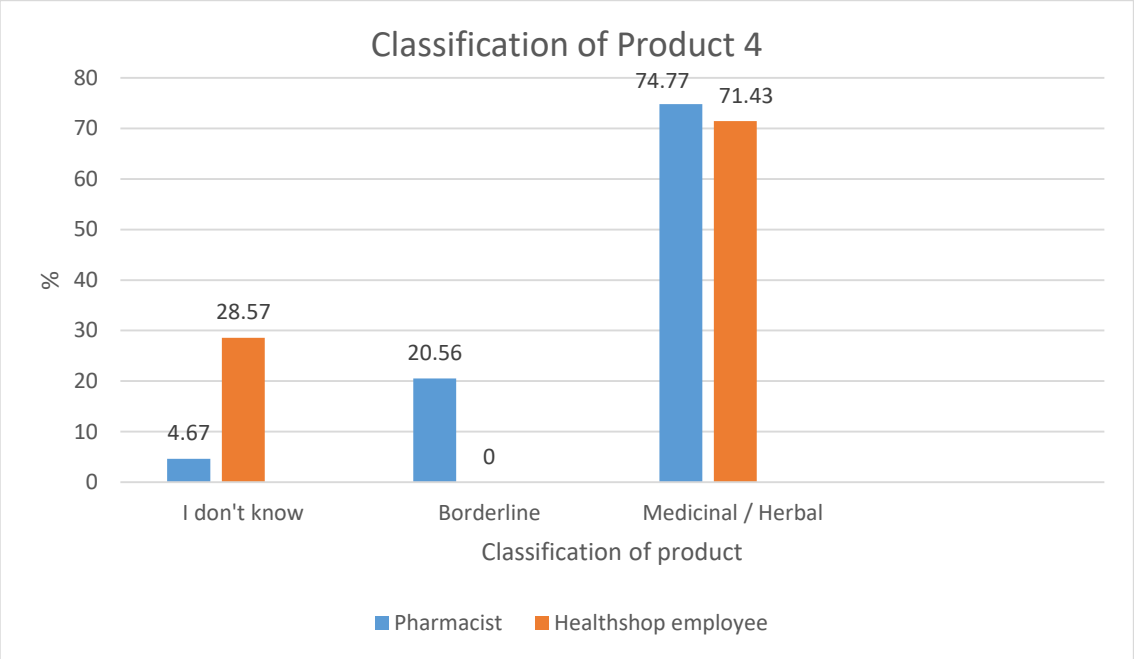


Figure 3.5: Health shop employees and pharmacist response for classification of herbal product 4 (N=121)

3.5 Attitudes and Confidence levels on herbal Products

For the confidence and attitude assessment, mean scores show that pharmacists agree with the statements that herbal products have beneficial effects, less side effects, placebo effects and significant interactions when taken with conventional medicines. Health shop employees agree that herbal products have beneficial effects and less side effects. The Mann-Whitney test showed that there was statistically significant difference ($p<0.05$) in responses related to statements about products having less side effects than conventional medicines and significant interactions with conventional medicines.

Table 3.7: Health shop employees and pharmacists' attitudes on herbal products (N=121) (Likert scale where 1=strongly agree and 5= strongly disagree).

Practice		n	Mean	Standard Deviation
Do you agree that herbal products have beneficial effects?	Health Shop employees	14	2.31	1.601
	Pharmacist	107	2.25	0.967
Do you agree that herbal products have less side effects than conventional medicines?	Health Shop employees	14	2.15	1.281
	Pharmacist	107	3.24	1.243
Do you agree that herbal products have a placebo effect?	Health Shop employees	14	3.00	1.528
	Pharmacist	107	2.82	1.265
Do you agree that herbal products have been sufficiently studied?	Health Shop employees	14	3.38	0.650
	Pharmacist	107	3.75	1.061
Do you agree that herbal products can have significant interactions with conventional medicines?	Health Shop employees	14	3.23	1.092
	Pharmacist	107	1.92	1.020
How comfortable are you giving advice to patients on herbal products?	Health Shop employees	14	3.23	0.927
	Pharmacist	107	3.48	1.003
How confident are you when it comes to finding current resources on herbals?	Health Shop employees	14	2.69	0.751
	Pharmacist	107	3.12	1.133

3.6 Public Survey on Herbal products

For the public survey on herbal products, 150 people accepted to complete the questionnaire.

Table 3.8: Demographic characteristics of respondents for public survey (N=150)

Characteristic	n (%)
Gender	
Male	20 (13.3)
Female	130 (86.6)
Age (years)	
Range	18-70
18-30	2
31-50	79
51-70	69
Level of Education	
Secondary	20 (13.3)
Post-secondary	43 (28.6)
Tertiary	40 (26.6)
Post tertiary	47 (31.3)

Results of the public survey showed that 126 respondents (84%) make use of herbal products and 56.4% (n=84.6) co-administer herbal medicines with conventional medicines. Further analysis of the survey results showed that 58.73% (n=88) of respondents do not inform their doctor they are taking herbal products.

Figure 3.6 shows that green tea, cranberry and ginseng were the three most commonly consumed herbal products by those surveyed.

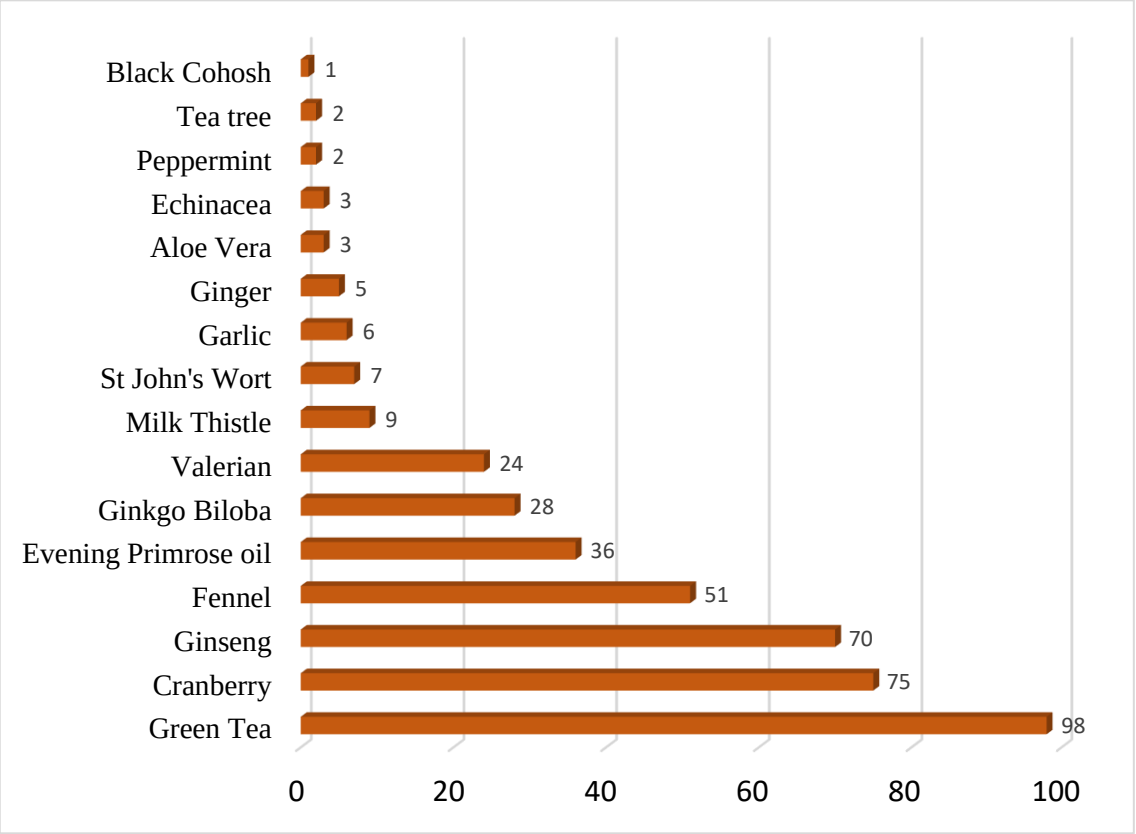


Figure 3.6: Commonly used herbal products by respondents (N=150).

Fifty four percent (n=81) of the respondents admitted to prefer purchasing herbal products from pharmacies, as compared to other sources including health shops, supermarkets, online purchase and gyms as illustrated in Figure 3.7. Sixty five percent (n=98) of the respondents seek advice on herbal products from pharmacists, 19% (n=29) from doctors and 16% (n=24) from health shop employees.

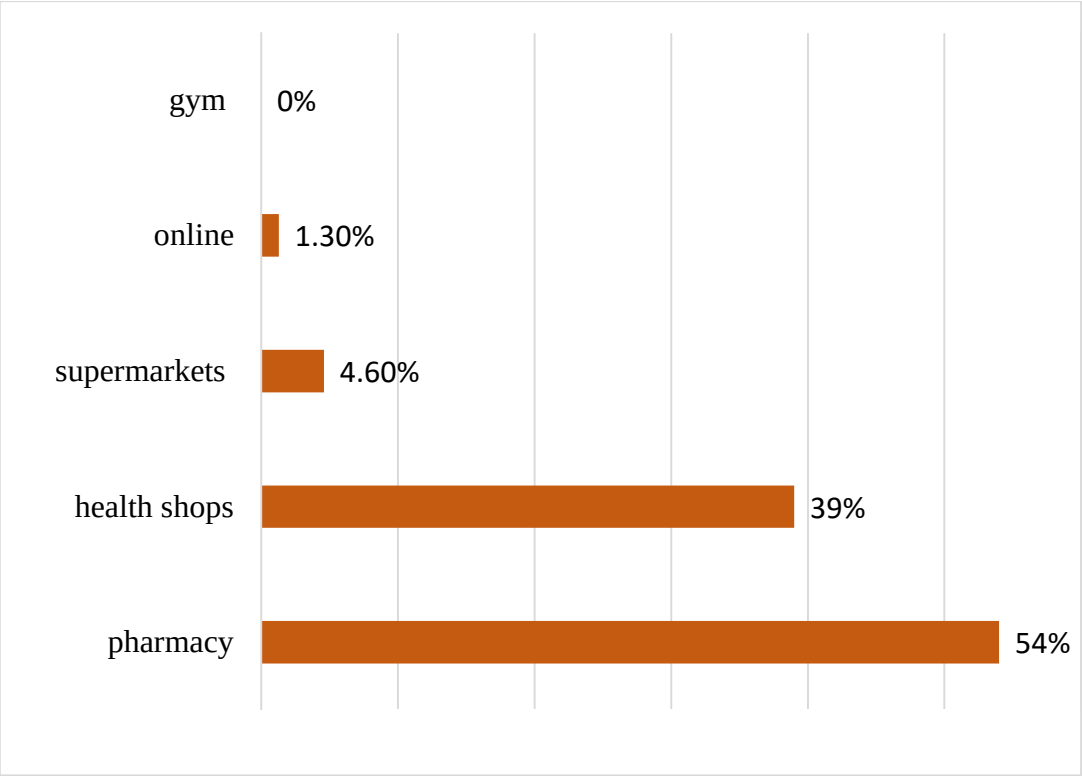


Figure 3.7: Outlet preference to purchase herbal products from (N=150)

One fourth of the respondents think that use of herbal medicine/ supplements is harmful. Thirty one percent (n=47) of those surveyed believe that combining herbal and conventional drugs can be dangerous.

