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I am very delighted to introduce a new scientific journal 'Eastern Mediterranean University Journal of Pharmaceutical Sciences'. This journal is prepared by Eastern Mediterranean University Faculty of Pharmacy faculty members. It is dedicated to any discipline under the category of pharmaceutical sciences. Research articles, short communications, and reviews in pharmaceutical, chemical, botanical, and microbiological research areas are all aimed to be presented within the scope of the journal. It is also important to note that research studies particularly prepared for thesis projects of pharmacy students in their final years before graduation are also highly encouraged to be submitted to the journal for publication.

The journal is aimed to be published for three times a year. The language is English. It is also noteworthy to state that it is the first journal in pharmaceutical field published in Cyprus. Besides, the journal is a peer-reviewed journal and the manuscripts submitted are subject to a review process to get acceptance to be published within the journal.

Best wishes and thank you in advance for your contribution to the Journal of 'Eastern Mediterranean University Journal of Pharmaceutical Sciences'.

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Short papers: Short papers are limited to 5 typewritten pages and maximum of 2 supplementary materials (schemes, tables, figures).

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HONEY PLANTS OF GUZELYURT (MORPHOU) IN NORTH CYPRUS

Authors (11 pt.)

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Correspondence: E-mail of the corresponding author is written **(10 pt.)**.

cagintheking@gmail.com

Abstract

Briefly give the objectives, methods, results and conclusions in maximum 200 words **(11 pt.)**.

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Should indicate the subject of the article which is generally based on a brief interpretation of the related literature. The novelty and the aim of the study should be clearly stated.

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Book: Cotton CM, (1994).Ethnobotany Principles and Applications .John Wiley and Sons Ltd. England

Book chapter: Bonati A (1988). Industr and conservation of medicinal plants. In Akerele O., Heywood, V. and Synge H. (eds). *The Conservation Medicinal Plants*, p.141-148 Cambridge University Press UK

Dissertation (Thesis): Demirci S (2010). Andırın (Kahramanmaraş) İlçesinde Etnobotanik Bir Araştırma.Unpublished MScThesis (superviser Prof Neriman Özhatay), Istanbul University, Istanbul.

Research Report: Özhatay N, Akalın E, Yeşil Y, Demirci S, Güler N, Ersoy H (2010). Flora of Yıldız Mountains (Yıldız Mountains Biosphere Project Report Series No. 3), Prepared for the Ministry of Environment and Forestry, Ankara.
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UNEP-WCMC (2009) Species suggested for review on the basis of the Analysis of 2007 (EC annual reports, SGR 49/8/3), Prepared for the European Commission. UNEP-WCMC, Cambridge.

Electronic resources: (2014) World Nuclear Association. Radioisotopes in Medicine, http://www.world-nuclear.org/info/inf55.html,www.world-nuclear.org/info/inf55.html. Accessed 13.10.2014.
Treglia G, Ceriani L, Sadeghi R, Giovacchini G, Giovanella, L. (2014) Relationship between prostate-specific antigen kinetics and detection rate of radiolabelled choline PET/CT in restaging prostate cancer patients: A meta-analysis, *Cli Chem Lab Med*. http://www.reference-global.com/toc/cclm/current Accessed 16.09.2014

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CONTENTS

THE INVESTIGATION OF THE INTERACTION OF SEVERAL ANTIPSYCHOTIC DRUGS WITH HUMAN CHOLINESTERASE ENZYMES

Sonia Sanajou[1], Shalaleh Nourhashemi[1], Amirhossein Fallah[1], Tugba Ercetin[1], Mustafa Fethi Sahin[1], Hayrettin Ozan Gulcan[1*]

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ABSTRACT

Phenothiazines and butyrophenones are one of the important antipsychotic group of drugs. They have been utilized for many years for treatment of schizophrenia and other psychotic disorders. They are the main constituents of the first generation, also referred as typical, antipsychotic drugs. They are known for their potential to antagonize dopamine D_2 receptors. With respect to their structures, they are able to cross the blood brain barrier and interact with various types of receptors. In order to investigate their potential to interact with cholinesterase enzymes, within this research, we have designed a series of experiments. Although, earlier studies have shown that some of those compounds have the potential to inhibit cholinesterase enzyme, for the first time, we have evaluated their potential to inhibit human isoforms of acetylcholinesterase and butyrylcholinesterase. The results strongly pointed out that phenothiazines are selective and potent inhibitors of the human butyrylcholinesterase enzyme.

Key words: Phenothiazines, Butyrophenones, Human cholinesterase inhibitory potential

INTRODUCTION

Moreover, they have ability to act like quinidine and show effect on cardiac system (Dougherty and Marraffa 2014; Jaszczyszyn et al. 2012). It was shown that these compounds are not specific on dopaminergic system, since they can also interact with some other receptors within the central nervous system (Darvesh et al., 2010). In particular, some of them are known to inhibit cholinesterase enzymes that have been investigated on the cholinesterase enzymes obtained from various species but human (Darvesh et al., 2010). For instance some phenothiazine derivatives such as chlorpromazine and ethopropazine were reported to be BuChE inhibitor molecules, although there are used to treat schizophrenia (Darvesh et al., 2005). This selectivity was attributed both to the structural organization of chlorpromazine and ethopropazine and derivatively smaller and different organization of the active side of AChE (Darvesh et al., 2013). However, the derivatives of these compounds synthesized were shown

to have different selectivity in a such a way that the N-10-amide derivatives of phenothiazines were found the inhibitors of BuChE, while there carbamate analogs were found to show selectivity towards AChE (Darvesh et al., 2010). They block dopaminergic receptors by interacting to D_1 and D_2 receptors (Jaszczyszyn et al., 2012; Mayoclinic, 2016; Sudeshna & Parimal, 2010).

Although, the cholinesterase inhibitors potential of some antipsychotic drugs are known , a detailed study has not been accomplish so far to show their interaction with human cholinesterase enzymes therefore, within this research, we have utilized chlorpromazine, trifluperazine, perphenazine, thioridazine and haloperidol antipsychotic agents and measured their IC_{50}s to inhibit human cholinesterase enzymes.

MATERIALS AND METHODS

Chlorpromazine, trifluperazine, perphenazine, thioridazine and haloperidol are obtained from Sigma Aldrich (CA, USA). Their purity was more than 99% as stated on their labels, therefore, no other purification was conducted on the compounds.

Determ*ination of AChE and BChE inhibitory activities*

The modified spectrophotometric method of Ellman (1961) was used to determine of AChE and BuChE inhibitory activities of 5 compounds (Chlorpromazine, Trifluperazine, Perphenazine, Thioridazine and Haloperidol) (Ellman, Courtney, Andres, & Featherstone, 1961). The enzymes used for cholinesterase activity studies were, human recombinant AChE (HuAChE) (Sigma) and human recombinant BuChE (Sigma).

Acetylthiocholine iodide and butyrylthiocholine chloride (Sigma, St. Louis, MO, USA) were employed as substrates of the reaction. 5, 5´-Dithio-bis (2-nitrobenzoic) acid (DTNB, Sigma, St. Louis, MO, USA) was used for the measurement of the cholinesterase activity. Other reagents and conditions, briefly, 50 mM Tris HCl buffer (pH 8.0), 6.8 mM DTNB, 2 µl of sample solutions and 10 µl of AChE/BChE solution were added in a 96-well microplate. The reaction was then initiated with the addition of 10 µl of acetylthiocholine iodide/butyrylthiocholine chloride. The hydrolysis of acetylthiocholine iodide/butyrylthiocholine chloride was monitored by the formation of the yellow 5-thio-2-nitrobenzoate anion as a result of the reaction of DTNB with thiocholines, catalyzed by enzymes at a wavelength of 412 nm utilizing a 96-well microplate reader (Varioskan Flash, Thermo Scientific, USA) and incubated for 15 min at 27°C. The measurements and calculations

were evaluated by using SkanIt Software 2.4.5 RE for Varioskan Flash software. Percentage of inhibition of AChE and BuChE was determined by comparison of rates of reaction of samples relative to blank sample (methanol) using the formula (E-S)/E x 100, where E is the activity of enzyme without test sample and S is the activity of enzyme with test sample. The experiments were done in triplicate. Donepezil hydrochloride, rivastigmine (Sigma-Aldrich,USA), and Galantamine hydrobromide (from Lycoris sp. Sigma-Aldrich, St. Louis, MO, USA) used as reference compounds. The IC_{50} value obtained for each test compound with standard compounds (Ercetin, Senol, Erdogan Orhan, & Toker, 2012; Gulcan et al., 2014).

RESULT AND DISCUSSION

The potential of test compounds concomitant to the reference molecules to inhibit human cholinesterase enzymes were tested employing the Ellman's method as described in materials and method section. Accordingly, the results obtained are shown in Table 1. The activity of reference molecules was found parallel to the literature (Darvesh et al., 2013). Rivastigmine was found BuChE selective, while galantamine and donepezil showed selectivity towards AChE. Within the test conditions employed donepezil was found to be most potent cholinesterase inhibitor molecule.The four phenothiazine derived antipsychotic agent employed within this research all have shown potential to inhibit human recombinant cholinesterase enzymes. These phenothiazine compounds were all shown to possess selectivity towards BuChE. In addition, their BuChE inhibitory potential were found higher to the activity of the three drug molecules used as reference within the study. Although the phenothiazines employed have shown lower activity in comparison to galantamine, and donepezil in terms of AChE inhibition, it has been found better and comparable to the activity of rivastigmine. Thioridazine was found to be the most potent inhibitor among the phenothiazines employed.

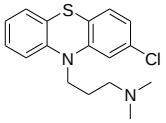
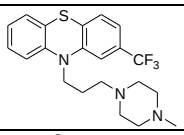
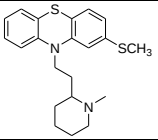
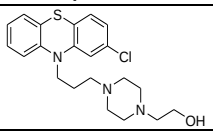
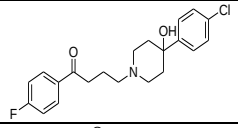
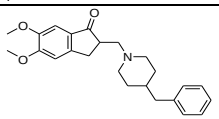
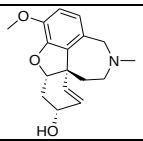
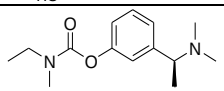
Haloperidol, a butyrophenone class antipsychotic agent, displayed quite different properties. First of all, haloperidol displayed selectivity towards AChE, rather than to BuChE seen for phenothiazines. Furthermore, its AChE inhibitory potential was lower than the potential of phenothiazines. It is noteworthy to mention that its BuChE inhibitory potential was the lowest one among the compounds tested.

The results definitely have shown that antipsychotic agents, depending on the class, have varying potentials to inhibit human cholinesterase enzymes. Both the phenothiazine class test compounds and the haloperidol have Aryl-spacer- tertiary amine pharmacophore, however; the organization of the pharmacophore is different in such a way that the spacer group in phenothiazines sources out from the center of the phenothiazine ring, while it is linked to the terminal of a relatively small aryl group in haloperidol. This aids in a T-shape Aryl-Spacer

organization in phenothiazine type BuChE inhibitors, while it is linear in haloperidol. This reveals out a bulkier aryl group organization in phenothiazines. In fact, it is known that the peripheral binding site of BuChE is larger in comparison the peripheral binging site of AChE (Rahman & Choudhary, 2014). Therefore, the organization of the Aryl group in phenothiazines does not fit the relatively smaller peripheral binding site of the AChE.