CHAPTER 4

DISCUSSION

4.1 Herbal medicines and patient safety

The use of herbal products is on the increase and research related to herbal medicines is being given more importance as evidenced by the increase in publications and studies about herbal products. The concept of patient safety in relation to the use of herbal products is considered to be a major issue as reflected by publications encountered during the literature review conducted in this study. Ensuring safety, efficacy and quality of herbal products are considered to be important and this can be attained by addressing factors causing limitations at various levels starting from the manufacturing process, the national authorities, pharmacist and health shop employees and the consumer as shown in Figure 4.1.

Knowledge and understanding about various issues related to use of herbal products, particularly by those handling such products (mainly pharmacists and health shop employees), is another key element to ensure patient safety. Lack of knowledge about issues such as interactions, side-effects and use of herbals in special populations could result in a clinically significant negative impact on the patient (Loya et al, 2009).

Public attitudes towards use of herbal products is another important aspect which merits particular attention. Public misinformation about herbal products is based on the false belief that herbal products are ‘natural’ and hence automatically safe. This could be attributed to incorrect ways of advertising about herbals to which the general public is subjected to through different media sources.

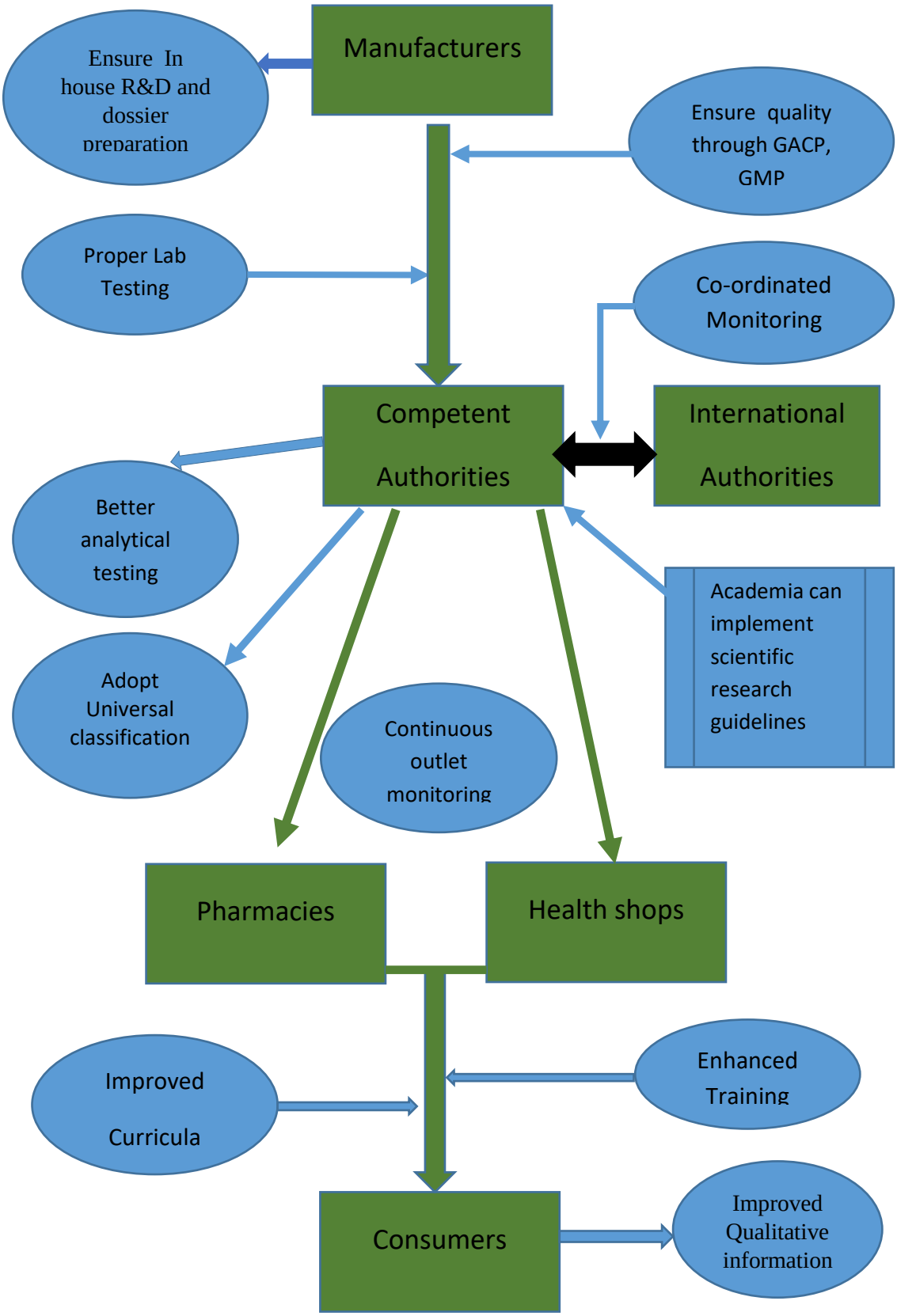


Figure 4.1: A schematic flowchart, suggesting how various stakeholders can improve the safety of HMPs.

The wide promotion of herbal products in the media coupled with health claims that are not substantiated exposes the public to increased health risks particularly when there is co-administration of herbal products with conventional drugs. Issues related to regulation, knowledge and public attitudes towards use of herbal products, were the three main aspects on which this research was carried out to determine whether herbal products are really safe for the patient.

4.2 Ensuring patient safety through regulation

One of the major issues to ensure patient safety is the way herbal products are regulated by national authorities. The EU Directive 2004/24/EC was introduced with the intention of allowing herbal medicinal products to be classified, since prior to this directive herbal medicinal products could not be registered as medicines. The TUR registration scheme was introduced with the intention of providing a regulatory framework by which herbal products could penetrate the pharmaceutical sector within the EU, provided traditional use of the products for a specified period was indicated. Through the introduction of this system, the safety of herbal medicines became justified and acceptable within the EU by allowing a time frame to fulfil this requirement based on traditional use. The success of such a system remains debatable.

According to the Eurocam, figures show, that by the end of 2015, over 1500 THMPs have been registered under this scheme. While this figure may indicate a successful number of registered products, the quoted figure represents the total registered number of products in a decade, in all 28 EU member states. This figure might be inflated since

it may include same products that have been registered in more than one EU member state (Eurocam, 2011).

Figure 4.2 Illustrates the total number of HMP registered under Traditional Use Registration after Directive 2004/24/EC. The total number of registrations that took place throughout Europe annually from 2004 until 2015 was of 1,577.

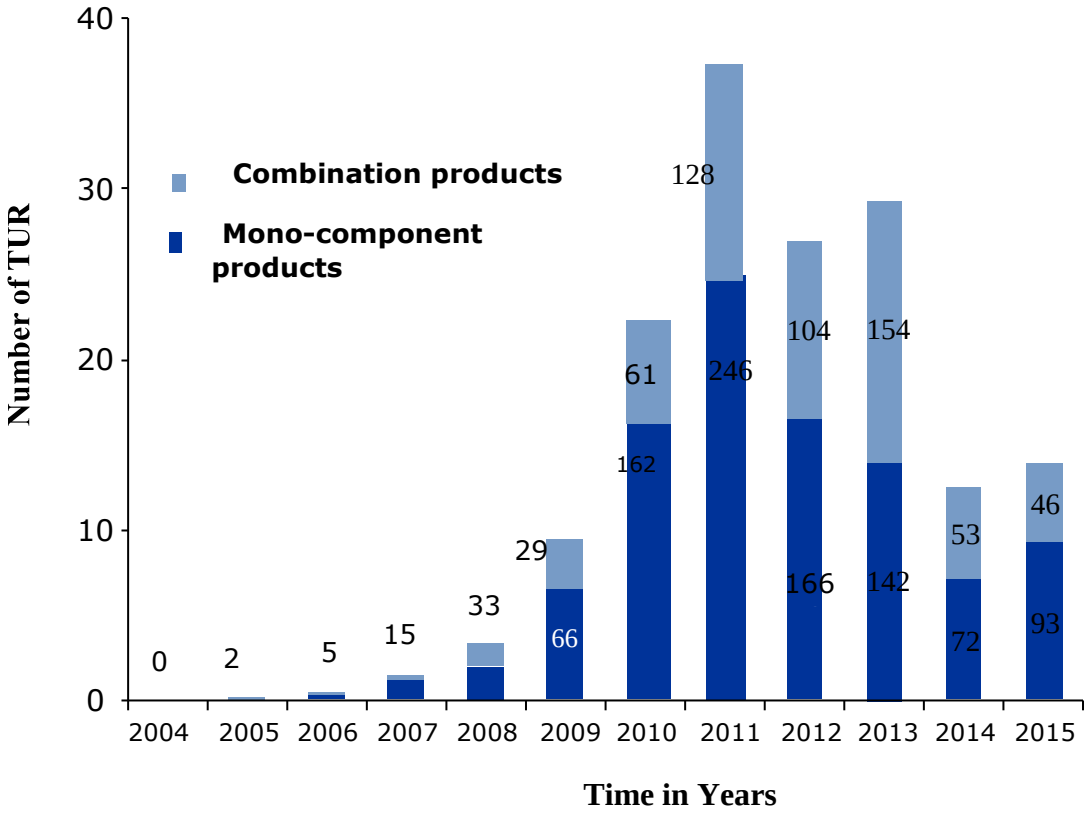


Figure 4.2: Total annual number of Traditional Use Registrations Marketing Authorizations for HMPs in the EU

Adopted from EMA, 2016d. Uptake of the traditional use registration scheme and implementation of the provisions of Directive 2004/24/EC in EU Member States EMA/HMPC/322570/2011 Rev. 6. London: EMA; 2016

In 2011, the highest peak in the graph coincides with the end of the 7 year period allowed by the EU for all EU member states to come up to date with Directive 2004/24/EC which would mean that unless the HMP is registered it cannot be sold on the market to the public.

Further analysis of TUR registration figures, show that Austria, UK, Poland and Germany, represent the leading EU member states that granted the highest number of registrations as highlighted in the table 4.1. Registration fees had a significant impact on the number of registrations achieved. Discrepancies were noticed in registration fees in different EU member states. In Italy the registration fee amounts to 50,000 euro for each product. These high fees are reflected in the number of TUR applications in a ten year period. There is a lack of harmonisation between EU member states thus limiting availability of herbal products (Eurocam, 2011). It was noticed that TUR does not take into consideration medicines of Asian tradition such as Ayurveda or the popular traditional Chinese medicine. Such a limitation was acknowledged by the European Commission and such an issue should be assessed and an independent legal framework should be considered for such products (Eurocam, 2011).

Table 4.1: Total number of TUR applications in EU Member states since implementation of EU Directive 2004/24/EC

Member State	TUR applications received	TUR applications under assessment	TUR granted	TUR refused	TUR applications withdrawn by applicant
Total	**2629**	**654**	**1577**	**215**	**183**
Austria	214	18	195	0	1
Belgium	83	46	21	6	10
Bulgaria	33	15	15	2	1
Croatia	29	9	19	0	1
Cyprus	6	5	1	0	0
Czech Republic	72	7	58	2	5
Denmark	11	6	0	4	1
Estonia	14	2	12	0	0
Finland	24	3	11	1	9
France	171	137	23	0	11
Germany	495	64	263	109	59
Greece	33	11	12	6	4
Hungary	110	49	61	0	0
Ireland	83	35	40	0	8
Italy	18	2	10	2	4
Latvia	25	1	20	0	4
Lithuania	30	0	13	15	2
Netherlands	78	22	43	2	11
Poland	310	77	197	19	17
Portugal	17	5	11	0	1
Romania	27	22	5	0	0
Slovakia	8	1	5	2	0
Slovenia	33	8	25	0	0
Spain	152	34	90	27	1
Sweden	84	9	69	0	6
United Kingdom	447	59	344	18	26
(Norway)	22	7	14	0	1

(Luxembourg, Liechtenstein Malta and Iceland were found to have no applications)

Adapted from EMA, 2016d. Uptake of the traditional use registration scheme and implementation of the provisions of Directive 2004/24/EC in EU Member States EMA/HMPC/322570/2011 Rev. 6. London: EMA; 2016.

Figure 4.3 represents the total number of WEU registrations that took place annually in Europe, since EU Directive 2004/24/EC. The total number of WEU marketing authorisations that took place was of 768.

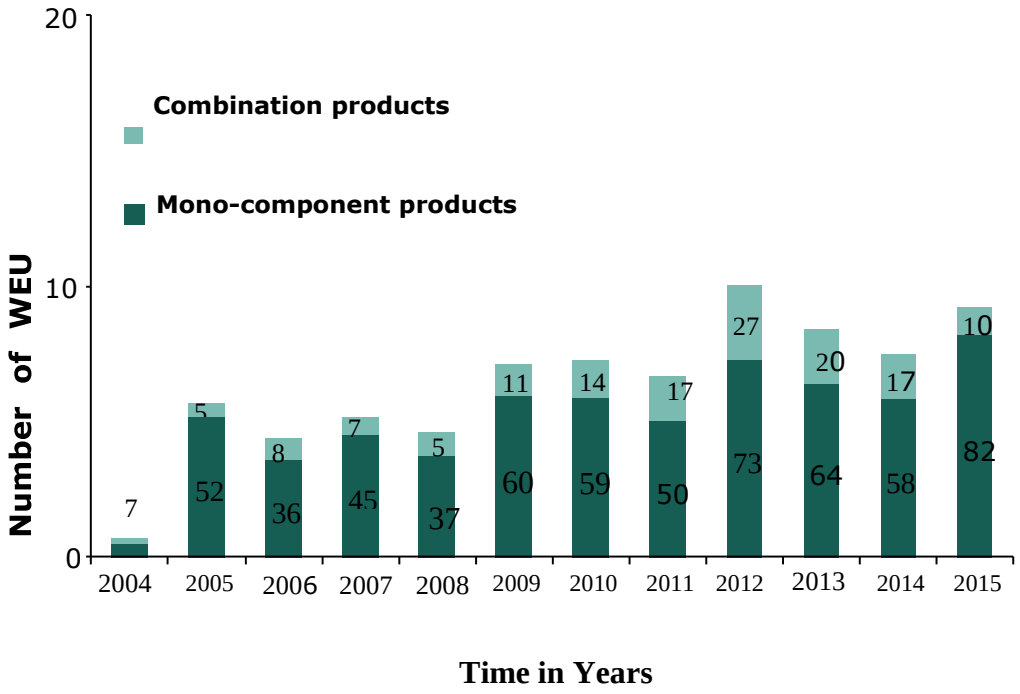


Figure 4.3: Total annual number of WEU MA for HMP in the EU per year

Adopted from EMA, 2016d. Uptake of the traditional use registration scheme and implementation of the provisions of Directive 2004/24/EC in EU Member States EMA/HMPC/322570/2011 Rev. 6. London: EMA; 2016

Table 4.2: Total number of WEU MA applications for HMP by EU Member since implementation of EU Directive 2004/24/EC

Member State	WEU MA applications received	WEU MA applications under assessment	WEU MA granted	WEU MA refused	WEU MA applications withdrawn by applicant
Total	**1292**	**304**	**768**	**62**	**152**
Austria	59	8	51	0	0
Belgium	26	4	17	1	4
Bulgaria	13	2	11	0	0
Croatia	48	7	32	7	2
Cyprus	5	5	0	0	0
Czech Republic	69	15	33	6	15
Denmark	13	8	4	1	0
Estonia	13	0	8	0	5
Finland	30	7	8	0	15
France	59	33	22	0	4
Germany	425	59	278	22	66
Greece	21	9	10	1	1
Hungary	40	14	21	0	5
Ireland	5	0	4	0	1
Italy	3	0	0	2	1
Latvia	30	4	24	0	2
Lithuania	52	10	24	9	9
Netherlands	33	8	18	1	6
Poland	69	35	24	2	8
Portugal	26	6	12	6	2
Romania	53	34	19	0	0
Slovakia	51	19	28	4	0
Slovenia	55	5	44	0	0
Spain	27	0	27	0	0
Sweden	53	6	41	0	6
United Kingdom	3	2	1	0	0
(Norway)	11	4	7	0	0

(Luxembourg, Malta and Iceland were found to have no applications)

Adapted from EMA, 2016d. Uptake of the traditional use registration scheme and implementation of the provisions of Directive 2004/24/EC in EU Member States EMA/HMPC/322570/2011 Rev. 6. London: EMA; 2016.

In the U.S, the Food and Drug Administration (FDA), is the body that regulates dietary supplements. In 1994, the Dietary Supplement Health and Education Act (DSHEA) was introduced as a form of regulatory framework applicable for dietary supplements in the U.S. The aim of this act was to enhance patient safety by granting patients access to dietary supplements but at the same time it gave the FDA the authority to take action against dietary supplements that posed a risk to patients' health. The FDA in the U.S. regulates finished dietary supplements and the ingredients. Before marketing, it is the responsibility of the manufacturer of the dietary supplement (or the ingredients) to ensure product safety. Once on the market, it is the FDA responsibility to monitor safety to withdraw any unsafe supplements. In the U.S, dietary supplements may be divided in those placed on the market before the introduction of the DSHEA and those placed on the market post–DSHEA. Products marketed before the passage of DSHEA (1994) were considered to hold a history of safe use. Following the introduction of the DSHEA, manufacturers were requested to inform the FDA, 75 days before marketing so as to allow FDA to examine data related to safety issues of any new ingredients and possibly denying permit for release of new product in the market. Labelling must not misinform the patient in that it should be truthful and not misleading (FDA, 2016).

In the EU, medicinal products including HMPs to be placed on the market must satisfy requirements of quality, safety and efficacy, and only if evidence demonstrating these 3 requirements is given then medicines obtain a marketing authorisation. The simplified registration (TUR) allowed those herbal medicines that previously could not ensure all 3 requirements to be regularised. As a result, today all herbal substances and preparations utilised throughout the EU member states, have established community monographs which can be harmoniously utilised by all member states to speed up the registration process and thus ensure availability to EU citizens. The HMPC is the responsible body

in charge of regulating HMP for EMA, with the intention to achieve and maintain international standards such as those instilled by International Conference on Harmonization (Poveda, 2015).

4.3 Ensuring patient safety through pharmacist knowledge

Consumers are increasingly opting for herbal products to treat different diseases, and the majority of these patients buy their products from pharmacies and health food shops. Such a trend was confirmed in this study, which showed that over 90% of consumers interviewed opted to purchase herbal products from pharmacies (54%) and health food shops (39%). It was found that 65% of the consumers interviewed prefer the pharmacist as a source for advice related to herbal products. Other studies investigating from where patients prefer to obtain their source of information related to use of herbal products show contrasting opinions. Studies by Levy, 1999; and Gul et al, 2007 showed that consumers view the pharmacist as a knowledgeable and dependable source of information about herbals (Levy, 1999; Gül et al, 2007). Studies by Traulsen and Noerrestat, and Kwan et al showed that consumers do not rely on pharmacist's advice solely but resort to other sources (Traulsen and Noerreslet 2004; Kwan et al, 2008).

The pharmacist as a healthcare professional is in a position to give advice to consumers about the use of herbal products and thus ensure patient safety through provision of evidence based information. Since consumption of herbal products is on the increase it is not surprising that community pharmacists are receiving more enquires about herbal products. Such enquiries about use of herbals vary from general information to a more technical type of information such as interactions, side effects and contraindications. To provide the correct information to the patient, the pharmacist needs to be sufficiently

trained about the subject and should have access to necessary information when required. Pharmacists need more quality information about safety issues, interactions and indications and uses of herbal products from informational resources such as the pharmacy information systems. Such availability of information could benefit the pharmacist in addressing issues related to use of herbal products. Pharmacists should know how to interpret any information provided. This could be achieved through continuing educational courses integrated within the respective curricula, conferences and seminars. In a study by Welna et al, 2003, it was concluded that with the increase in popularity of herbal products, community pharmacists are faced with more enquires about the products, since pharmacists are readily and easily accessible by the public (Welna et al, 2003; Al-Arifi, 2013).

In this study, the knowledge of pharmacists and health shop employees in Malta, about different issues related to use of herbals, was assessed. Results showed that both pharmacists and health shop employees were not sufficiently knowledgeable about the subject. This was evidenced by the score attained by both group of participants (mean score = 27.60 / 56.00), confirming that both groups need to be more trained and educated in order to give the best possible advice to patients. Further analysis of results showed that there was no statistical significant difference in knowledge score between pharmacists and health shop employees. It was noticed that both pharmacists and health shop employees found difficulties in answering questions related to indications of herbal medicals and side-effects. For example 71% (n=10) of health shop employees did not know about a serious interaction involving St. John's wort, while over half (n=36) of the pharmacists did not answer questions related to indications of Saw Palmetto. As

a result patients may receive incorrect information about interactions between herbal – prescription drugs or inadequate disease treatment.

One of the major problems of using herbal medicines together with conventional medicines is the potential interactions which could result in a clinically significant impact on the patient's health. Patients who opt to consume herbal products assume that such products are automatically safe since they are considered to be 'natural'. The high number of case reports of herb-drug interactions documented clearly show that herbal products are not safe because they are natural. It is not yet clearly understood which mechanisms lead to such herb-drug interactions but these interactions take place both at a pharmacokinetic and pharmacodynamic level. This implies that herbal products may lead to medicines effect to be increased, decreased or even mimicked. There is the possibility that the herbal product has therapeutic characteristics that act synergistically to those of the drug being taken concomitantly resulting in an additive effect. Ephedra, when used with amphetamines or benzodiazepines, may result in supratherapeutic effects which may complicate the medical condition being treated. Alternatively, a counteracting effect can occur when medicines are taken together such as ephedra and anti-hypertensive medicines. Herbal products can cause pharmacokinetic interactions which can result in changes in absorption, distribution, metabolism and excretion of drugs (Rivera et al, 2013).

In studies carried out by (Bush et al, 2007; Loya et al, 2009) to determine widespread presence of herb-drug interactions in the elderly population, it resulted that 30-40% of the older generation had a potential interaction between their medication and the herbal supplement. Besides pharmacokinetic interactions, herbal products could also be involved in interactions which alter pharmacological activity of the co-administered

drug. Herbal products can have an impact on blood glucose levels and blood pressure when taken with hypoglycaemic and anti-hypertensives, with detriment to the patient's health. This implies that patient should inform healthcare professionals about any herbal products which they might consume, and such patients should be monitored to prevent complications (Rivera et al, 2013). Table 4.3 highlights possible interactions, including potential severity between herbals and conventional medicines.

There are factors which can have an impact on the extent to which herb-drug interactions occur. These include individual characteristics of medicines and herbs, patient factors such as co-morbidities, medication taken concurrently and genetics. Studies showed that co-administration of herbals and conventional drugs result in significant potential interactions and occur more commonly in patients suffering from chronic conditions, with the result that this could have an effect on the patient's compliance to treatment (Rivera et al, 2013).