It is noteworthy to state that, although phenothiazines are cholinesterase inhibitors, they exert anticholinergic side effects (Sims, 1995). This is mainly attributed to their potential to bind to cholinergic receptors and to antagonize them (Sims, 1995) . However, considering the fact that the number of studies to find out original compounds designed to selectively inhibit BuChE, it is still important to question the chemical organization of phenothiazines yielding out BuChE selective cholinesterase inhibitor agents. Our results within this research have shown that phenothiazines can also inhibit human cholinesterase enzymes, selective to BuChE. Regarding the previous data obtained for the potential of phenothiazines to inhibit cholinesterase enzymes from various sources rather than human is in agreement with our findings.

Table 1: The potential of the test compounds to inhibit human recombinant cholinesterase enzymes

The test compound	Molecular structure	IC_{50} (µM) Human rec. AChE	IC_{50} (µM) Human rec. BuChE
Chlorpromazine		15.6 ± 0.2	3.4 ± 0.2
Trifluoperazine		9.8 ± 0.1	1.8 ± 0.2
Thioridazine		16.7 ± 0.6	0.6 ± 0.1
Perphenazine		11.6 ± 0.3	3.5 ± 0.1
Haloperidol		25.7 ± 1.4	144.6 ± 0.7
Donepezil		0.010 ± 0.0	9.6 ± 0.5
Galantamine		0.9 ± 0.1	12.6 ± 0.4
Rivastigmine		37.6 ± 0.3	15.9 ± 0.8

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Jaszczyszyn, A., Gąsiorowski, K., Świątek, P., Malinka, W., Cieślik-Boczula, K., Petrus, J., & Czarnik-Matusewicz, B. (2012). Chemical structure of phenothiazines and their biological activity. *Pharmacol Rep*, ***64***(1), 16–23.

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HONEY PLANTS OF GUZELYURT (MORPHOU) IN NORTH CYPRUS

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ABSTRACT

This study was aimed to determine melliferous / honey plants visited by honey bees in Güzelyurt (Morphou). Melliferous plants or honey plants bear any substance that is collected by bees to produce honey. Honey has been used frequently, especially in traditional medicine, because it is easily obtained, cheap, safe and has no side effects. The properties of honey are different due to floral sources. The study area is located in North Cyprus, which is one of the richest floristic area in the region. The major objectives of this project are to identify the plant sources used for the production of local honey in Güzelyurt (Morphou) North Cyprus.

According to the results, 40wild species, including an endemic species, Onopordum cyprium (Photo 1.and 11) and cultivated plant species of the flowering plants were determined.

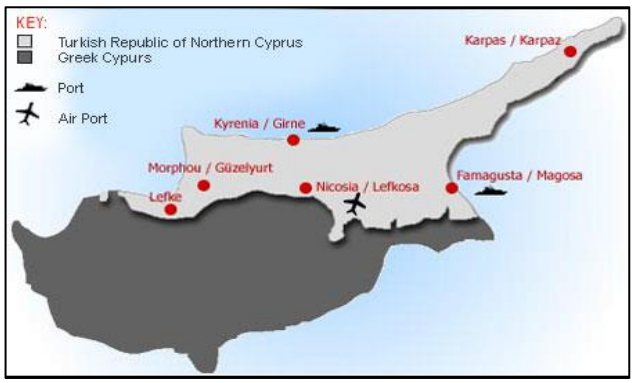
Key words: Honey plants, Güzelyurt (Morphou), North Cyprus.

Figure 1: *Onopordum cyprium* an endemic species to Cyprus (photo taken by Sami Tompson).

INTRODUCTION

Honey is the most frequently used bee product and it is stored in honey stomach of bees when they harvest nectar. The nectar contain enzymes which breakdown the larger sugar, sucrose, in the nectar into glucose and fructose. Its colour varies in different regions due to the variety of plant species. The known effects of honey in human body is as follows: Antibacterial, antimicrobial, anti-inflammatory, antiparasitic, anti-oxidant effects, shortening the duration of diarrhoea and even complimenting chemotherapy or representing a satisfactory alternative or complimentary means of chemoprophylaxis or chemotherapy. Raw states of honey include; 20% water, 2 predominant natural sugars, 11 enzymes, 14 minerals, 21 amino acids and vitamins A, B- mentinodomplex, C, O, E, and K, beta-carotene, minerals, and enzymes. There are various floristic studies carried out in Turkish Republic of North Cyprus (TRNC) (Snogerop, S., Gustafsson, M., Bothner, R.1990., Stephenson, R. 1993). The vascular flora of TRNC according to a number of researchers is about 1257 species; 19 of which are endemic (Meikle, 1977, 1985, Viney 1994, 1996).

In the project, Güzelyurt region was chosen because of its rich flora and honey production. Due to the various species in the flora and richness of the *Citrus* trees in the region Güzelyurt is a an important location for beekeepers. There are 107 beekeepers registered in the area. This number is about 1/2 of the total number of beekeepers in North Cyprus. Most of the colonies in North Cyprus are located in this region. Güzelyurt District is a district of Northern Cyprus. It consists only of the Güzelyurt sub-district. Its population was 30,590 in the 2011 census, but this included Lefka; with its current borders, its population was 18,946, constituting 6.6% of the population of Northern Cyprus. Güzelyurt District was formed on 1 June 1998 via separation from Lefkoşa District. Lefke (Lefka) had been its second sub-district until 27 December 2016 (TRNC Census 2006, District population census 2011, Kıbrıs Postası, 2016).



Map 1: Northern Cyprus with the districts (Settlements of Güzelyurt District – Aydınköy – Akçay - Aşağı Bostancı – Gayretköy – Güneşköy - Güzelyurt İkidere – Kalkanlı – Mevlevi – Şahinler – Serhatköy – Yayla - Yukarı Bostancı – Yuvacık - Zümrütköy)

MATERIALS and METHOD

Field Studies

Field studies took place in two 6-month terms after obtaining the information about the areas where the flowering plants around the hives were collected. During the collection process, in addition to personal observations, some general information was taken: The experience and knowledge of beekeepers, which plants the bees visited, and which plants pollen and nectar are received. Also flower colour, plant general structure and properties of the leaves of plants were recorded for future features that will help in the promotion of both.

Plant specimens were collected around the beehives in Yayla Settlement. A total of 60 plant samples were collected during the field studies conducted between October 2016 and April 2017. Photographs of all collected samples were taken in the natural distribution and the samples were pressed as herbarium specimens for identification. The samples that have been determined scientifically have been placed in the Herbarium of the Faculty of Pharmacy of Eastern Mediterranean University (E.M.U.) that is established for the first time in E.M.U. University, in Magusa of North Cyprus.

Herbarium Studies

Herbarium is a plant museum in which pressed plant-dried specimens are placed in a certain systematic order and scientific studies are carried out with these specimens. Herbarium that serves as a documentation center is a counseling service for scientists who will work in all plant-related areas.

How to prepare a herbarium specimen?

When a plant is collected from the field 10 steps should be applied to the herbarium entrance:

1. Collection of plant specimens.
2. All necessary information (detailed location, habitat, etc.) related to the sample collected is noted in the land register book.
3. The sample is pressed in accordance with the rules for drying. The pressing process is continued until the sample is completely dry, by changing the wetting paper every 2 days.
4. The dried samples are kept at -25 °C in order to remove insects and insect’s eggs at least 2 days.
5. The sample taken from deep freezing is attached to the herbarium sample cartoons in accordance with the rule.
6. The scientific name of the attached sample is determined by the experts. This process is called plant identification.
7. The name of the glued sample is determined.

8.The identified samples are registered in the herbarium registry or database and a herbarium inentory number is given.

9.The labels and cards containing the information entered in the herbarium registry or the database are prepared and the labels are affixed to the cardboard.

10.Prepared specimens are preserved by proper storage.

Herbarium of Eastern Mediterranean
University Faculty of Pharmacy**EMUP**

Nom. : *Malva sylvestris*

Common Name : Ebemgömeci, Gömeç

Fam. : Malvaceae

Loc. : Güzelyurt Yayla

Dat. : 18.03.2017

Alt : 36m

Leg. : Çağın Korkmazer **Det :**N:Özh.&Ç.Kork

Nectar / Polen : ☐☐ **No : 042**

Figure 2: An example of Herbarium label of honey plants

Figure 3: Herbaryum specimen of *Malva sylvestris*

Pollen Studies

Honey specimens were taken from the beekeepers standing in the field. Honey plants of Güzelyurt were determined by the method of the comparison of the pollen of the collected plants with the pollen contained in these honey specimens. Thus, the plant source of honey produced in the borders of studied area has been scientifically revealed.As a result of various microscopic studies, it has been tried to prove that plant pollen is present in honey. After all the collected plants have been dried carefully, herbarium work has been done and all the plants

in the project have been pressed. All these studies have been examined in bee hives in Güzelyurt region. Due to our limited time, we only worked with 45 plant species and 9 tree species collected in the region. We have also reported the bee products obtained from these plants as well as other medicinal uses of plants.

Honey specimens were taken from the bees placed in the field and the detection studies were carried out by comparing the pollens contained in these specimens to those of collected plants. Used materials are as follows: Microscope, aceto-orcein, glycerin gelatin, microscope slide, coverslips, needle, to get pollen, spatula, heater.

Figure 4: Çağın Korkmazer in laboratory studies examining pollen grains

Pollen grains found in flower honey that is light yellow color honey. It is harvested in the spring season.

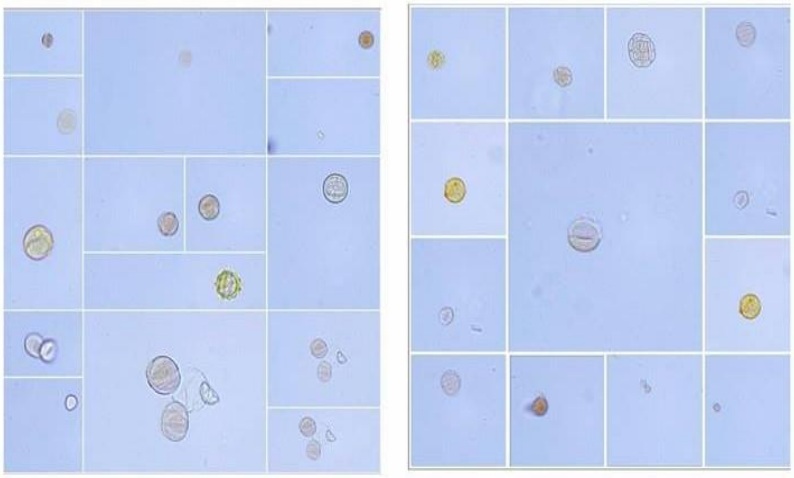


Figure 5: Pollen grain in honey (Güzelyurt region).