Pharmacists can have a fundamental role in patients taking herbal products by establishing any significant health issues with the patient and other health care providers. More appropriate counselling and monitoring of patients can be targeted towards identification of potential adverse effects. The pharmacist should have the necessary skills to identify and understand if a herbal supplement taken by a patient is appropriate or not. This is because the pharmacist can review a patient's drug regimen including co-morbidities. As part of a multidisciplinary team, the pharmacist can contribute in research and document use of herbal medicine. The pharmacist can publish results obtained for the better knowledge of others. It is important that information about herbal products is integrated across the curriculum, and designed specifically so that pharmacists obtain higher skill in this area. With the proper knowledge and oral

communication skills, pharmacists can optimise critical appraisal skills to obtain valuable information on conventional medicines and on herbal medicines.

Table 4.3: Interactions between herbals and conventional medicines

Alternative medicine	Interacting drug	Possible outcome	Severity and level of evidence*	Comments / Proposed mechanisms
Gingko	Warfarin, antiplatelet drugs	↑ bleeding risk	**Major**, level D	Antiplatelet activity after several weeks
Kava	CNS depressants	↑ drug effect	**Major**, level A	Additive somnolence
Evening primrose oil	Antiplatelet drugs, warfarin	↑ drug effect	Major, level B	Contains gamma-linolenic acid, probable anticoagulant
St John's wort	Alprazolam	↓ drug levels & effect	**Major**, level B	Increased clearance; half-life reduced by 50%
	Amitriptyline	↑ drug effect	**Major**, level B	Increased risk of serotonin syndrome
	Antidepressants, tramadol	↑ drug effect	**Major**, level D	
	Pethidine	↑ drug effect	**Major**, level D	
	Non-nucleoside reverse transcriptase inhibitors, protease inhibitors	↓ drug levels & effect	**Major**, level B	Induces CYP3A4
	Oral contraceptives	↓ drug levels	**Major**, level B	Risk of breakthrough bleeding/contraceptive failure
	P-glycoprotein substrates e.g. digoxin,fexofenadine, irinotecan	↓ drug levels & effect	**Major**, level B	Induces intestinal P-glycoprotein
	Warfarin	↓ drug effect	**Major**, level B	Induces CYP1A2, CYP2C9 and CYP3A4
Valerian	Alprazolam	↑ drug levels	**Major**, level B	CYP3A4 inhibitor. Alprazolam increased by 19% in one study.
	CNS depressants	↑ drug effect	**Major**, level D	Pharmacodynamic effect
Major	Strongly discourage use concomitantly since serious adverse outcome could occur. If used, patient should be monitored for potential adverse effects.			
Moderate	Use cautiously or avoid combination as a significant adverse outcome could occur. If used, monitor for potential adverse outcomes.			

Level of evidence ratings:
A High-quality randomised controlled trial(RCT) or meta-analysis
B Non-RCT, literature review, clinical cohort or case-control study, historical control or epidemiologic study
C Consensus or expert opinion
D Anecdotal evidence; in vitro or animal study or theoretical based on pharmacology

Adapted from Moses G, McGuire T. Drug interactions with complementary medicines. Australian Prescriber. 2010; 33(6):177-180

4.4 Ensuring patient safety through patient awareness

Herbal products are promoted by the media, including social media as part of marketing strategies which often is unethical. A major contributing factor to why the herbal market has grown is because of the advancement of internet, allowing consumers to obtain herbal products from any part of the world. In a study carried out by Morris and Avorn on how herbal products are marketed on the social media, it was found that 81% of websites advertised health claims, 50% of which claimed to treat, prevent and cure specific diseases, even though regulations forbid it (Morris and Avorn, 2003). These 'false' allegations together with the misconception that herbals are 'natural' and automatically safe are contributing to rapid increase in sales of herbals. Industries are making use of this pathway to increase their sales by making claims about these products as being safe and effective but in reality such claims cannot be established. Systems that verify the authenticity of the product and the companies that sell such products are still lacking, placing full responsibility onto the consumer.

Public misinformation about use of herbals could have significant impact on patient's health and safety. Results from this study have shown that 55% (n=83) of the respondents in the survey carried out, think that herbal products are harmless. Nearly two-thirds of the respondents either do not know or else think that combining herbals and conventional drugs is not dangerous. Fifty six percent (n=84) of the respondents admitted co-administering herbals and conventional drugs and in 59% (n=89), doctors were not aware about this. Results from this study, confirm trends from other similar surveys that public misinformation together with the patient's attitude that herbals are 'naturally' safe is contributing to misuse of herbals with potential implications on their health and safety (Tachjian et al, 2010)

4.5 Limitations

A small number of health shop employees and pharmacists participated in the study.

Since respondents had the possibility of giving an ' I don't know' response, this may have led to some respondents to self- doubt and refrain from giving a 'Correct' or 'Incorrect' answer which might have influenced the results.

While respondents were instructed not to make use of any references or sources of information when answering the questionnaire, an element of bias might have been present if sources were consulted. Pharmacists and health shop employees are urged to consult with reliable sources when their knowledge is limited on a herbal product at hand in everyday life.

With regards to the public survey different results might have been obtained if members of the public had been recruited from outlets other than the pharmacy.

4.6 Further studies

Based on the outcomes and findings the following recommendations are being made for further evaluation. A greater participation by pharmacists and health shop employees in this study, could help give a better indication of knowledge and attitudes of those responsible in handling these herbal products.

Based on the results obtained by pharmacists in this study, it is evident that training of pharmacists in the area of complementary alternative medicines should be considered and or improved in undergraduate and post graduate curricula.

Health shop employees should be offered a more in depth training as part of the curricula within the MCAST course currently offered.

Complementary to the national adverse reaction system, another system specific for herbal medicinal products should be considered to allow health care professionals to report any adverse reactions. Pharmacists should have ready access to relevant sources of information.

4.7 Conclusion

There are various stakeholders involved to ensure safety of herbal medicinal products as was highlighted in this research study. These include the manufacturers, the national authorities, pharmacists and health shop employees and the patient.

This research was the first of its kind to evaluate knowledge and confidence of both pharmacists and health shop employees in Malta. The results obtained show that there is a need to empower both pharmacists and health shop employees with scientific information about herbal medicinal products to improve their knowledge.

Outcomes from this research indicate that patient safety may be jeopardized due to the co-administration of herbal medicines with conventional medicines and this would require a high level of pharmacist intervention.

From a regulatory aspect, the way herbal medicines are classified is intended to safeguard the interests of the patients, but there are still many loopholes in the system which need to be addressed to ensure that herbals are safe.

Since HMPs are to be classified as a category of medicines whereby quality, safety and efficacy are ensured as for conventional medicines, the time has come whereby authorities and manufacturers work in unison to undertake proper research to demonstrate effectiveness. It is only by improving research and carrying out proper

randomized controlled clinical trials as occurs with conventional medicines that safe HMPs can be ensured for the patients.

Pharmacists and health shop employees need to be prepared more appropriately to be capable of giving the proper advice to consumers, and this can be achieved through improved and revised programs in the current curricula provided.

REFERENCES

Abdel-Shafy H, Mansour M. A review on polycyclic aromatic hydrocarbons: Source environmental impact, effect on human health and remediation. Egyptian Journal of Petroleum. 2016; 25(1):107-123.

Al-Arifi M. Availability and needs of herbal medicinal information resources at community pharmacy, Riyadh region, Saudi Arabia. Saudi Pharmaceutical Journal. 2013; 21(4):351-360.

Alkharfy K. Community pharmacists' knowledge, attitudes and practices towards herbal remedies in Riyadh, Saudi Arabia. Eastern Mediterranean Health Journal. 2010; 16(9):988-993

Ananthi R, Chandra N, Santhiya S, Ramesh A. Genotoxic and antigenotoxic effects of Hemidesmus indicus R. Br. Root extract in cultured lymphocytes. Journal of Ethnopharmacology. 2010; 127(2):558-560.

Andrade L, Santos D, Castro D, Guillo L, Chen-Chen L. Absence of antimutagenicity of Cochlospermum regium (Mart. and Schr.) Pilger 1924 by micronucleus test in mice. Brazilian Journal of Biology. 2008; 68(1):155-159.

Ariño A, Herrera M, Estopañan G, Juan T. High levels of ochratoxin A in licorice and derived products. International Journal of Food Microbiology. 2007; 114(3):366-369.

Attard E. Herbal Medicinal Products. Is your product a herbal medicine? 2010.

Barnes J. Pharmacovigilance of Herbal Medicines, A UK Perspective. Drug Safety. 2003; 26(12):829-851.

Baye H, Hymete A. Lead and Cadmium Accumulation in Medicinal Plants Collected from Environmentally Different Sites. Bulletin of Environmental Contamination and Toxicology. 2009; 84(2):197-201.

Blumenthal M, Brinckmann J, Wollschlaeger B. The ABC clinical guide to herbs. Austin, Tex: American Botanical Council; 2003: 303-305

Brendler T, Philips L. A practical guide to licensing herbal medicinal products. 1st ed. London: Pharmaceutical Press; 2009.

Bush T, Rayburn K, Holloway S, Sanchez-Yamamoto D, Allen B. Adverse interactions between herbal and dietary substances and prescription medications: a clinical survey. Altern Ther Health Med. 2007; 13(13):30-35.

Calixto J. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). Braz J Med Biol Res. 2000; 33(2):179-189.

CAM, 2011. Complementary and Alternative Medicine (CAM): The research priorities for its use in citizens' health and healthcare systems reform [Internet]. Cam-europe.eu. 2011 [cited 5 January 2017]. Available from: http://www.cam-europe.eu/

Castro D, Santos D, Ferreira H, Santos S, Chen-Chen L. Cytotoxic and mutagenic activity of Cochlospermum regium Mart. (Algodãozinho-do-campo) in mice. Revista Brasileira de Plantas Medicinais. 2004; Volume 6 (3): 15-19.

Chang Z, Kennedy D, Holdford D, Small R. Pharmacists' Knowledge and Attitudes toward Herbal Medicine. Annals of Pharmacotherapy. 2000; 34(6):710-715.

Chen-Chen L, Sena M. Atividade tóxica e mutagênica do óleo de copaíba (Copaifera langsdorfii Desfon) em camundongos. Rev Bras Planta Med. 2002; 5 37–40.

Claeson P. Requirements on efficacy of herbal medicinal products. Journal of Ethnopharmacology. 2014;158: 463-466.

Commission of the European Communities. Proposal for amending the directive 2001/83/EC as regards traditional herbal medicinal products. 2002/0008 (COD). Brussels: European Commission, 2002.

Coon S, Stevens V, Brown J, Wolff S, Wrobel M. Comparison of dietary supplement product knowledge and confidence between pharmacists and health food store employees. Journal of the American Pharmacists Association. 2015; 55(2):161-168.

Cosyns J, Jadoul M, Squifflet J, de Plaen J, Ferluga D, Van Ypersele de Strihou C. Chinese herbs nephropathy: A clue to Balkan endemic nephropathy? Kidney International. 1994; 45(6):1680-1688.

D'Ovidio K, Trucksess M, Weaver C, Horn E, Mcintosh M, Bean G. Aflatoxins in ginseng roots. Food Additives and Contaminants. 2006; 23(2):174-180.

Dghaim R, Al Khatib S, Rasool H, Ali Khan M. Determination of Heavy Metals Concentration in Traditional Herbs Commonly Consumed in the United Arab Emirates. Journal of Environmental and Public Health. 2015; 2015:1-6.

Dharmananda S. Safety issues affecting herbs: Pyrrolizidine Alkaloids. 1st ed. [Portland, Or.]: [ITM]; 2001: 1-12

Di Stasi L, Oliveira G, Carvalhaes M, Queiroz-Junior M, Tien O, Kakinami S et al, Medicinal plants popularly used in the Brazilian Tropical Atlantic Forest. Fitoterapia. 2002; 73(1):69-91.

Dunnick J, Nyska A. The Toxicity and Pathology of Selected Dietary Herbal Medicines. Toxicologic Pathology. 2012; 41(2):374-386.

Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Frontiers in Pharmacology. 2014;(4):1-10.

EMA, 2004. Final Concept Paper on the Implementation of Different Levels of scientific Evidence in Core Data for Herbal Medicinal Drugs? (EMEA 2004) [Internet]. London: EMA; 2004. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500018048.pdf

EMA, 2006a. Guideline on non-clinical documentation for herbal medicinal products in applications for marketing authorization (Bibliographical and mixed applications) and in applications for simplified registration." Ref. EMEA/HMPC/32116/2005 [Internet]. EMA; 2006. Available from:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003576.pdf

EMA, 2006b. Guideline on non-clinical documentation for herbal medicinal products in applications for marketing authorization (Bibliographical and Mixed applications) and in applications for simplified registration" REF. EMEA/HMPC/32116/2005. EMA; 2005.

EMA, 2006c. Guideline on the limits of genotoxic impurities CPMP/SWP/5199/02 EMEA/CHMP/QWP/251344/2006. London: EMA; 2006.

EMA, 2008a. Guideline on the assessment of genotoxicity of herbal substances/preparations [Internet]. EMA, 2008 [cited 3 December 2016]. Available from:http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003569.pdf

EMA, 2008c. Guideline on the assessment of genotoxicity of herbal substances and preparations (EMEA/HMPC/107079/2007). London: EMA; 2008.

EMA, 2008d. Guideline on the specification limits for residues of metal catalysts or metal reagents. EMEA/CHMP/SWP/4446/2000. London: EMA; 2008.

EMA, 2008e. ICH Topic S2 (R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use. Ref EMEA/CHMP/ICH/126642/2008. London: EMA; 2008.

EMA, 2009a. Procedure for European Union guidelines and related documents within the pharmaceutical legislative framework (EMEA/P/24143/2004 Rev. 1. London: EMA; 2009.

EMA, 2009b. Guideline on Quality of combination herbal medicinal products /traditional herbal medicinal products (EMEA/HMPC/CHMP/CVMP/214869/2006) [Internet]. EMA. 2008 [cited 1 December 2016]. Available from:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003286.pdf

EMA, 2009c. Guideline on selection of test materials for genotoxicity testing for traditional herbal medicinal products Ref. EMEA/HMPC/67644/2009. London: EMA; 2009.

EMA, 2011a. Guideline on quality of herbal medicinal products/traditional herbal medicinal products, EMA/CPMP/QWP/2819/00 V2. EMA; 2011.

EMA, 2011b. Guideline on quality of herbal medicinal products /traditional herbal medicinal products [Internet]. London: EMA; 2011. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/09/WC500113209.pdf

EMA, 2014. Reflection paper on microbiological aspects of herbal medicinal products and traditional herbal medicinal products EMA/HMPC/95714/2013. EMA; 2014.

EMA, 2016a. Guideline on the assessment of clinical safety and efficacy in the preparation of European Union herbal monographs for well-established and traditional herbal medicinal products EMA/HMPC/104613/2005 Rev. 1. London: EMA; 2016;

EMA, 2016b. Public statement on contamination of herbal medicinal products/traditional herbal medicinal products with pyrrolizidine alkaloids. London: EMA; 2016.

EMA, 2016c. Reflection paper on Polycyclic Aromatic Hydrocarbons in herbal medicinal products/traditional herbal medicinal products Ref EMA/HMPC/300551/2015. 2016

EMA, 2016d. Uptake of the traditional use registration scheme and implementation of the provisions of Directive 2004/24/EC in EU Member States EMA/HMPC/322570/2011 Rev. 6. London: EMA; 2016.

EMA, 2016e. Concept paper on the revision of the “Guideline on nonclinical documentation for herbal medicinal products in applications for marketing authorization (bibliographical and mixed applications) and in applications for simplified registration” EMA/HMPC/353983/2016. London: EMA; 2016.

Ernst, 2002. Toxic heavy metals and undeclared drugs in Asian herbal medicines. Trends in Pharmacological Sciences. 2002; 23(3):136-139.

EU Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal. 2001; 311:67–128.

EU Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements (Text with EEA relevance). OJ L. 2002; 29(183):0051-0057.

EU Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (Text with EEA relevance). OJ L 159. 2003; 46-94.

EU Directive 2004/24/EC of the European Parliament and of the council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official Journal of European Union [Internet]. 2004; Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2004_24/dir_2004_24_en.pdf

EU Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products. OJ L 262. 1976:169–200.

EU Regulation (EC) No 726/2004. Laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. EU Parliament and Council; 2004.

EU Commission, 2015. EudraLex - EU Legislation - European Commission [Internet]. Ec.europa.eu. 2015 [cited 30 November 2016]. Available from: http://ec.europa.eu/health/documents/eudralex/index_en.htm

European Pharmacopoeia, 2014. Determination of aflatoxin B1 in herbal drugs. 8th ed. Ph. Eur; 2014. p. 276.

European Pharmacopoeia, 2016. Microbiological quality of herbal medicinal products for oral use and extracts used in their preparation. 9th ed. European Council; 2016. p. 591. Accessed Nov 2016

Facchinetti F, Pedrielli G, Benoni G, Joppi M, Verlato G, Dante G et al. Herbal supplements in pregnancy: unexpected results from a multicentre study. Human Reproduction. 2012; 27(11):3161-3167.

Fan T, Deal G, Koo H, Rees D, Sun H, Chen S et al. Future development of global regulations of Chinese herbal products. Journal of Ethnopharmacology. 2012; 140(3):568-586.

FDA, 2016. Dietary Supplements [Internet]. Fda.gov. 2016 [cited 5 April 2017]. Available from: https://www.fda.gov/food/dietarysupplements/default.htm

Global Industry Analysts, Inc. Herbal Supplements & Remedies: A Global Strategic Business Report [Internet]. 2015. Available from: http://www.strategyr.com

Gromek K, Drumond N, Simas P. Pharmacovigilance of herbal medicines. International Journal of Risk & Safety in Medicine. 2015; 27(2):55-65.

Gül H, Omurtag G, Clark P, Tozan A, Ozel S. Nonprescription medication purchases and the role of pharmacists as healthcare workers in self-medication in Istanbul. Med. Sci. Monit. 2007; 13:PH9–PH14. Med Sci Monit. 2007; 13(PH9-PH14).

Heinrich M. Quality and safety of herbal medical products: regulation and the need for quality assurance along the value chains. British Journal of Clinical Pharmacology. 2015; 80(1):62-66.

Hooyenga P, Witkamp R, Groen K. Herbal products: Marketing strategies and legislation. Int J Green Pharm. 2009; 3(4):270.

Ifeoma O, Oluwakanyinsola S. Screening of Herbal Medicines for Potential Toxicities. New Insights into Toxicity and Drug Testing [Internet]. 1st ed. 2013. Available from: https://www.intechopen.com/books/new-insights-into-toxicity-and-drug-testing/screening-of-herbal-medicines-for-potential-toxicities

Jena G, Kau C, Ramarao L. Genotoxicity testing, a regulatory requirement for drug discovery and development: impact of ICH guidelines. Indian Journal of Pharmacology [Internet]. 2002; 34:86-99. Available from: http://medind.nic.in/ibi/t02/i2/ibit02i2p86.pdf

Jordan S, Cunningham D, Marles R. Assessment of herbal medicinal products: Challenges, and opportunities to increase the knowledge base for safety assessment. Toxicology and Applied Pharmacology. 2010; 243(2):198-216.

Kosalec I, Cvek J, Tomić S. Contaminants of Medicinal Herbs and Herbal Products. Archives of Industrial Hygiene and Toxicology. 2009; 60(4)485-501.

Kroes B. The legal framework governing the quality of (traditional) herbal medicinal products in the European Union. Journal of Ethnopharmacology. 2014; 158:449-453.

Kwan D, Boon H, Hirschkorn K, Welsh S, Jurgens T, Eccott L et al. Exploring consumer and pharmacist views on the professional role of the pharmacist with respect to natural health products: a study of focus groups. BMC Complementary and Alternative Medicine. 2008; 8(1):40.

Levy S. Healthcare 2000’ reveals consumer view of R.Ph.s. Drug Topics. Drug Topics. 1999; 143(64).

Locatelli C, Melucci D, Locatelli M. Toxic Metals in Herbal Medicines. A Review. Current Bioactive Compounds. 2014; 10(3):181-188.

Loya A, González-Stuart A, Rivera J. Prevalence of Polypharmacy, Polyherbacy, Nutritional Supplement Use and Potential Product Interactions among Older Adults Living on the United States-Mexico Border. Drugs & Aging. 2009; 26(5):423-436.

Mann R, Andrews E. Pharmacovigilance. 1st ed. West Sussex, UK: Chichester; 2002.

Marcus D, Snodgrass W. Do No Harm: Avoidance of Herbal Medicines During Pregnancy. Obstetrics & Gynecology. 2005; 106(2):410-411.

Marques R, de Medeiros S, Dias Cda S, Barbosa-Filho J, Agnez-Lima L. Evaluation of the mutagenic potential of yangambin and of the hydroalcoholic extract of Ocotea duckei by the Ames test. Mutation Research/Genetic Toxicology and Environmental Mutagenesis. 2003; 536(1-2):117-120.

McKenna L, McIntyre M. What over-the-counter preparations are pregnant women taking? A literature review. Journal of Advanced Nursing. 2006; 56(6):636-645.

Melo-Reis P, Bezerra L, Vale M, Canhête R, Chen-Chen L. Assessment of the mutagenic and antimutagenic activity of Synadenium umbellatum Pax latex by micronucleus test in mice. Brazilian Journal of Biology. 2011; 71(1):169-174.

Moreira D, Teixeira S, Monteiro M, De-Oliveira A, Paumgartten F. Traditional use and safety of herbal medicines. Revista Brasileira de Farmacognosia [Internet]. 2014; 24(2):248-257. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-695X2014000200248

Morris C, Avorn J. Internet Marketing of Herbal Products. JAMA. 2003; 290(11):1505.

Moses G, McGuire T. Drug interactions with complementary medicines. Australian Prescriber. 2010; 33(6):177-180.

Mulware S. Trace elements and carcinogenicity: a subject in review. 3 Biotech. 2012; 3(2):85-96.

Okatch H, Ngwenya B, Raletamo K, Andrae-Marobela K. Determination of potentially toxic heavy metals in traditionally used medicinal plants for HIV/AIDS opportunistic infections in Ngamiland District in Northern Botswana. Analytica Chimica Acta. 2012; 730:42-48.

Pallivalapila A, Stewart D, Shetty A, Pande B, Singh R, McLay J. Use of Complementary and Alternative Medicines During the Third Trimester. Obstetrics & Gynecology. 2015; 125(1):204-211.

Petrovska B. Historical review of medicinal plants′ usage. Pharmacognosy Reviews. 2012; 6(11):1.