RESULTS

As a result of various microscopic studies, it has been tried to prove that pollen is present in honey and identy the spcies or family . After all the collected plants have been dried carefully, herbarium work has been done and all the plants in the project have been prepared as herbarium specimen, identfied mounted and labeled.

Due to the limited time, only spring honey was investigated and 40 wild species were determined. Wild species detected were presesented on the Table 1. The cultivated plants were mainly fruit trees and cultivated vegetables are given as follows:

1 *Schnis molle* **2** *Eucalyptus camaldulensis*

3 *Prunus dulcis* **4** *Prunus persica*

5 *Prunus spinosa* **6** *Citrus limon*

7 *Citrus sinensis* **8** *Lycium ferocissimum*

9 *Phacelia tanacetifolia* **10** *Solanum lycopersicum*

11 *Vicia faba*

Table 1.List of wild honey plants distributed in Güzelyurt (Morphou), TRNC.

Scientific Name	Common Name	Turkish Name
Acacia cyanophylla	Mimosa saligna	Kıbrıs Akasyası
Anthemis palaestina	Chamomile	Papatya
Asphodelus aestivus	Asphodel	Çiriş otu
Calicotome villosa	Hairy thorny broom	Azgan
Cardaria draba	Hoary cress	Kedi otu
Chrysanthemum coronarium	Crown daisy	Papatya
Cistus monspeliensis	Montpellier cistus	Laden Otu
Cistus parviflorus	Rockrose	Küçük Çiçekli Laden
Convolvulus althaeoides	Mallow bindweed	Boru Çiçeği
Ecballium elaterium	Squirting cucumber	Eşek Hıyarı
Echium angustifolium	Hispid viper's-bugloss	Dar Yapraklı Engerekotu
Echium plantagineum	Purple viper's-bugloss	Kuzudili Yapraklı Engerekotu
Erodium malacoides	Mediterranean stork's bill	Dönbaba
Erodium moschatum	Whitestem filaree	İğnelik
Eruca vesicaria	Rocket	Roka
Ferula communis	Giant fennel	Çakşır otu
Gladiolus italicus	Wild gladiolus	Kılıç otu
Heliotropium hirsutissimum	Heliotrope	Aygün çiçeği
Inula conyzae	Ploughmn's spikenard goniza	Gölge Andız otu
Lamium album	White dead nettle	Beyaz Ballıbaba
Malva nicaeensis	French mallow	Gömeç ilmikotu
Malva sylvestris	High mallow	Büyükebegümeci
Medicago murex	Spiny medick	Dişlek Yonca
Mentha longifolia	Mint	Nane
Moraea sisyrinchium	Barbary nut	Yumrulu Süsen
Onopordum cyprium	Cyprian donkey	Thistle Eşek Dikeni
Orchis italica	Naked man orchid	Tavşan Topuğu Orkidesi
Oxalis pes-caprae	Bermuda buttercup	Ekşilice
Papaver dubium	Blindeyes	Gelincik
Polygonum arenarium	European knotweed	Kumsal Çoban Değneği
Prasium majus	White hedge-nettle	Çalıbaba
Raphanus raphanistrum	Wild radish	Yabani Turp
Salvia fruticosa	Greek sage	Adaçayı
Sinapis arvensis	Field mustard	Lapsana Yabani Hardal
Smyrnium olusatrum	Alexanders	Yabani Kereviz
Tamarix tetrandra	Four-stamen tamariks	Ilgın Ağacı
Thymus capitatus	Thyme	Tülümbe
Thymus vulgaris	Common thyme	Kekik
Tragopogon porrifolius	Common salsify	İskorçina
Vicia sativa	Common	Yabani Fiğ

Asphodelus aestivus

Asphodelus aestivus with honey bee

Malva sylvestris with honey bee

Crateagus monogyna with honey bee

Figure 6: Photos of some honey plants determined in the study area.

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EVALUATION OF SPORTS PHARMACY IN TURKEY AND NORTH CYPRUS AS A NEW IMPORTANT FIELD FOR PHARMACISTS

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ABSTRACT

Sports have substantial socioeconomic and political importance worldwide and are today consideredto be an integral part of society. In the the world,almost all people are doing sports. Participation in sports and exercise is undertaken at all levels, from amateur enthusiasts to elite athletes.

Pharmacists are the drug experts who know contraindications, usages and side effects of drugs very well. People can have problem related with sports like injury, muscle pain, sprain etc. For these conditions, pharmacist is one of the the closest counseling person for patient. Sports pharmacy can be defined as area that is related with sports and pharmacist.

Doping is the one of the biggest problem in sport activity for Turkey, North Cyprus and for other countries. Some athletes do doping unconsciously. Pharmacists know all effects of drugs and they can control and inform the athletes about drugs that have doping effects. For decreasing these problems, sport pharmacists are needed in Turkey, North Cyprus and in other countries.

Athletes who are representing us at olympics have their own doctor, physiotherapist and coach. Moreover, they also need pharmacists. There is a growing need for specialist pharmacists in the area of sport and exercise.

The specialty of sports pharmacy covers,awareness of drugs in sports in the community, medicine & industry for both performance modification and the prevention and treatment of disease, knowledge of therapeutic use of drugs in sports and how pharmacist interventions can support sports related illness or injury, use of pharmacotherapy to prevent sport-related illness or injury and maintain well-being, safe and rational use of nutrition and supplements to optimise performance.

This research is the first study about sports pharmacy in Turkey and North Cyprus. The aim of the study was to increase awareness of pharmacists about sports pharmacy which is a new area for them. Moreover, in this study two survey were applied to pharmacists and pharmacy students and together withthese surveys, awareness of pharmacists and pharmacy students were determined.

Key Words: Sports Pharmacy, Doping, Role of Pharmacist

INTRODUCTION

Sports have substantial socioeconomic and political importance worldwide and are today considered to be an integral part of society. Participation in sports and exercise is undertaken at all levels, from amateur enthusiasts to elite athletes.

Pharmacists can be the first port of call for people engaging in sports who require advice on drug treatment or general health care. However, few pharmacy programs incorporate sports pharmacy as part of the curriculum.As illustrated by studies, pharmacy students in Japan (Saito et al. 2013) and Syria (El-Hammadi and Hunien 2013) did not have sufficient learning opportunities concerning doping in sports. Pharmacy graduates can, therefore, lack knowledge and skills about doping and anti-doping in sports and be ill-equipped to provide advice on safe, effective, and legal use of drugs for athletes.

Pharmacists are frequently approached by people who engage in sport and exercise for advice about drug treatment or on general healthcare associated with their participation in sport. There is a growing need for specialist pharmacists in the area of sports and exercise in order to fulfil this valuable healthcare role. These specialists may be described as sports pharmacists.The specialty of Sports Pharmacy covers,awareness of drugs in sport in the community, medicine & industry for both performance modification and the prevention and treatment of disease,knowledge of therapeutic use of drugs in sports and how pharmacist interventions can support sports related illness or injury, use of pharmacotherapy to prevent sport-related illness or injury and maintain well-being, safe and rational use of nutrition and supplements to optimise performance.Sports pharmacy aims to highlight the emerging role of the pharmacist in the area of sports medicine. The aim of the study is toemphasize the importance of pharmacist's involvement at international sporting events including the Commonwealth and Olympic Games.

The aim of the present study was to collect and examine all the important information available, to make the concept of sports pharmacy accessible to everyone and to raise the awareness of the pharmacists about this topic, which is expected to become very important in the future. It has been planned that the sports pharmacy is designed to be an important sub-field so as to help to understand and develop this concept.

The present study was undertaken to understand the level of sport pharmacywell in order to force the new important concept 'sport pharmacist' and to develop an effective awareness in this subject. Parallel to the aims of the study, two types of surveys were applied to pharmacists pharmacy students.

GENERAL INFORMATION

Sports and Pharmacist

People who are doing sports can have health problem such as muscle pain, injuries. Athletes who do thesports professionally can also have health problems and they may need to use drugs. In these conditions, they need to use medicines. Pharmacist is the person who know the medicines very well and is expert of the drugs therapeutic uses, adverse effects, drug interactions with drugs, foods, etc. Athletes doesn't know the if drug have doping effect or not but pharmacist dfo have thesegeneral information. Pharmacist know the effects of drugs in the body very well. Because of these reasons, pharmacist and athletes should be in the same area similar to athlete's doctor, athletes coach. There is also a new term which is sports pharmacy but this term didn't improve yet in all countries.

Sports Pharmacy

Sports Pharmacy is becoming important as a specialist field that is beginning to develop all over the world. Sports pharmacy can be defined as a science that examines the effects of sports on human health, the products used for athletes in this respect and the pharmaceutical products useful for reducing the harmful effects of the interactions of the drugs to be used in a possible situation and how their production should be. With such a broad scope, sports pharmacy will also be able to offer new career opportunities on behalf of our profession. Protecting and maintaining athletes' health is a team work. An application model is ideal where health professionals such as sports physicians, sports pharmacists, physiotherapists, conditioners and masseurs should interact with each other. We have observed that some countries have a special interest in this issue and that they have achieved much more successful results because of accepting the title of Sports Pharmacy as an effective specialty. Countries such as the United States, Britain, Japan and Canada have achieved significant sporting achievementsinternationally. Of course, the contributions of the services provided by a wide range of healthcare providers, as well as systematic and planned study programs, are of course very important. The most important topic is timing in sports. With the right timing, the most appropriate steps can be planned for many sporting concepts such as injury, recovery, development, prevention.

Role of Sports Pharmacist

Pharmacist can help athletes by giving information about banned drugs and monitoring doping test and can help to prevent test mistakes and helps to prevent doping.

Another way pharmacists can help athletes who are subject to drug testing is to promote them to get in contact with their sports governing associations to ensure that their medications and supplements are not banned.

If athletes do need a banned drug for legitimate medical reason, pharmacist can suggest them to go their sports governing associations and apply for an exception (Meghan 2016).

Within the scope of protective and preventive health services, it is the basic duty of the pharmacists to specialize in sports pharmacy, to lead the sports in the right way in the lives of the individuals.

On the other hand, it is among the duties of sports pharmacists to provide consultancy services on Food Supplements and Performance enhancing products, which are preferred to increase the quality of life and to support the continuity of being healthy.

Another important topic is the use of medicines in sports and the control of situations that can arise due to conscious or unconscious drug usage.The most tragic results of doping practices and prevention is also the interest and knowledge of sports pharmacists.

Sportsman Health Consultancy services, which can be presented in a more conscious and qualified manner in our pharmacies, will be able to support the development of conscious athletes. In addition to determine which products or supplements can be used by the athletes, sports pharmacists also can give information to sportsman about the products or medicines that should not be used. Integrating pharmacy sciences will be of utter benefit to the prevention of banned substance use and doping control in the field of sports and athletic health, an area where science and technology can be used most efficiently. The main factor in choosing non-irreversible ways for the athletes was determined as lack of knowledge and unconsciousness. Support consultancy services offered by sports pharmacists will be able to prevent undesirable effects and consequences.

Countries that have sports pharmacist

Japan

Japan Anti Doping Agency(JADA) launched the “Sports Pharmacists System” in partnership with the Japan Pharmaceutical Association in 2009. The Sports Pharmacist System is to certify the qualified pharmacists who are trained to have accurate knowledge in anti-doping and who can provide the appropriate information on medicine and the effects of drugs on health. Those certified pharmacists are also expected to provide anti-doping education program to the athletes particularly from the pharmaceutical perspective.

They start educating athletes from primary school. By this way, conscious athletes are raised. They have web site and in this website they have educational videos and subjects.

JADA Eligibility for Sports Pharmacist

- A fully-qualified and licensed pharmacist
- No age restriction
- The applicants should complete both “Basic” and “Practical” courses delivered by JADA and obtain the required minimum score in the exam
- Required for annual seminar course and recertification

Certification Program in Japan

The qualified sports pharmacist must annually take part in a practical lecture course in order to maintain a certification.

For certification renewal, before the certification expires, the sports pharmacists need to take both “Basic” and “Practical” lectures and also obtain the minimum score in the examination.

How sports pharmacist work in Japan

- Available for 24 hours, either via telephone, fax or email
- At local drug store/pharmacist across Japan – face to face accessibility to the knowledge of prohibited substances and anti-doping regulations
- Web searching system. JADA web site allows anyone to look for the closest Sports Pharmacists

Azerbaijan

European Olympics Games and Baku Islamic Solidarity games are the most recent examples for pharmacy applications in sports. In 2015; European Olympic Committees Medical and Antidoping Commission were created. There were two Athlete Villages for the Baku 2015 Games, each containing a comprehensive array of medicines to provide the medicine requirements of accredited athletes, team officials, European Games Family, and other residents of the Villages. The main pharmacy in the Baku Athlete Village was operated in a similar style as an outpatient dispensary and was the co-ordinating point of medicine supply for the athlete and spectator medical facilities at all venues. The operation period of the service was 28 days between 3rd June and 30th June 2015, which started at the opening of the Athlete Village and ended at the close. The service to spectators covered 17 days of Games competition. The pharmacy was staffed by 9 pharmacists: 7 local Azerbaijan pharmacists and 2 international pharmacists with experience of delivering pharmacy services at previous Olympic and Commonwealth Games. The Baku Polyclinic Pharmacy was situated in a purpose-built polyclinic located in the athletes’ residential area. The pharmacies dispensed prescriptions written by Baku European Games Olympic Committee (BEGOC) doctors and

also by around 233 visiting team doctors from the 41 different countries that had a medical practitioner as one of their officials. Pharmacy clinical services provided the medicine needs for 6000athletes of 50 countries who competed in 253 events across 20 sports in 16 competition venues (Baku 2015). Mark Stuart is the pharmacist for the International Olympic Committee (IOC) Medical Commission and European Olympic Committees (EOC) Medical and Anti-Doping Commission. He is a pharmacist specialised in pharmacy and medical services for international multi-sport games and is registered in the UK, Australia and Azerbaijan. He has worked with medical and anti-doping services for numerous Olympic, Paralympic, European and Commonwealth Games as part of the organising committee. He is presently the pharmacist member of the International Olympic Committee Medical Commission and European Olympic Committees Medical and Anti-Doping Commission, and current member of the World Anti-Doping Agency Prohibited List Committee. He is also the UK editor for the GlobalDro online athlete resource for drugs in sport.Table-1 represents the list of countries where sports pharmacy specialty have been applied and the Table-2 gives the future locations for sport pharmacy application area.

Table 1: List of countries that have applied sports pharmacy.

2000	Sydney - Olympic Games
2002	Manchester – Commonwealth Games
2004	Athens – Olympic Games
2006	Turin – Olympic Winter Games
2006	Melbourne - Commonwealth Games
2008	Beijing – Olympic and Paralympic Games
2014	Glasgow
2015	Baku – European Games
2016	Rio
2017	Baku – Islamic Solidarity Games

Table 2: Future places for sport pharmacy application area.

2020	Tokyo – Summer Olympics
2022	Qatar – FIFA World Cup

Qatar

Qatar is contributing to Pharmacy in a global significance. It is developing the pharmacy workforce in various events. Qatar is holding FIFA World Cup 2022. This is leading to a significant development in the area of pharmacy and sports pharmacy not only regionally, but also as globally (Awaisu et al. 2015).

Rio

In Rio 2016, Mark Stuart had been closely involved in a number of activities, including selecting 300 medicines for the formulary, advising on the design of the premises, establishing a governance framework for the pharmacy service and providing training to pharmacists and other healthcare professionals on drugs in sport. He had visited Rio in 2015 during the test events to advise on the safe management of drugs at the competition venues for rowing and at beach volleyball in a stadium built on Copacabana Beach.

During the Olympic Games in August 2016, he was responsible for overseeing the governance aspects of the pharmacy services on behalf of the IOC Medical Commission Games Group. He had also monitor patterns of medicines usage by athletes and spectators to assist public heath surveillance.

Additionally, he had inspected doping control stations at Olympic venues to ensure that the operations are being run in accordance to the World Anti-Doping Agency regulations, and support athletes undergoing the IOC Therapeutic Use Exemption process if they require banned drugs for legitimate therapeutic use (Stuart M, 2016).

Slovenia

Slovenia is also one of the countries that supports sports pharmacy. Slovenia has a website in the related area which is called SLOADO. Their aim is to create a generation accompanying athletes and achieve their goals without the use of prohibited substances and methods. SLOADO committed to ensuring the conditions for fair play and doping-free sports and to support effective education and information. The guiding principle of the educational program, and the information is to protect the spirit of sports from doping and establishing an environment that promotes and enhances sports without the doping among athletes who want to compete free of banned substances.

According to these examples, commission for Olympic Games in Turkey and North Cyprus can be created and sports pharmacists should be the part of the team comprising athletes' doctors, coach, physiotherapist etc...

Inclusion of sports pharmacists in the team would have the following advantages:

- Increase in the trust and knowledge of athletes related with anti-doping and Prohibited List
- To engage with the athletes to understand their needs
- Athletes can have face-to-face conversation at the hospital, pharmacy or drug store across Turkey and North Cyprus.

- Since the certification is publicly recognised, the quality and standard can be sustained and consistency in information can be managed.

Doping-Antidoping

What is doping and doping substances?

Doping is known to be the serious issue for athletes. This makes it important for pharmacists to have further interaction with the athletes to ensure their drug safety. Education is considered to be one of the crucial roles of sports pharmacy and these pharmacists are specialized in the usage of the drug by the athletes. We investigated the interests and comprehension of the students of pharmacy in terms of drug usage, doping, and supplement usage by using various questionnaire. This investigation was done to know students' understanding of sports pharmacy as part of their higher educational program. The investigation resulted in a negative attitude of the students towards doping and drug usage by the athletes. However, out of all the students, only sixteen percent of them attended the lectures. In addition, thirty percent of the students did know that few drugs might contain over-the-counter drugs. Whereas about seventy percent of the students had a positive image and interest. Only one third of the respondents thought the supplement as food and they attained their information from unreliable media. More education on such issue would enlighten students about sports pharmacy and make their scope broader for further studies and research.

Doping applies to athletes in all forms, regardless of the athlete's age, or the level of their play and it is also a social problem mainly among young generations in most of the countries.

The reasons that doping is prohibited are;

1) The value of the posts is taken away,
2) The fundaments of sports spirit and principles is harmed,
3) It causes harm to your health, and
4) Source of drugs may cause abuse which is a harmful effect for people.

The public along with the athletes needs to have general knowledge about doping and its effects. However, due to a limitation in information about doping, such a knowledge of the public is limited. It is necessary for pharmacists who are specialists in drug usage and have many opportunities to administer drugs to the general public to participate in anti-doping activities in the role of "sports pharmacists."

There are two variations of doping: Intentional and unintentional doping which is done by the athlete's due to lack of knowledge regarding this matter. Doping substances are classified into three categories: Permanently prohibited ones which include anabolic androgenic steroids or peptide hormones, growth factors. Another one comprises substances prohibited for the

competition, like optical isomers or glucocorticosteroids and the last category includes substances, such as alcohol or beta-blockers that are banned in a specific sports. Since ephedrine and pseudoephedrine, which are components of Ma Huang, are banned in competition and are often compounded in combination cold remedies, athletes must take extra precaution regarding their usage. However, few violations of doping occur due to ephedrine or pseudoephedrine, since the athletes do not have entire knowledge of doping violation. Although all sportsmen and athletes are required to understand and recognize World Anti-Doping Code (WADC), it is tough to do so. Hence, it become the responsibility of the sport's pharmacist to help these professionals regarding the issue (Saito et al., 2013).

Substances or drug related doping are generally grouped under 3 titles:

1. Drugs for blood and blood circulation and cardiac system
2. Drugs for central nervous system (Stimulant type drugs)
3. Drugs affecting protein and cell metabolism

First two group drugs mostly show sudden and short effect but they are dangerous.

World Anti Doping Agency

The World Anti-Doping Agency (WADA) was founded in 1999, in Switzerland to promote, coordinate and, monitor drug usage in sports. The organization was created by the International Olympic Committee(IOC) in Canada. The committee has been adopted by more than 600 Sports organizations throughout the world. WADA is funded by various national governments and the IOC. The main activities of the agency include scientific research, education, development of anti-doping capacities, and monitoring the World Anti-Doping codes. It is also enforced by the UNESCO nternational Convention against Doping in Sports. Prohibited drug list is established each year by WADA.

Sports supplements that are used today

Use of performance-enhancing supplements occurs at all levels of sports, from recreational athletes to professional athletes. Although some supplements do increase athletic performance, many have no proven benefits and have side effects.

Nutritional supplements are categorized into the following categories:

I. Apparently Effective.

Ergogenic supplements which are categorized in this category;

1) Buffer agents
2) Creatine
3) Caffeine
4) Nitric Oxide.

II. Possibly Effective.

III. Too Early To Tell.

IV. Apparently Ineffective.

Given the widespread use of performance enhancing supplements, physicians, and dietitians should be prepared to counsel athletes about their effectiveness, safety and legality. Supplements have been divided into several sub-groups such as those claimed to increase endurance performance, strength/size adaptions or boost general health. There is however considerable evidence behind the effectiveness of caffeine, creatine, nitrates, beta alanine, antioxidants and vitamin and therefore these have been given special consideration**.**

Energy drink usage by athletes

Energy drink is a type of beverage that contains stimulant drugs, usually including caffeine, which is marketed as providing mental and physical stimulation. Energy drinks are widely used today. Energy drinks has become an indispensable drink for those who are particularly busy with adrenaline buffs and sporting activities. Energy drinks contain caffeine, taurine, amino acids, glucuronolactone, sugar or other sweeteners and herbal extracts. Also, they contain inositol, ginseng, vitamin complexes, guarana, carnitine, etc. in different proportions. Some of the energy drinks produced today include poppy seed extract. Taurine is an amino acid. In times of stress and intense physical activity, the body may suffer taurine loss. Like taurine, caffeine and glucuronolactone also give energy to the body. However, continuous use of these substances has harmful effects on the body. In energy drinks, there are substances that are mixed with blood quickly. The stimulant effect of these substances in our bodies occurs in a short time and gives an energy to our body. However, this benefit can be transformed into a permanent wound in the future.