Poveda R. Regulation of Herbal (Traditional) Medicinal Products in the European Union. Pharmaceutical Regulatory Affairs: Open Access. 2015; 04(02): 1000142.

Rashidi M, Deokule S. Associated fungal and aflatoxins contamination in some fresh and market herbal drugs. J Microbiol Biotechnol Res. 2013; 3(1):23-31.

Regner G, Gianesini J, Von Borowski R, Silveira F, Semedo J, Ferraz A et al. Toxicological evaluation of Pterocaulon polystachyum extract: A medicinal plant with antifungal activity. Environmental Toxicology and Pharmacology. 2011; 31(1):242-249.

Rivera J, Ceballos R, Loya A. Use of Herbal Medicines and Implications for Conventional Drug Therapy Medical Sciences. Alternative & Integrative Medicine. 2013; 02(06): 1000130.

Sackett D, Rosenberg W, Gray J, Haynes R, Richardson W. Evidence based medicine: what it is and what it isn't. BMJ. 1996; 312(7023):71-72.

Sahoo N, Manchikanti P, Dey S. Herbal drugs: Standards and regulation. Fitoterapia. 2010; 81(6):462-471.

Shaban N, Abdou K, Hassan N. Impact of toxic heavy metals and pesticide residues in herbal products. Beni-Suef University Journal of Basic and Applied Sciences. 2016; 5(1):102-106.

Shaw D, Graeme L, Duez P, Williamson E, Chan K. Pharmacovigilance of Herbal medicines. Journal of Ethnopharmacology. 2012; 140:513-518.

Shin I, Seo C, Ha H, Lee M, Huang D, Huh J et al. Genotoxicity assessment of Pyungwi-san (PWS), a traditional herbal prescription. Journal of Ethnopharmacology. 2011; 133(2):696-703.

Silano V, Coppens P, Larrañaga-Guetaria A, Minghetti P, Roth-Ehrang R. Regulations applicable to plant food supplements and related products in the European Union. Food & Function. 2011; 2(12):710.

Spiteri M, Attard E, Serracino-Inglott A, Azzopardi L. Compilation of a herbal medicine formulary for herbal substances in Malta and its usefulness amongst healthcare professionals. Journal of Young Pharmacists. 2013; 5(1):22-25.

Sponchiado G, Adam M, Silva C, Silva Soley B, de Mello-Sampayo C, Cabrini D et al. Quantitative genotoxicity assays for analysis of medicinal plants: A systematic review. Journal of Ethnopharmacology. 2016;(178):289-296.

Sweileh W, Abu Arrah E, Taha A, Sawalha A, Salah O, Jamous R et al. Dispensing practices, attitudes and knowledge of pharmacists towards herbal products in Palestine. Ibnosina J Med Biomed Sci. 2013; 5(3):123-30.

Tachjian A, Maria V, Jahangir A. Use of Herbal Products and Potential Interactions in Patients with Cardiovascular Diseases. Journal of the American College of Cardiology. 2010; 55(6):515-525.

Tovar R, Petzel R. Herbal Toxicity. Disease-a-Month. 2009; 55(10):592-641.

Traulsen J, Noerreslet M. The new consumer of medicine – the pharmacy technicians' perspective. Pharmacy World & Science. 2004; 26(4):203-207.

Tripathy V, Basak B, Varghese T, Saha A. Residues and contaminants in medicinal herbs—A review. Phytochemistry Letters. 2015; 14:67-78.

UNECE. Globally harmonised system of classification and labelling of chemicals. New York and Geneva: UNECE; 2011.

Vanherweghem J, Degaute J. The Policy of Admission to the Education in Medicine and Dentistry in the French-Speaking Community of Belgium. Acta Clinica Belgica. 1998; 53(1):2-3.

Wegener T, Deitelhoff B, Silber-Mankowsky A. Drug safety aspects of herbal medicinal products. Wiener Medizinische Wochenschrift. 2015; 165(11-12):243-250.

Welna E, Hadsall R, Schommer J. Pharmacists' Personal Use Professional Practice Behaviors and Perceptions Regarding Herbal and Other Natural Products. Journal of the American Pharmacists Association. 2003; 43(5):602-611.

WHO Global survey: National policy on traditional medicine and regulation of herbal medicines [Internet]. Geneva: World Health Organization; 2005. Available from: http://apps.who.int/medicinedocs/pdf/s7916e/s7916e.pdf

WHO, 1998. Quality control methods for herbal materials [Internet]. GENEVA: WHO; 1998. Available from: http://apps.who.int/medicinedocs/documents/h1791e/h1791e.pdf

WHO, 2003. Guidelines on good agricultural and collection practices (GACP) for medicinal plants. WHO; 2003.

WHO, 2004. Guidelines on safety monitoring of herbal medicines in pharmacovigilance systems". Geneva: WHO; 2004.

WHO, 2007. WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues". Spain: WHO; 2007.

Wiedenfeld H. Plants containing pyrrolizidine alkaloids: toxicity and problems. Food Additives & Contaminants: Part A. 2011; 28(3):282-292.

Wiesner J. Challenges of safety evaluation. Journal of Ethnopharmacology. 2014; (158):467-470.

Wilt T, Ishani A, Stark G, MacDonald R, Lau J, Mulrow C. Saw Palmetto Extracts for Treatment of Benign Prostatic Hyperplasia. JAMA. 1998; 280(18):1604.

Yang L, Wang L, Pan J, Xiang L, Yang M, Logrieco A. Determination of ochratoxin A in traditional Chinese medicinal plants by HPLC–FLD. Food Additives & Contaminants: Part A. 2010;27(7):989-997.

Yimam M, Lee Y, Hyun E, Jia Q. Reproductive and Developmental Toxicity of Orally Administered Botanical Composition, UP446-Part III: Effects on Fertility and Early Embryonic Development to Implantation in Sprague Dawley Rats. Birth Defects Research Part B: Developmental and Reproductive Toxicology. 2015; 104(4):166-176.

APPENDICES

Appendix A

University of Malta Research ethics Committee approval letter

L-UNIVERSITÀ TA' MALTA

Msida – Malta
Skola Medika
Sptar Mater Dei

UNIVERSITY OF MALTA

Msida – Malta
Medical School
Mater Dei Hospital

Ref No: **49/2016**

Monday 8th August 2016

Ms. Alexandra Curmi
Olympia
Jules Verne Street
San Pawl tat-Targa
Naxxar

Dear Ms. Alexandra Curmi,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

Classification of Herbal Medicinal products: What is Safe for the Patient

The University Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

Email: umms@um.edu.mt • ***Web:*** http://www.um.edu.mt/ms

Appendix B

Survey on Classification of

Herbal Supplements

Survey on Classification of Herbal Supplements

Welcome to my survey,

My name is Alexandra Curmi and I am currently reading for a PharmD course offered by the University of Malta in collaboration with the University of Illinois, Chicago.

As part of this course, I am required to undergo a research project. The dissertation I have chosen is entitled: Classification of Herbal Medicinal Products: What is safe for the patient?

Briefly, the aim of this thesis will be to evaluate whether current pharmacists and health food shop employees have sufficient and adequate knowledge to be able to advice patients or clients who choose to use herbal products. By assessing this it will be possible to see whether a restructuring of the current coursework currently given will be required.

In order to fulfill this task, a questionnaire was designed to determine what the knowledge, attitudes and perception of both Pharmacists and Health food shop employees is on Herbal products?

The questionnaire is divided in 4 sections:

- The First section will collect general Background data
- The Second will consist of a questionnaire to assess Knowledge on Herbal products
- The Third will assess how Pharmacists/Health shop employees classify Herbal products.
- The Fourth will assess general attitudes and confidence levels on Herbal products.

It requires approximately 10 minutes to fill in.

Incomplete surveys are counted as invalid, so I will appreciate your full response and honest answers.

This research has been approved by the University of Malta in collaboration with the University of Illinois, Chicago.

It is being supervised by Profs Lilian Azzopardi, Head of Pharmacy Department, Dr Janis Vella from the Department of Pharmacy and Profs Everaldo Attard, Associate Prof. Agricultural Chemistry and Pharmacognosy.

I thank you for your attention

Alexandra Curmi B.Pharm (Hons)

SECTION 1: PRELIMINARY

What is your Gender?

o Female o Male

What is your Age?

o 18-30 o 31-50 o 51-70

Qualifications

o Diploma o Bachelor or greater

o Alternative medicine course o Other

State the number of years of working experience

o less than 10 o between 10 and 20 o more than 20

Specify Occupation

o pharmacist o Health Shop Assistant

Highlight Area

o Community o Industry o Hospital o Other

SECTION 2 : KNOWLEDGE ASSESSMENT

Gingko Biloba may be used to improve which of the following conditions?

	Correct	Incorrect	Do Not Know
cognitive impairment	o	o	o
quality of life in mild dementia	o	o	o
fatigue	o	o	o
stress	o	o	o

Black cohosh may be used for which of the following conditions?

	Correct	Incorrect	Do Not Know
post menopausal	o	o	o
symptoms	o	o	o
profuse sweating	o	o	o
respiratory infections	o	o	o
enhance immunity	o	o	o

Saw palmetto is commonly used for which of the following conditions?

	Correct	Incorrect	Do Not Know
symptomatic treatment of headache	o	o	o
symptomatic relief of benign prostatic hyperplasia	o	o	o
help slow memory loss	o	o	o
relief of depressive symptoms	o	o	o

Echinacea can cause which of the following potential side effects?

	Correct	Incorrect	Do Not Know
hypersensitivity reactions in the form of rash	o	o	o
bronchospasm with airway obstruction	o	o	o
increased urination	o	o	o
bowel perforation	o	o	o

St john's wort interacts with which of the following conventional medicines?

	Correct	Incorrect	Do Not Know
warfarin	o	o	o
protease inhibitors (indinavir, amprenavir)	o	o	o
oral contraceptives	o	o	o
simvastatin	o	o	o

Bitter Fennel is indicated for which conditions?

	Correct	Incorrect	Do Not Know
bloating and flatulence	o	o	o
minor spasms in menstrual periods	o	o	o
liver conditions	o	o	o
joint and muscular inflammation	o	o	o

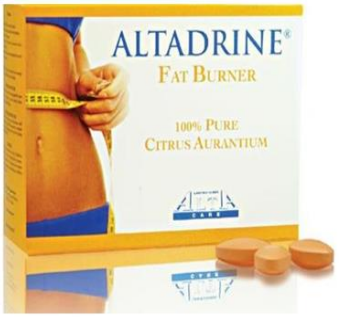
Which herbal product may be used to decrease cholesterol levels?

	Correct	Incorrect	Do Not Know
garlic	o	o	o
gingko biloba	o	o	o
hawthorn	o	o	o
horse chestnut seed	o	o	o

SECTION 3: CLASSIFICATION OF HERBAL PRODUCTS

By looking at the dose and ingredients of each product given, Classify each product?

PRODUCT 1: ALTADRINE®



INGREDIENTS	per tablet	per 100 g
Citrus aurantium extract (Tit. 6% synephrine)	200.00 mg	25.64 g
Maltodextrin	175.75 mg	22.53 g
Guarana extract (Tit. 12% caffeine)	100.00 mg	12.82 g
Micro crystalline cellulose	80.00 mg	10.26 g
Lactoserum protein	50.00 mg	6.41 g
Magnesium oxide	50.00 mg	6.41 g
Vitamin C	40.00 mg	5.13 g
Tri calcium phosphate	40.00 mg	5.13 g
Film coating	30.00 mg	3.85 g
Magnesium stearate	7.00 mg	0.90 g
Zinc oxide	6.25 mg	0.80 g
Vitamin B5	1.00 mg	0.13 g

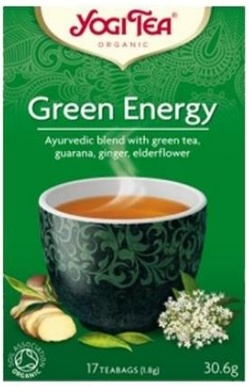
Classify the herbal product

- o Medicinal product
- o Herbal supplement
- o Medicinal/herbal supplement (Borderline)
- o I don't know

State the reasons why you chose to classify the product accordingly?

Your Answer

PRODUCT 2: YOGI TEA



Green Energy Ingredients

green tea (68%)*
lemon grass*
guarana (7%)*
peppermint*
ginger (3%)*
natural flavor, elderflower (2%)*
black pepper*
dried kombucha drink*
lemon verbena*

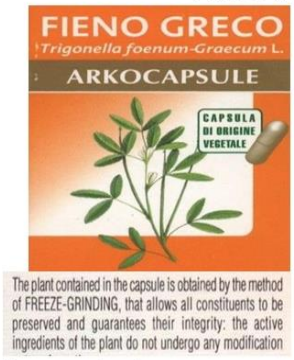
Green Energy Ingredients

- o Medicinal product
- o Herbal supplement
- o Medicinal/herbal supplement (Borderline)
- o I don't know

State the reasons why you chose to classify the product accordingly?

Your Answer

PRODUCT 3: FENUGREEK



DIRECTIONS FOR USE:
Take 1-2 capsules twice a day with a large glass of water, preferably before meals. Do not exceed the recommended daily dosage.

INGREDIENTS: *Fenugreek* (Trigonella foenum-Graecum L.) seed powder. Capsule shell of plant origin: hydroxypropyl methyl cellulose.*
**Powder obtained by freeze-grinding of Fenugreek seeds, containing a minimum of 0.4% trigonelline.*
Contains no added starch, colouring agents, flavours or yeast.

To be kept out of the reach of young children.
Food supplements should not be used as a substitute for a varied and balanced diet and healthy lifestyle.
To be kept away from light, heat and humidity.
Best before end date: see bottom of box.

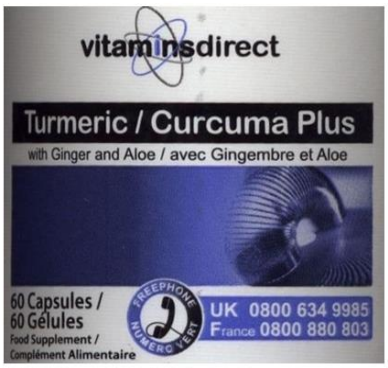
Classify the product

- o Medicinal product
- o Herbal supplement
- o Medicinal/herbal supplement (Borderline)
- o I don't know

State the reasons why you chose to classify the product accordingly?

Your Answer

PRODUCT 4: TURMERIC/CURCUMA PLUS



SUGGESTED DAILY INTAKE: Take one capsule daily with water or as directed by a Health Care Professional.

NUTRITIONAL INFORMATION:
Per daily consumption of one capsule provides:

Turmeric Powder	385mg
Ginger Root Extract (10:1)	60mg
Equivalent to 600mg of Ginger	
Aloe Vera Concentrate (200:1)	20mg
Equivalent to 4000mg of Aloe Vera	
Turmeric Extract (10:1)	15mg
Equivalent to 150mg of Turmeric	

INGREDIENTS: Turmeric Powder *(Curcuma Longa)*, Gelatin (capsule shell), Ginger Root Extract *(Rhizoma Zingiber Officinale)*, Aloe Vera Extract *(Aloe Barbadensis)*, Turmeric Extract *(Curcuma Longa)*, anti-caking agents: Magnesium Stearate, Silicon Dioxide.

TEL: 0800 634 9985
www.vitaminsdirectonline.co.uk

CARE & SAFETY ADVICE:
- Do not exceed the recommended intake
- Keep out of the reach and sight of children
- Please consult your healthcare professional if you are pregnant, breast-feeding or if you are taking any medication
- Check bottle seal is intact before use
- Not to be used as a substitute for a varied and balanced diet and healthy lifestyle

60 Capsules Food Supplement

Store in a cool, dry place. For Batch Number and Best Before date, please see opposite side.

Product Code: 102059

Vitamins Direct (UK) Limited
Registered in England No: 3561477
500-600 Witan Gate West
Buckinghamshire MK9 1SH

Classify the product

- o Medicinal product
- o Herbal supplement
- o Medicinal/herbal supplement (Borderline)
- o I don't know

State the reasons why you chose to classify the product accordingly?

Your Answer

SECTION 4: ATTITUDES & CONFIDENCE LEVELS ON HERBAL PRODUCTS

Do you agree that herbal products have beneficial effects?

	1	2	3	4	5	
Strongly Agree	o	o	o	o	o	Strongly Disagree

Do you agree that herbal products have less side effects than conventional medicines?

	1	2	3	4	5	
Strongly Agree	o	o	o	o	o	Strongly Disagree

Do you agree that herbal products have a placebo effect?

	1	2	3	4	5	
Strongly Agree	o	o	o	o	o	Strongly Disagree

Do you agree that herbal products have been sufficiently studied?

	1	2	3	4	5	
Strongly Agree	o	o	o	o	o	Strongly Disagree

Do you agree that herbal products can have significant interactions with conventional medicines?

	1	2	3	4	5	
Strongly Agree	o	o	o	o	o	Strongly Disagree

How comfortable are you giving advice to patients on herbal products?

	1	2	3	4	5	
Strongly Agree	o	o	o	o	o	Strongly Disagree

How confident are you when it comes to finding current resources on herbals?

	1	2	3	4	5	
Strongly Agree	o	o	o	o	o	Strongly Disagree

Appendix C

Public survey on Herbals

(English/Maltese)

Public Survey Consent Form:

I, _____(participant's name), understand that I am being asked to participate in a survey/questionnaire activity that forms part of the required coursework that Alexandra Curmi is carrying out for the University of Malta, in collaboration with the University of Chicago, Illinois. It is my understanding that this survey/questionnaire has been designed to gather information about the following subjects or topics:

I understand that my participation in this project is completely voluntary and that I am free to decline to participate, without consequence, at any time prior to or at any point during the activity.

I understand that any information I provide will be kept confidential, used only for the purposes of completing this assignment, and will not be used in any way that can identify me.

I have read the information above. By signing below and returning this form, I am consenting to participate in this survey/questionnaire project.

Participant name _____
Signature: _____
Date: _____

If you have other questions concerning your participation in this project, please contact me or my supervisor:

Alexandra Curmi B. Pharm(Hons)

Mobile Nos: 99849441

Email: alexandra.curmi.98@um.edu.mt

Dr Janis Vella (Supervisor)

Mobile Nos: 99867999

Email: janis.vella@um.edu.mt

Section 1 :Demographics

What is your gender?

- [ ] Male
- [ ] Female

What is your age?

- ○ 18-30
- ○ 31-50
- ○ 51-70

What is your highest level of education?

- ○ Secondary
- ○ Post secondary
- ○ Tertiary
- ○ Post-Tertiary

Section 2:Herbal product use

Have you ever made use of Herbal products?

- ○ Yes
- ○ No

If yes, are you taking any other conventional medicine/s?

- ○ Yes
- ○ No

If Yes, is your Doctor aware of this?

- ○ Yes
- ○ No

From where would you feel comfortable to purchase Herbal products?

- ☐ Pharmacy
- ☐ Health Food shops
- ☐ Supermarkets
- ☐ Online
- ☐ Gym

Section 2:Herbal product use

Who would you feel confident to ask for advice on herbal products?

- [ ] Pharmacist
- [ ] Health food shop employee
- [ ] Doctor
- [ ] Gym instructor

From the list below, state which herbals you have made use of?

- [ ] valerian
- [ ] gingko biloba
- [ ] ginseng
- [ ] evening primrose oil
- [ ] fennel
- [ ] green tea
- [ ] cranberry
- [ ] milk thistle
- [ ] black cohosh
- [ ] Other: _____

Section 3: Perception about Herbals

In your opinion, using herbal medicines and herbal dietary supplements is harmless

- [ ] Agree
- [ ] Disagree
- [ ] I don't know

In your opinion, combining herbals and conventional drugs is not dangerous

- [ ] Agree
- [ ] Disagree
- [ ] I don't know

BACK SUBMIT

Servej pubbliku

Jiena, _____(isem il-participant), nifhem li qed niġi mitlub nieħu sehem f'dan is-servej pubbliku li huwa parti mix- xogħol neċessarju għal kors li Alexandra Curmi qeda tagħmel għall-università' ta' Malta kif ukoll ma l-università' ta Chicago, Illinois. Nifhem li l-iskop ta' dan il-kwestjonarju huwa biex jiġbor informazzjoni fuq l-użu u l-konsum ta prodotti erbali.

Il-parteċipazzjoni tiegħi f'dan il-proġett huwa volontarju, u meta nixtieq jien nista nwaqqaf il-parteċipazzjoni tiegħi minn dan il-servej.

Kull informazzjoni li jiena nagħti jibqa' kunfidenzjali u jintuża biex jitlesta dan il-kwestjonarju biss.

Jiena qrajt l-informazzjoni mniżżla kollha.

Bil-firma tiegħi nagħti l-kunsens tiegħi biex nieħu sehem f'dan il-proġett.

Isem il-Participant _____

Firma: _____

Data: _____

Għal aktar domandi jew tagħrif id-dettalji tiegħi huma: :

Isem ta' l-studenta: Alexandra Curmi

Telefon number: 99849441

Indirizz tal-email: alexandra.curmi.98@um.edu.mt

Servej Pubbliku fuq Prodotti Erbali

L-Ewwel Taqsima: Dettalji Demografici

Is-sess

- [ ] Ragel
- [ ] Mara

Eta'

- ○ 18-30
- ○ 31-50
- ○ 51-70

Livell ta' edukazzjoni

- ○ Skola sekondarja
- ○ Skola post sekondarja
- ○ Skola tertiarja

NEXT

Servej Pubbliku fuq Prodotti Erbali

It-Tieni Taqsima: Użu ta' prodotti erbali

Qatt użajt prodotti erbali ?

- [ ] Iva
- [ ] Le

Qed tieħu xi medicina konvenzjonali magħhom

- ◯ Iva
- ◯ Le

Jekk ir-risposta tiegħek kienet iva, It-tabib tiegħek jaf li inti qed tieħu dawn il-prodotti erbali ?

- ◯ Iva
- ◯ Le

Kieku kellek tixtri xi prodotti erbali, minn fejn taħseb l-aktar li tħossok komdu li tixtrihom ?

- ◯ Mill-ispiżerija
- ◯ Mill-ħanut li jbiegħ prodotti tal-ikel u saħħa
- ◯ Mis-supermarket
- ◯ Minn xi sit elettroniku
- ◯ Minn Gym

Servej Pubbliku fuq Prodotti Erbali

It-Tieni Taqsima: Użu ta' prodotti erbali (Ikompli)

Lil min isaqsi, kieku jkollok bżonn parir fuq prodotti erbali?