Energy Drink Contents

Caffeine; has a moderately stimulating effect on the central nervous system, depending on the amount consumed. When taken at 40 mg, it usually improves the mood, causing energy, alertness and increased ability to concentrate (Harland 2000). Caffeine intake causes an acute increase in heart rate and blood pressure (Tofler 2001). The most important effect of caffeine on the gastrointestinal tract is that it increases the secretion of acid, leading to symptoms such as gastritis and reflux (IFICF 2008).Caffeine decreases insulin sensitivity and increases the risk of type 2 Diabetes Mellitus (Lee 2005).

Taurine; is one of amino acids containing thiol. In a normal diet, the amount of taurine is 40-400 mg/day. Taurine is found in the central nervous system at different densities in both neurons and glial cells. It is the free amino acid that is mostly found in the skeletal and heart

muscle cell (Kendler 1989). Taurine decreases the anxiety by increasing gamma amino butyric acid level. It also increases the level of dopamine so has a positive effect on locomotor activity (Eppler 1999).

Glucuronolactone; is a product of glucose metabolism that is synthesized in the liver. Glucuronolactone which is found in energy drinks is synthetic. There is no scientific evidence that glucuronolactone has a detoxifying effect, but there is no indication that it may have harmful effects as well.

Inositol; enhances the sensitivity of nerve cells to serotonin and the signal level in the brain of serotonin. Low inositol levels associate with depression, anxiety or panic attacks. 200 mg daily is sufficient for the body. High dose caffeine use (> 500 mg/day) reduces the inositol level in the body (Wehr 1990).

Guarana; is the seed of the '*Paullinia cupana*' plant that grows in South America. It is the richest source of caffeine in the world. Apart from caffeine, it contains theobromine, theophylline and tannin. Clinical trials have shown that theophylline stimulates the heart and central nervous system, increases attention and relieves fatigue. It also has a strong diuretic activity and is useful in the treatment of asthma as it reduces bronchospasm (Pizza 1999).

Ginseng; is derived from the roots of *Panax ginseng* and *Panax quinquefolius* plant. It ıncreases energy, libido, body resistance and memory. The daily dose is 300-400 mg of root extract (Attele 1999).

B vitamins and glucose; are water soluble. One liter of Red Bull contains 150 mg of B vitamins, any excess of which could be readily excreted by a normally functioning renal system. Upon ingestion, glucose is either utilized as an energy substrate or stored in the liver and muscles. The ingestion of 108g of carbohydrate (4 cans of Red Bull) should not represent a problem for the kidneys. The exception is the diabetic population for whom such an amount of glucose could cause glycosuria (presence of glucose inurine) and the accompanying excessive water loss into the urine with resultant dehydration (Lewis 2013).

Diuretic effect of the most common energy drink ingredients are;

B vitamins and glucose

Glucuronolactone

Taurine

Caffeine

Side Effect of Energy Drinks

Several studies and several reports from international societies have described the possible negative effects that the habitual consumption of energy drinks may have on health.To date

there is little information on the adverse effects that acute ingestion of energy drinks may have on the physical performance and perceived fatigue of athletes (Mora-Rodriguez and Pallarés 2014).

Using surveys to evaluate the adverse effects of energy drinks found that 120mL of the marketed Redline Xtreme energy drink (~2.0mg/kg of caffeine) considerably improved the participants' subjective feelings of energy and focus, while no differences were detected for the feelings of fatigue and alertness. These data are dependent with the findings of who found that recreationally active subjects consuming a commercial energy drink (caffeine dose not reported) felt greater focus and energy as well as less fatigue (compared to a placebo treatment) before and during a time-to-exhaustion test. These positive effects disappeared immediately after exercise. Similarly, the mood state scores for vigor were significantly greater and fatigue scores significantly lower 60min after the ingestion of a noncommercial, self-prepared, sugar-free energydrink(5mg/kgofcaffeine) compared to a placebo drink.

In sports events lasting longer than half a day, the negative side effects generated by the ingestion of a sufficient amount of energy drink to ensure caffeine doses higher than 6mg/kg in the mornings, and 3mg/kg in the afternoons, could neutralize the ergogenic effects of caffeine and result in decreased physical performance (Lewis 2013).

Risk groups for energy drinks;

- ✓ Patient who has cardiovascular disorders
- ✓ Pregnant woman
- ✓ Who are making nutritional diet
- ✓ Children
- ✓ Alcohol users
- ✓ And people who are interested in sports or athletes are in the big risk group.

These people should not use energy drinks because energy drinks are very harmful for these groups and mostly for the athletes.

MATERIALS AND METHODS

In this study, two different surveys were carried out. Survey one was filled out by pharmacy students who are registered to Eastern Mediterranean University. Second survey was filled out by 50 community pharmacists who work in North Cyprus and Turkey.The aim of the second survey was to analyse and evaluate the current attitude of pharmacist related with sports pharmacy in North Cyprus and Turkey. Both surveys are shown in Table-3 ,Table-4.

Table 3: Question of Survey 1.

1. Would you like to include sports pharmacy in your education curriculum?
( ) Yes ( ) No If your answer is YES, please answer to second and third question.
1. I would like to take sports pharmacy as a; ( ) Main Course ( ) Area Elective
2. How many hours per week do you want to take the sports pharmacy course?
( ) 1 hour ( ) 2 hour ( ) 3 hour ( ) 4 hour
3. Would you like to do make a career in sports pharmacy? ( ) Yes ( ) No
4. Would you like to take sports pharmacy as a master's course? ( ) Yes ( ) No

Table 4: Question of survey 2

1. Gender
( ) Female ( ) Male
2. Age
( ) 22-28
( ) 28-34
( ) 34-40
( ) More than 40
3.How long have you been pharmacist?
( ) 1-4 year
( ) 4-8 year
( ) 8-12 year
( ) More than 12 year
4. Have you heard sports pharmacy before?
( ) Yes ( ) No
If the answer is YES, where and how did you hear?
( ) Congress ( ) Web page ( ) Professional Publications
( ) Social Media ( ) Others
5. What is your level of knowledge about athletic products?
( ) Very good ( ) Good
( ) Medium ( ) Less
6. Do you think athlete's products are healthy?
( ) Yes ( ) No ( ) I am not sure
7. Do you have any sources about the content and activity of athletes' products?
( ) Yes ( ) No ( ) Yes but insufficient
8. Do your resources support the counseling services you offer?
( ) It supports more. ( ) Supported enough.
( ) Partially supported. ( ) It does not support in any way and it is insufficient.
( ) Other (Please specify).....
9. From whom and where do you get help for information on athletes' products?
( ) Doctor ( ) Nutritionist ( ) Coach
( ) Internet ( ) Magazines and books
( ) Television ( ) Other (Please specify).....
10. Which of the following would you prefer to get more up-to-date and more qualified information about athletes' products?
( ) From the web presentations of instructors ( ) From Congress
( ) From TEB trainings ( ) Professional training programs
( ) Other (Please specify).....
11. Mark the following proposals as true or false.
●Protein powders are suitable for every athlete.
True ( ) False ( )
● Excessive consumption of amino acid containing supplement products causes acute gastrointestinal system disorders such as severe stomach aches and diarrhea.
True ( ) False ( )
● Long term use of amino acids can lead to liver and kidney problems.
True ( ) False ( )
● Athletes can use any kind of medication.
True ( ) False ( )
● Analgesics and similar medicines have no effect on nutritional benefits.
True ( ) False ( )
● It is important for health to know the harmful effects of additives in energy drinks to health.
True ( ) False ( )
● Amphetamine is not a doping agent.
True ( ) False ( )

● Neurological and psychostimulant drugs (eg Concerta, Nootropil, Ritaline ... etc) have no effect on the athletic doping analysis.
True ( ) False ( )
● It is important for athletes to know whether food supplements interact with over-the-counter medicines.
True ( ) False ( )
●Adolescent athletes should not use any supplement.
True ( ) False ( )
●Some OTC drugs may show doping effect.
True ( ) False ( )
●Herbal products never show doping effect.
True ( ) False ( )

12. Do you have information at the basic level about definitions such as ergogenic product / substance method?
( ) Yes ( ) No

13. Do you sell supplement support products?
( ) Yes ( ) No

Protein bars	YES	NO
Whey protein	YES	NO

14.If your answer is yes, which supplements do you sell?

L-arginine	YES	NO
L-carnitine	YES	NO
L-glutamine	YES	NO
CLA	YES	NO
BCAA	YES	NO
Creatin	YES	NO

15.Do you support non-prescription drug anabolizine medication?
( ) Yes ( ) No

16.Does the consumer choose their own athletic products?
( ) Yes ( ) No

17. Do you provide counseling service for sportsman's products?
( ) Yes ( ) No

18.Did you use your pharmacist identity to indicate that you did not recommend the athlete product and that it was not appropriate to use it?
( ) Yes ( ) No

19. How effective is the advanced consulting service provided by the customer for the sale of athletes' products?
( ) Very efficient ( ) Effective
( ) Partially effective ( ) Ineffective

20.Do you keep records about the products you sell?
( ) Yes ( ) No

21.Would you like to have a registration system?
( ) Yes ( ) No

22.Mark drugs with doping effect on table below

	YES	NO
Xanax(Alprazolam)		
Ventolin(salbutamol)		
Diamorfin HCl (diamorfin)		
Beloc Zok(metoprolol)		
Tamoxifen(tamoxifen)		
Aldactone(spironolactone)		

Source for the 22nd question: https://play.google.com/store/apps/details?id=tr.gov.saglik.sporcusagligi

RESULTS

Results of Survey 1 for students

The results of questions for survey 1 were shown in Figure1-6.

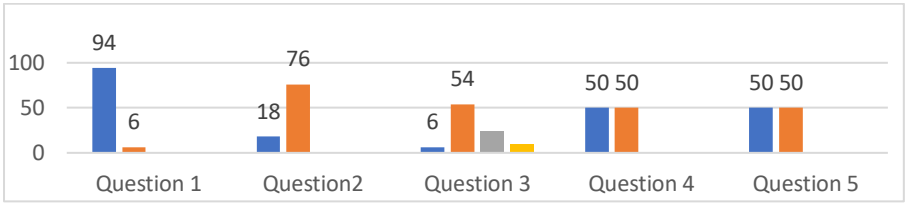

Figure 1: All result of the student survey questions (%).

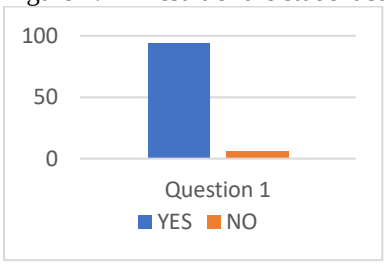

Figure 2: Answers for question 1 (%).

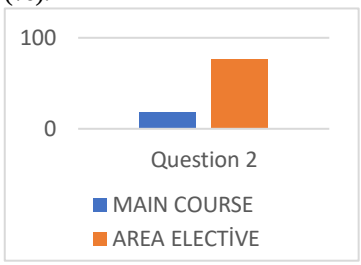

Figure 3: Answers for question 2 (%).