- ○ Lil-ispiżjar
- ○ Lil-impjiegat fil-ħanut li jbiegħ prodotti tal-ikel u sahha
- ○ Lil-Tabib
- ○ L-istruttur tal-gym

Mill-lista li ġejja, immarka liema prodotti erbali użajt:

- ☐ valerian
- ☐ gingko biloba
- ☐ ginseng
- ☐ evening primrose oil
- ☐ fennel
- ☐ green tea
- ☐ cranberry
- ☐ milk thistle
- ☐ black cohosh

BACK NEXT

Servej Pubbliku fuq Prodotti Erbali

It-tielet Taqsima: Perċezzjonijiet dwar prodotti erbali

L-użu ta prodotti erbali ma jgħamilx ħsara

- [ ] Naqbel
- [ ] Ma Naqbilx
- [ ] Ma Nafx

l-użu kontemporanju ta prodotti erbali u medicina konvenzjonali mhuwiex perikoluż

- [ ] Naqbel
- [ ] Ma Naqbilx
- [ ] Ma nafx

BACK SUBMIT

Appendix D

Pharmacists and Health shop employees mean knowledge score

Statement (Correct answer)	Pharmacists Response					
		Correct		Incorrect		Don't Know
	n	(%)	n	(%)	n	(%)
1.Gingko Biloba improves cognitive impairment (correct)	83	78	8	7	16	15
2.Gingko Biloba may improve the quality of life in mild dementia (correct)	54	50	17	16	36	34
3.Gingko Biloba may improve fatigue (incorrect)	16	15	82	77	9	8
4.Gingko Biloba may be used to improve stress (incorrect)	37	35	44	41	26	24
5.Black cohosh may be used to relieve post-menopausal symptoms (correct)	59	55	2	2	46	43
6.Black cohosh may be used for relief of profuse sweating (correct)	19	18	19	18	69	64
7.Black cohosh may be used to relieve respiratory infections (incorrect)	29	27	10	9	68	64
8. Black cohosh may be used to enhance immunity (Incorrect)	26	24	9	8	72	67
9.Saw palmetto is commonly used for symptomatic treatment of headache (Incorrect)	36	34	14	13	57	53
10.Saw palmetto is commonly used for symptomatic relief of benign prostatic hyperplasia (Correct)	68	64	3	3	36	34
11.Saw palmetto is commonly used to help slow memory loss (Incorrect)	43	40	1	1	63	59
12.Saw palmetto is commonly used to relief from depressive symptoms (Incorrect)	49	46	2	2	56	52
13. Echinacea can cause hypersensitivity reactions in the form of rash (correct)	70	65	9	8	28	26
14.Echinacea can cause potential side effects such as bronchospasm with airway obstruction (correct)	25	23	32	30	40	37
15.Echinacea can cause increased urination as a side effect (Incorrect)	4	4	10	9	57	53
16.Echinacea use can result in bowel perforation (Incorrect)	46	43	3	3	58	54
17. St john's wort interacts with warfarin (Correct)	98	92	2	2	7	7
18. St john's wort interacts with protease inhibitors such as indinavir, amprenavir (correct)	68	64	5	5	34	32

19.St john's wort interacts with oral contraceptives (correct)	83	78	6	6	18	17
20. St john's wort interacts with simvastatin (Correct)	48	45	17	16	42	39
21. Bitter Fennel is indicated to relief bloating and flatulence symptoms (correct)	82	77	2	2	23	21
22. Bitter Fennel is indicated for minor spasms in menstrual periods (correct)	36	34	22	21	49	46
23.Bitter Fennel is indicated in liver conditions (Incorrect)	41	38	8	7	58	54
24. Bitter Fennel is indicated for joint and muscular inflammation relief (Incorrect)	44	41	2	2	61	57
25. Garlic may be used to decrease cholesterol levels (Incorrect)	10	9	84	79	12	11
26. Gingko Biloba may be used to decrease cholesterol levels (Incorrect)	60	56	7	7	40	37
27. Hawthorn may be used to decrease cholesterol levels (Incorrect)	26	24	21	20	60	56
28. Horse Chestnut may be used to decrease cholesterol levels (Incorrect)	38	36	7	7	62	58

Statement (Correct answer)	Health Shop Employees					
		Correct		Incorrect		Don't Know
	n	N (%)	n	N (%)	n	N (%)
1.Gingko Biloba improves cognitive impairment (correct)	10	71	0	0	3	21
2.Gingko Biloba may improve the quality of life in mild dementia (correct)	12	86	0	0	1	7
3.Gingko Biloba may improve fatigue (incorrect)	9	64	1	7	3	21
4.Gingko Biloba may be used to improve stress (incorrect)	8	57	0	0	5	36
5.Black cohosh may be used to relieve post-menopausal symptoms (correct)	9	64	2	14	2	14
6.Black cohosh may be used for relief of profuse sweating (correct)	6	43	2	14	5	36
7.Black cohosh may be used to relieve respiratory infections (incorrect)	10	71	0	0	3	21
8. Black cohosh may be used to enhance immunity (Incorrect)	6	43	0	0	7	50
9.Saw palmetto is commonly used for symptomatic treatment of headache (Incorrect)	6	43	3	21	4	29
10.Saw palmetto is commonly used for symptomatic relief of benign prostatic hyperplasia (Correct)	13	93	0	0	0	0
11.Saw palmetto is commonly used to help slow memory loss (Incorrect)	10	71	0	0	3	21
12.Saw palmetto is commonly used to relief from depressive symptoms (Incorrect)	9	64	0	0	4	29
13. Echinacea can cause hypersensitivity reactions in the form of rash (correct)	11	79	2	14	0	0
14.Echinacea can cause potential side effects such as bronchospasm with airway obstruction (correct)	3	21	2	14	8	57
15.Echinacea can cause increased urination as a side effect (Incorrect)	10	71	0	0	3	21
16.Echinacea use can result in bowel perforation (Incorrect)	10	71	3	21	0	0
17. St john's wort interacts with warfarin (Correct)	4	29	2	14	7	50
18. St john's wort interacts with protease inhibitors such as indinavir, amprenavir (correct)	2	14	3	21	8	57

19.St john's wort interacts with oral contraceptives (correct)	5	36	0	0	8	57
20. St john's wort interacts with simvastatin (Correct)	0	0	3	21	10	71
21. Bitter Fennel is indicated to relief bloating and flatulence symptoms (correct)	9	64	3	21	2	14
22. Bitter Fennel is indicated for minor spasms in menstrual periods (correct)	10	71	2	14	1	7
23.Bitter Fennel is indicated in liver conditions (Incorrect)	11	79	0	0	2	14
24. Bitter Fennel is indicated for joint and muscular inflammation relief (Incorrect)	11	79	0	0	2	14
25. Garlic may be used to decrease cholesterol levels (Incorrect)	0	0	13	93	0	0
26. Gingko Biloba may be used to decrease cholesterol levels (Incorrect)	10	71	0	0	3	21
27. Hawthorn may be used to decrease cholesterol levels (Incorrect)	5	36	0	0	8	57
28. Horse Chestnut may be used to decrease cholesterol levels (Incorrect)	7	50	0	0	6	43

Appendix E

Pharmacists and Health shop employees mean knowledge score for each question

Statement	Pharmacist	Health shop Employee
	Mean	Mean
1. Gingko Biloba may be used to improve which of the following conditions? [cognitive impairment]	1.63	1.54
2. Gingko Biloba may be used to improve which of the following conditions? [quality of life in mild dementia]	1.17	1.85
3. Gingko Biloba may be used to improve which of the following conditions? [fatigue]	1.68	0.85
4. Gingko Biloba may be used to improve which of the following conditions? [stress]	1.17	0.62
5. Saw palmetto is commonly used for which of the following conditions? [symptomatic treatment of headache]	0.60	0.92
6. Saw palmetto is commonly used for which of the following conditions? [symptomatic relief of benign prostatic hyperplasia]	1.30	2.00
7. Saw palmetto is commonly used for which of the following conditions? [help slow memory loss]	0.42	0.77
8. Saw palmetto is commonly used for which of the following conditions? [relief of depressive symptoms]	0.50	0.69
9. Echinacea can cause which of the following potential side effects? [hypersensitivity reactions in the form of rash]	1.39	1.85
10. Echinacea can cause which of the following potential side effects? [bronchospasm with airway obstruction]	0.93	0.62
11. Echinacea can cause which of the following potential side effects? [increased urination]	0.56	0.77
12. Echinacea can cause which of the following potential side effects? [bowel perforation]	0.49	1.23
13. St John's wort interacts with which of the following conventional medicines? [warfarin]	1.85	0.77
14. St John's wort interacts with which of the following conventional medicines? [protease inhibitors (e.g. indinavir, amprenavir)]	1.32	0.54
15. St John's wort interacts with which of the following conventional medicines? [oral contraceptives]	1.61	0.77

16. St John's wort interacts with which of the following conventional medicines? [simvastatin]	1.04	0.23
17. Black cohosh may be used for which of the following conditions? [post-menopausal symptoms]	1.12	1.54
18. Black cohosh may be used for which of the following conditions? [profuse sweating]	0.53	1.08
19. Black cohosh may be used for which of the following conditions? [respiratory infections]	0.46	0.77
20. Black cohosh may be used for which of the following conditions? [enhance immunity]	0.41	0.46
21. Bitter Fennel is indicated for which conditions? [bloating and flatulence]	1.55	1.54
22. Bitter Fennel is indicated for which conditions? [minor spasms in menstrual periods]	0.88	1.69
23. Bitter Fennel is indicated for which conditions? [liver conditions]	0.53	0.85
24. Bitter Fennel is indicated for which conditions? [joint and muscular inflammation]	0.45	0.85
25. Which herbal product may be used to decrease cholesterol levels? [garlic]	1.66	1.69
26. Which herbal product may be used to decrease cholesterol levels? [gingko biloba]	0.69	0.77
27. Which herbal product may be used to decrease cholesterol levels? [hawthorn]	0.64	0.38
28. Which herbal product may be used to decrease cholesterol levels? [horse chestnut seed]	0.49	0.54

Appendix F

Approved FIP

World Congress of Pharmacy

and Pharmaceutical

Sciences 2017 Abstract

Accepted FIP Abstract

Abstract Submission Pharmaceutical sciences Natural Products FIP-618 Classification of herbal medicines: what is safe for the patient? Alexandra Curmi*

Background: The use of herbal medicines is on the increase. One of the possible reasons for the popular use of herbal medicines may be due to the misconception that herbal medicines are 'natural' and hence safe.

Purpose: To evaluate knowledge and confidence of pharmacists and health shop employees with regards to use of herbal medicines, to evaluate perception and attitudes towards herbal medicines and to analyze classification of herbal medicines within the EU from a regulatory aspect.

Methods: A questionnaire was disseminated to 107 pharmacists and 14 health shop employees to determine knowledge and perception on herbal products and classification of herbal medicines. Another questionnaire was disseminated randomly to 150 members of the general public, to determine their perception and attitudes toward use of herbal products. A review on how herbal medicines are regulated within the EU was carried out.

Results: There was no significant difference between pharmacists and health shop employees in mean knowledge score (27.06 vs 28.15 out of 56 respectively). Fifty-six percent of the public interviewed co-administer herbal and conventional medicines and 65% prefer to seek advice about herbals from the pharmacist. From a regulatory aspect despite efforts to regularize herbal medicines, there are still loopholes which need to be addressed.

Conclusion: There is need to empower pharmacists and health shop employees with scientific information about herbal medicines to improve their knowledge. Co-administration of herbal medicines with conventional medicines may jeopardize patient safety and this requires a higher level of pharmacist intervention.