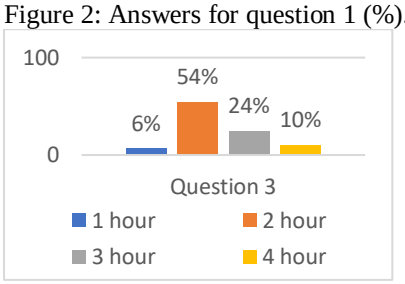

Figure 4: Answers for question 3.

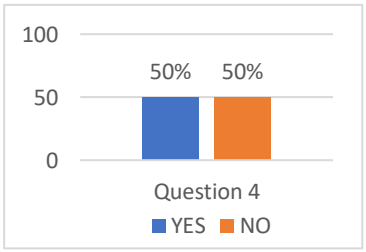

Figure 5: Answers for question 4.

Figure 6: Answers for question 5 (%).

Results of Survey 2

Results of the questions of survey 2 were shown in figure7-10.

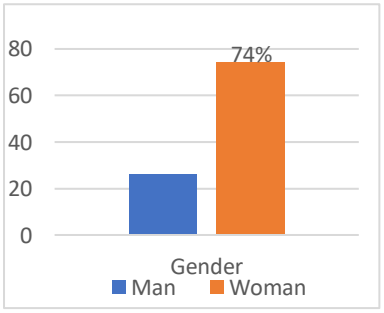

Figure 7: Gender of pharmacists.

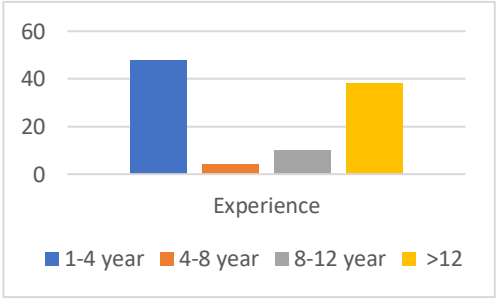

Figure 8: Experience of pharmacists (%).

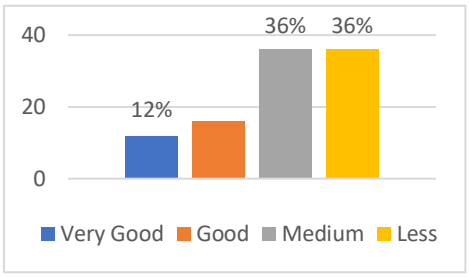

Figure 9: Knowledge about sports pharmacy.

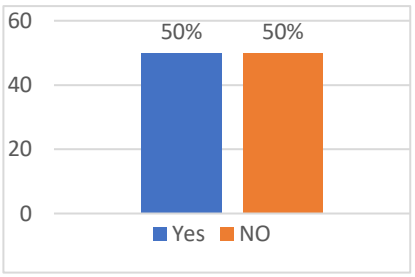

Figure 10: Knowledge about athletic products.

DISCUSSION and CONCLUSION

94% of the pharmacy students participated in the survey responded positively to the participation of sports pharmacy in the education curriculum. Although sports pharmacy is a new field, the number of students considering a career in this field is 50%. This is a relatively meaningful outcome for an area that is very new to our country yet and where even official application areas do not become evident.

On the other hand, community pharmacy is the most preferred application area of the pharmacy profession in current conditions.In this sense, 50% is even more meaningful given the presence of a significant number of career plans on community pharmacy. As a result of this determination, it becomes even more meaningful that the sports pharmacy course is chosen as an elective course not as a main course. Sports pharmacy counseling can be provided by seminars and vocational training in pharmacies. The rate of preference of sports pharmacy given as master's degree program was determined as 50% by Cypriot and Turkish pharmacy students. Like the other countries such as Japan, Azerbaijan and others, sports pharmacy can be planned as a career in Turkey and North Cyprus. As a result, pharmacy students were found to be interested in sports pharmacy and sports pharmacyshould be regarded as an area that can be integrated into existing pharmacy applications with a 2-3-hour training program and it is of interest.

25 pharmacists had no idea about sports pharmacy but other 25 pharmacists had heard sports pharmacy before via social media, seminars and other web pages. 12% of pharmacists who are interested in athletic products in relation to athletes' health are very well informed about their athletic products. 36% of the respondents pointed out the importance of sports pharmacy in that they had very little information on athletic health products and 36% state that information levels were moderate. 48% of participants were found to have 1-4 years of experience, 4% have 4-8 years of experience, 10% have 8-12 years of experience and 38% have more than 12 years of professional experience. We observed that the 56% of pharmacists over 34 years who had

professional experience over 8 years do not have any idea about the subject at the moment. The fact that the younger generation is more relevant and knowledgeable about the subject can be evaluated in terms of the professional future. The pharmacy profession is composed of many components. The professional responsibilities of pharmacists are quite extensive and increasing day by day. The process becomes even more difficult when many legal responsibilities and practices that need to be followed are added. Our pharmacists at the beginning of their professional career can still be interested in new titles without intensifying their involvement in this spiral.

In the 25-person group, who had ideas and knowledge about sports pharmacy, congresses, professional publications, internet and social media were reported to be influential by40%, 24% and 68% of students, respectively. The effectiveness of the social media has been emphasized once more with these survey findings. 24% of the pharmacists rated the athletes' products as unhealthy. Paracelsus told that "All things are poison, and nothing is without poison, the dosage alone makes it so a thing is not a poison." In parallel to the saying of Paracelsus, we can tell that sports supplements are not unhealthy. The important thing is dose and usage way as Paracelsus said. 38% of pharmacists were not sure about the subject. It is necessary to treat athletes' products in a very broad scope. The judgement should be done by evaluating negative or positive effects on health by dividing it into main groups as nutritional supplement, ergogenic, performance enhancing, doping effective substances, prohibited substances or methods.

42% of the participants did not consider the available resources to be inadequate. We do not have a sufficient number of domestic and foreign sources about sports sciences and pharmacy applications. It is absolutely necessary to update the existing sources with updated information. When the existing resources were questioned about the extent to which our pharmacists support their counseling services, the result also supports the previous inquiry.50% are partially supported where as 22% did not support it at all. A total of 72% of students pointed out that the group resource deficiency or insufficiency was too high. In Japan there is a certificate program for pharmacist and we can apply this education program in our country and our pharmacists can give counseling to their customers who are interested with sport.

The study population was questioned in order to obtain information about the athlete's products. We have found that a total of 42 applications heard about it from physicians, dietitians and coaches. In addition, web sources, TV, books and magazines were identified as the vehicles of awaraness by 43 respondents. It should not be forgotten that many different methods can be

applied to reach the information, but the important thing is that the accuracy of the information obtained and the reliability are questioned.

Occupational training, congress information sharing and training programs within the academy of TEB.Information preferred by our participants has not been updated. Significantly, in view of the pharmacists online training required. New generation education practices and classical education processes blended.

Ergogenic products covers ingredients that have suitable usage and proper planning group for performance, Professional and high-level athletes. This definition has to be embraced and included to our consulting field. Thirty pharmacists reported that they were selling their ergogenic substance / product in their pharmacy while 20 participants reported that they did not sell these products. However, in the previous questionnaire, 30 participants reported that they had no knowledge of the ergogenic product / substance. In this case, we can tell that such products are generally available on demand in pharmacies. In terms of athletes' health, an inquiry was made about the sale of prescription drugs from the pharmacy of anabolizan products, which is a very important subject title. 6 participants indicated that they approve this operation. When scientific approach to the subject is required, we suggest that anabolic products should be used under the expert control and absolutely appropriate dose terms in terms of development and performance balancing of high level athletes and that optimal planning should be done in terms of toxicity and side effect. The preference for non-prescription delivery of these group products with a high impact capacity and high likelihood of side effects should never be a commercial concern. This current state is a engrossing for us pharmacists. Pharmacists like us have to be very active about the subject that concerns human life and usage of drugs without control. This subject has to be controlled properly. The correct application that pharmacists are not only chosen for product supply by making product identification with information on the internet or stuffing with the remote is the right method of application when the pharmacist has more say in this area as necessary.

According to the survey results, most of the pharmacists do not know that the doping effect of commonly sold drugs such as aldactone, beloc zok, ventolin and tamoxifen. In this regard, we can make our pharmacists aware about doping by making training courses. Because pharmacists are the first person who communicate patient much more than other health service worker by giving consultancy service we can make patient and athletes aware about doping.

Awareness is lower than in other countries, but the awareness of pharmacists is not bad, even though sport pharmacy is a newly emerging issue in our country. It is a fact that the awareness

of our pharmacists and the training programs to be done will increase. This awareness can be further increased by establishing a website like Japan, Slovenia and other countries.

CONCLUSION

Sports pharmacy is a new but very important area for pharmacists and athletes. By looking at the countries who have sports pharmacist in their country we can see that their athletes more succesful than our athletes. Athletes do not know all the doping substances but they have pharmacist who know these substances and athletes can ask to their sport pharmacist everything about their drugs. By this way they reduce to use of unconscious doping substances. Also with educational program for athletes they learn the the harmful effect of the materials. Sport is the one way to introduce country to other countries. If our athletes do doping that means our country doesn't known with good sentences. But with sports pharmacy area we can educate our athletes and we can make seminars for athletes about clean sports.

This study is the first awareness work done in the field. This study has shown that;

- Pharmacy students and pharmacists are interested about this area.
- By using the methods and application which is used in other countries we can start sport pharmacy in our country.
- We can apply the similarity of the practice in Japan to cultivate conscious athletes in our country.
- We must increase awareness by organizing trainings and seminars for pharmacists.
- We must train our coaches to raise awareness in sports colleges.
- We should give training to the students about the athletic products by cooperating with the pharmacy faculties.
- We can establish sports pharmacy in cooperation with the Ministry of Sports, the Ministry of Health and Turkish Pharmacists Association.

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PROBIOTICS AND THEIR USES IN CLINICAL PRACTICE – AN OVERVIEW

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ABSTRACT

Probiotics**,** considered to have some benefits on human health when consumed in adequate amounts, are living microorganisms that can colonize intestine, mouth, mucous membranes, vagina, and skin. Probiotics have been tried for treating irritable bowel syndrome, enhancing immune system, maintaining balance in intestinal microbiota, preventing colorectal cancer, lactose intolerance, urinary tract infections, antibiotic-associated diarrhea and managing hepatic encephalopathy. They have been shown to display anti-hypercholesterolemic and antihypertensive impacts and have some positive effects on children and pregnant women. Their mechanism of action has been unexplored and related studies have become increasingly popular.

Lactobacillus and *Bifidobacterium* and the yeast *Saccharomyces cerevisiae* are microorganisms that are mostly utilized as probiotics. Lactic acid bacteria, including *Lactobacillus*species, can serve a dual function by being used in food fermentation and potentially imparting health benefits such as maintaining a healthy-immune system.

Safety of probiotics is a concern as they may result in bacteremia, fungemia, some side effects and may interact with immunosuppressive drugs leading to life threatening conditions. Further studies are needed to clarify the optimum dosage, duration of the treatment, usage of mix versus single-strain probiotics, cost effectiveness, hazards, counteractive effects to pathogens and usage in the treatment of various diseases.

Key words: Probiotic, *Saccharomyces cerevisiae*, *Lactobacillus*, *Bifidobacteria*

INTRODUCTION

Microorganisms colonizing certain parts of the body and living together with human without causing any disease under normal conditions, once named flora and now known as microbiome, interestingly outnumber the total number of human cells by ten-fold. Human microbiome, also called microbiota, consists of a mixture of genes and related products of trillions of bacteria, archae, microeucaryotes and viruses residing in different parts of the body and is considered as a barrier and a protective part of the human body. With recent developments in high-throughput DNA/RNA sequencing and computational technologies,

scientists have discovered uncultured microorganisms in the microbiome besides the cultured ones and stated that the diversity of human microbiome is much more than ever been thought. The “Human Microbiome Project”, which aims to characterize the components of microbiota in various parts of the human body by molecular methods so that effect of microbiome on human health and disease can be clarified, has led to many contributions to the science of human microbiome (Aagaard *et al*. 2015).

Probiotics are defined as “*live microorganisms conferring benefit to health when consumed in adequate amounts”* by Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) (Chen and Sears 2015).

Probiotics were first mentioned over a century ago by Elie Metchnikoff. Metchnikoff’s aim was to improve the health and dementia by controling the intestinal microbes using beneficial bacteria found in yogurt. In 1907, Metchnikoff anticipated that the acid producing bacteria in fermented milk products could prevent "fouling" in the colon and if consumed regularly could lead to a longer and healthier life (Mackowiak 2013). The first report on probiotics was published in 1965. Approximately 60% of more than 8000 probiotic related publications are human based studies. Various probiotics are currently marketed as food ingredients, dietary supplements, or “medical food” and international market of probiotics is enormous. However, the number of probiotics whose benefits have been proved by scientific studies is limited and vary from strain to strain and disease to disease (Aagaard *et al*. 2015).

Probiotics are live, beneficial microorganisms that are generally found in different anatomical locations in our body, e.g., intestine, mouth, viscous mucosal membranes, vagina and skin. *Lactobacillus* and *Bifidobacteria*, two frequently used probiotic bacteria, are found in the gastrointestinal (GI) microflora. In contrast to probiotics, prebiotics are indigestible substances (not living organisms) that may have beneficial effect on host by selectively stimulating the growth and/or activity of one or more but in general limited number of bacteria in the colon. The most commonly used prebiotics are inulin and fructooligosaccharide which are added to different foods containing fat and sugar. Addition of prebiotics to a formulation has been reported to stimulate the growth of only beneficial bacteria in the gastrointestinal tract. The treatment strategy in which probiotic and prebiotic are administered at the same time is called symbiotic (Chen and Sears 2015).

Probiotic preparations include highly variable microorganisms. Some probiotics include single microbes usually from the genera of *Lactobacillus, Streptococcus* and *Bifidobacterium* as bacteria and from the genus of *Saccharomyces* as fungi; whereas the others are composed of multiple distinct microbes. The commercial product VSL#3 that is composed

of eight strains of bacteria from the genera of *Bifidobacterium*, *Lactobacillus* and *Streptococcus* (*S. thermophilus*, *B. breve*, *B. longum*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. paracasei*, and *L. bulgaricus*) is one of the well-known example of such a probiotic containing a mixture of different bacteria. Apart from probiotics, lactobacilli and bifidobacilli are naturally present in fermented foodstuffs (e.g., yogurt, cheese, and sauerkraut), fermented vegetables, and olives. Probiotics is generally used as a supplement (pills, capsules, tablets and powders).Probiotics are becoming an attractive alternative treatment strategy as supplements due to their confirmed efficacy and safety in some diseases. However, the use of probiotics as supplements should be strictly regulated because of both some controversial results about the efficacy and safety and the lack of consensus on the optimum dosage (Chen and Sears 2015, Sanders 2009, Berman 2015).

Probiotics are named and classified by group, genus, species and strain as following:

Lactic acid bacteria (group)→*Lactobacillus* (genus)→*acidophilus* (species) →LA-5 (strain)

Bacteria and fungi that have received "Generally Recognized as Safe" (GRAS) status in United States are given in Table 1.

Table 1: Bacteria and fungi accepted as safe in probiotics by receiving GRAS ("Generally Recognized as Safe") Status in the United States (Chen and Sears 2015).

Bifidobacterium lactis strain Bb12 and *Streptococcus thermophilus* strain Th4
Bifidobacterium longum BB536
Bifidobacterium animalis subsp. *lactis* strains Bf-6, HN019, Bi-07, B1-04, and B420
Carnobacterium maltaromaticum strain CB1 (viable and heat treated)
Lactobacillus acidophilus, Lactobacillus lactis and *Pediococcus acidilactici*
Lactobacillus acidophilus NCFM
Lactobacillus casei subsp. *rhamnosus* strain GG
Lactobacillus casei strain Shirota
Lactobacillus reuteri strain DSM 17938
Lactobacillus reuteri strain NCIMB 30242
Lactobacillus rhamnosus strain HN001
Lactobacillus rhamnosus strain HN001 produced in a milk-based medium
Propionibacterium freudenreichii ET-3, heat killed
Saccharomyces cerevisiae strain ML01, carrying a gene encoding the malolactic enzyme from *Oenococcus oeni* and a gene encoding malate permease from *Schizosaccharomyces pombe*

Characteristics of Optimum Probiotics

The important characteristics of probiotic microorganisms were defined as follows by Food and Agricultural Organization of United Nations (FAO) and WHO (Chen and Sears 2015):

(1) Taxonomically categorized probiotics have to be placed in an internationally recognized culture collection

(2) Probiotics have to sustain their viability and stability after culturing, manipulation and during storage before ingestion

(3) Probiotics have to be resistant to gastric acid, biliary and pancreatic secretions

(4) A host response has to be induced once ingested

(5) They must have a functional or clinical benefit when consumed by the host in adequate amounts;

(6) They have to be safe in terms of both side effects and antibiotic resistance pattern.

Lactobacillus GG, one of the most frequently used probiotics, is chosen for probiotic intervention specifically because it survives the passage through the stomach, the acidic part of upper gastrointestinal system, multiplies in the intestine, adheres strictly to epithelial cells in vitro and prevents adherence of *E. coli* O157:H7 (enteropathogenic strain of *E. coli* that can lead to haemolytic uremic syndrome as a complication after foodborne infections), and produces some chemicals that are effective against some other pathogenic bacteria (Sanders *et al*. 2010).

Dosage

The effectiveness of probiotics depends on their doses. Because of the variety of probiotic organisms and variety in their administration route and delivery, no exact dosage can be provided for probiotics in general. Doses of probiotics are generally expressed in “colony forming units per millilitre” (CFU/ml). Although the effective dose varies among different probiotics, generally the minimum concentration of probiotic microorganism is accepted to be 10^6 cfu/ml. Studies related with the dose response effect of probiotics is also controversial depending on the type of the disease they are used for. Dose response effect has been determined for some diseases such as antibiotic associated diarrhea (AAD), whereas such an effect has not been determined for some other diseases (Sanders 2009, Ouwehand 2016, Kechagia *et al*. 2013). Since it changes from probiotic to probiotic, the concentration (dose) of the probiotic should be mentioned on the label. In addition to the dose of the probiotic, the label of probiotic preparations should include the genus, species and strain names of probiotics, the

end of the shelf-life of each probiotic strain, health claim, safety storage conditions and customer information (Chen and Sears 2015, Sanders 2009, Sanders *et al*. 2010).

Mechanisms of Action

Although the mechanisms of actions of probiotics have not fully been explored yet, clinical benefits of probiotics are thought to be due to enhancement of the epithelial barrier, inhibition of pathogen adhesion via adhering and occupying receptors on intestinal mucosa, secretion of antimicrobial substances and competitive (e.g., competition for nutrient) exclusion of pathogenic microorganisms. By colonizing the gastrointestinal system, probiotics interact not only with gastrointestinal cells but also with the elements of mucosal or systemic immune response. Probiotic bacteria are thought to interfere with natural killer cells, cytokine secretion, macrophage activation, and secretory IgA activity. The action of mechanisms of probiotics can be investigated under four main titles (Berman 2015, Reid 2016, Bermudez-Brito *et al*. 2012, Gogineni *et al*. 2013, Chen and Sears 2015):

a) Nutrient Competition: Within the gut, probiotics tend to compete with pathogenic microorganisms for the nutrients that they need in common for their growth and reproduction. Therefore, the more the beneficial microorganisms in the gut, the more the competition there will be between beneficial and pathogenic microorganisms.

b)Adhesion Competition: By adhering strongly to adhesion sites and occupying receptors on gut mucosa, probiotic bacteria prevent or limit the colonization (the first step of the infection) of bacteria that would lead to infections like acute gastroenteritis or deficiency in digestion and nutrient absorption within the gut.

c) Antimicrobial effect: Antimicrobial effect can either be achieved by bacteriocins, peptides or proteins produced by many species of lactic acid bacteria that have antimicrobial activity against other bacteria, or by the production of organic acids which have direct antimicrobial activity or may show indirect antimicrobial effect by reducing the pH of the gut.

d) Enhancement in digestion: Probiotic microorganisms act like an element of microflora in the gut after they adhere and produce enzymes that aid in the breakdown of polysaccharides eventually resulting in the generation of energy. Moreover, these microflora organisms both ferment carbohydrates which have not been digested in the upper parts of the gut and produces vitamins supplying a secondary source to the host.

e) Immune modulation: Some probiotic organisms such as *L. casei* have been shown to increase the secretion of immunoglobulin A; the main immunoglobulin that is responsible for the mucosal immunity, in the gut resulting in the reduced morbidity of bacterial gut

pathogens. *L. casei* has also shown to be related with reduction in the secretion of pro-inflammatory cytokines, thus showing an anti-inflammatory effect.

Side effects

In general, probiotics are accepted to be safe in case they are consumed in the right dose. However, theoretically, exposing humans to live microorganisms brings some risks. The potential side effects of probiotics can be summarized as follows (Berman 2015, Vandenplas *et al*. 2015, Doron and Snydman 2015):

a) Systemic infection: Lactobacillemia, the blood stream infection caused by *Lactobacillus*, has been reported as one of the most serious side effects of probiotics containing *Lactobacillus*. Probiotics have also been related with septicemia, fungemia and endocarditis. Immunocompromised people are the most important risk group for these probiotic related systemic infections.

b) Deleterious metabolic activities: The most dangerous deleterious metabolic effect related with the probiotics is related with D-lactate, produced by some probiotic strains, that interferes with the bile salt and lead to short bowel syndrome.

c) Over-stimulation of immune system: Although not confirmed by clinical studies, probiotics are suspected to have the potential to lead to inflammatory or autoimmune reactions as a result of their capability to stimulate immune system and induce cytokine secretion from various cells.

d) Gene transfer: Lactic acid bacteria have small extrachromosomal DNAs, called plasmids, which contain genes that result in the development of resistance to various antibiotics including tetracycline, chloramphenicol, macrolides, lincosamides and streptogramine. Plasmids are mobile DNA elements that can be transferred among different strains of bacteria by a type of recombination called conjugation. Conjugation results in the dissemination of antibiotic resistance among bacteria. Although such scientific evidence has not yet been found, possible resistance gene transfer via plasmids can lead to the dissemination of antibiotics resistance among the normal flora bacteria of the gut.

Clinical Applications of Probiotics

There are numerous studies related with the use of probiotics as one of the elements of the treatment in various diseases or clinical manifestations. Although probiotics have many indications, the most common indication for probiotics is acute diarrhea related with bacterial or viral infectious agents. Cochrane, a global network consisting of researchers, professionals and people interested in health and providing high quality systematic reviews, has numerous

valuable systematic data about the use of probiotics especially in gastrointestinal manifestations or infections (infectious diarrhea, AAD, *C. difficile* colitis, inflammatory bowel disease, necrotizing enterocolitis in preterm infants, irritable bowel syndrome (IBS) and collagenous colitis). Cochrane reviews also contain studies related with the use of probiotics in pediatric diarrhea, ulcerative colitis, Crohn's disease, hepatic encephalopathy, non-alcoholic fatty liver disease/steatohepatitis, hepatic postsurgical complications, allergic diseases, food hypersensitivity, eczema and bacterial vaginosis (Chen and Sears 2015, Berman 2015).

Some important examples of the clinical use of probiotics can be summarized as follows:

1. Diarrhea

a.) AAD: AAD and pseudomembranous enterocolitis are results of the overgrowth of toxigenic *Clostridium difficile* (recently it has been shown that overgrowth of *Klebsiella oxytoca* can also lead to AAD) after antibiotic (all types of antibiotics but especially clindamycin and beta-lactam antibiotics) consumption. AAD is among the most common side effects of antibiotic therapy in hospitalized patients; especially those hospitalized in intensive care units. Probiotics are frequently used as a part of the treatment in patients with AAD. The microbial ingredient of the probiotic used may change according to the type of the antibiotic that has led to AAD. For example, in clindamycin related AAD *B. longum* + *Lactobacillus* preparations; whereasin *β-lactam or tetracycline*-associated diarrhea *S. boulardii* preparations can be preferred (Berman 2015, Issa and Moucari 2014).

b.) Traveler's diarrhea

Traveler's diarrhea (TD), one of the most frequently detected forms of diarrhea, is detected among international travellers either during the travel or just after the return. It is an acute diarrhea that is clinically presented as watery stool more than three times a day together with one or more enteric symptoms, e.g., abdominal cramps. In some studies, probiotics have shown to be effective in the treatment and prevention of TD. In addition, some probiotics have been shown to reduce the risk of severe necrotizing enterocolitis in preterm infants and shorten the duration of infectious diarrhea. However, the use of probiotics in TD cases still remains controversial in general (Teitelbaum 2005, Chen and Sears 2015, McFarland 2007).

2. IBS

IBS is a disorder of chronic abdominal pain, changed bowel habit and abdominal inflation. There is now increasing evidence relating IBS to alterations in GI microbiota (Parkes *et al*. 2010) or to the interaction among the intestinal bacteria, gut barrier and the intestinal

immune system. Probiotics were suggested to repair the imbalance in the micro-flora and improve the quality of life in IBS patients (Thompson 2016). Different therapeutic approaches including probiotics have been used for the treatment of IBS. However, only a few of probiotics have been successful or had no side effect. Not all probiotics have been reported to be beneficial for IBS. Therefore, to select the specific strain whose efficacy has been shown was reported to be an important factor in the treatment (Moraes-Filho and Quigley 2015). On the other hand, the use of probiotic containing a mixture of different strains rather than single strain probiotics can be more effective in IBS. Together with data supporting the infectious diseases as a possible aetiology of IBS, multiple factors are now being thought to play a role in its development. The difference in the efficacy of different probiotics may be as a result of the multi-nature characteristic of the disease. Further studies are required in order to determine the most effective species/strains, the optimal dose and to determine whether a probiotic including a combination of different strains is better than a single strain (Thompson 2016, Moraes-Filho and Quigley 2015, Meier 2010).

3. Obesity

Obesity is a serious public health concern and is the most frequent cause of other health problems in developed countries. Obesity that can lead to the development of metabolic diseases both in adults and children is related with some external and internal factors including dietary habits, lifestyle and genetics. Human intestine has trillions of microbes that make up the gut microflora which plays an important role in human metabolism. Any change in the balance of the components of microflora may lead to obesity and metabolic syndrome (John and Mullin 2016). Diet has been shown to have a marked effect on the gut environment including gut transit time and pH. Therefore, a change in the intake of macronutrients including carbohydrates, proteins and fats can affect the composition of the intestinal microbiota (Maukonen and Saarela 2015). Probiotics have been suggested to play a role in the treatment of obesity and related metabolic disorders like hyperglycemia and dyslipidemia (Sanchez *et al.* 2015). In many studies carried out on animals and a few studies on humans, the genera *Lactobacillus* and *Bifidobacterium* have been reported to have multiple beneficial effects on metabolic syndromes, such as reduction in weight and visceral fat, and improvement in glucose tolerance (Park and Bae 2015, Teixeria *et al*. 2013).

Results of the studies related with the effect of probiotics on weight management are controversial. Besides studies reporting the weight reduction upon the use of probiotics, there are some studies in which probiotics have been reported not to have beneficial effect on the weight over the long term. On the other hand, in some studies chemicals (prebiotics) that induce

the growth and/or activity of commensal microorganisms have been reported to have more beneficial effect than probiotics because the latter may not lead to a change in gut microbiota in humans. Further studies should be conducted to clarify the effects of probiotics and gut microbiota on body weight and obesity (Sanchez *et al*. 2015, Park and Bae 2015).

4. Oral diseases

Oral cavity is an excellent niche for the colonization of bacteria due to the presence of suitable factors (e.g., nutrient, pH, and humidity) that are required for their growth. Bacterial colonization of the oral cavity in turn may result in dental caries, periodontal disease and halitosis.

Probiotics have the ability to modify the micro-environment by changing the environmental factors, such as the pH and the oxidation–reduction potential that are crucial for the colonization of bacteria. Moreover, bacteria used as probiotics both secrete several antimicrobial substances including organic acids, hydrogen peroxide, bacteriocins and compete with pathogenic microorganisms for the receptors that are present on human cells as bacterial adhesion sites (Bonifait *et al*. 2009). Probiotics act against caries via following mechanisms (Meurman 2005):

(a) Prevention of the adhesion, the first phase of infection, of bacteria to tooth surfaces via forming biofilm on tooth surface

(b) Competing with caries-related bacteria in terms of nutrient and attachment site

(c) Secreting antimicrobial substances so that they lead to reduction in bacterial colonization.

(d) Enhancing local and systemic immune system

(e) Regulating mucosal permeability

Probiotics obtained from dairy products such as *S. thermophilus* and *L. lactis* are capable to integrate themselves into a biofilm already formed on the hydroxyapatite surface. Such an integration may be followed by the interference with the developmental stages of caries by *Streptococcus sobrinus* (Singh *et al*. 2013). Probiotics utilized for dental caries selectively remove only the harmful pathogen without affecting the rest of the oral microenvironment (Hauikoja 2010).

Periodontal diseases are among the most common diseases encountered in dentistry. Gingivitis and periodontitis are two types of periodontal diseases. Gingivitis is the local inflammation of the gingiva whereas periodontitis is progressively related with the all supporting tissues of teeth including the alveolar bone. Periodontitis may be a result of various putative pathogens, including *Aggregatibacter*, *Tannerellaforsythia* and

Porphyromonasgingivalis (Gupta 2011). Probiotics residing in the gingival sulcus have been reported to have some beneficial effects such as reducing the number of the pathogen and strengthening the epithelial barrier, thus contributing to decreased susceptibility to infection (Singh *et al*. 2013).

Anaerobic microorganisms in the oral microflora are one of the leading causes of halitosis. These bacteria convert salivary and food proteins into amino acids which are in turn transformed into volatile sulphur compounds like hydrogen sulphide and methanethiol that are responsible for unpleasant odour. *Streptococcus salivarius* is used as the part of gums or lozenges to produce bacteriocins that would decrease the number of anaerobic bacteria that produce volatile sulphur compounds (Bonifait *et al*. 2009). In addition, lactic acid bacteria can also alter the oral microflora via the antimicrobial by-products such as carbon peroxide, organic acids, diacetyl, hydrogen peroxide, low molecular weight antimicrobial substances, bacteriocins and adhesion inhibitors that they generate (Meurman 2005).

Probiotic therapy is an interesting field and has recently gained attraction in oral medicine and dentistry. However, further researches especially related with their efficacy, action of mechanisms in oral cavity, capability of colonizing oral biofilms and interference with the components of the biofilm are required (Devine and Marsh 2009).

5. Skin diseases

Skin, surrounding the outer surface of the body, has a large surface area and is always exposed to physical, chemical, bacterial and fungal damages. Intact skin is a good barrier for microorganisms preventing their entrance into the body. In certain diseases such as eczema and acne, the barrier function of the skin is disrupted increasing the susceptibility of the affected person to infections. Eczema, a skin disease with itchy red rash, is more common in childhood than in adulthood. New treatment strategies depending on the alteration of the gut flora or reduction of inflammation in the gut have been implemented to control eczema, reduce its effect on the quality of life, decrease financial costs to the community and reduce its symptoms (Roudsari *et al*. 2013).

Preparations consisting of *Lactobacillus* spp. have attracted a considerable interest recently because people with eczema have been detected to show differences in terms of the components of their intestinal microbiota with respect to those without eczema. Although not proved yet, probiotics consisting of *Lactobacillus* GG have been shown to reduce the risk of eczema by two fold (Wickens *et al*. 2008). The mechanism of action of probiotics in treating eczema is thought to be related with reduction in the intestinal inflammation and intestinal

permeability leading to a change in antigen presentation in the gut-associated lymphoid tissue (Boyle *et al*. 2009).

The debate about the efficacy of probiotics on skin diseases is still going on. Several scientists who carried out studies on eczema patients using different probiotic strains reported that probiotics did not have any beneficial effect on whereas other scientists reported that probiotics could have positive effect on the treatments of skin diseases like atopic dermatitis depending on multiple factors, like the dosage, the time of administration of specific probiotic strains and the duration of exposure (Boyle *et al*. 2009, Boyle *et al*. 2008, Rather *et al*. 2016). To sum up, updated information lacks strong evidence to support the use of probiotics in the treatment of skin diseases.

6. Liver diseases

Liver can directly be influenced when the gut microbiota is altered due to the entry of gut bacteria or their metabolites into the liver through the liver-gut axis and the portal vein. The gut flora has been shown to be different in terms of its composition in patients with non-alcoholic fatty liver disease (NAFLD) compared to healthy human. Gut microbiota has been suggested by several scientists to be responsible for the progression of NAFLD to non-alcoholic steatohepatitis. Patients who had advanced liver cirrhosis can develop hepatic encephalopathy (HE) as a complication and HE is thought to be related with toxic metabolites (especially ammonia) produced by the gut flora (Minemura and Shimizu 2015).

Because of their ability to alter the gut flora and/or permeability of the gut, thus leading to a decrease in the production and absorption of ammonia, probiotics have been reported to be used in the treatment of HE (Minemura and Shimizu 2015).

Via endotoxemia and increasing the oxidative stress in the gut, alcohol abuse induces liver injury leading to liver fibrosis, fatty liver, alcoholic hepatitis and liver cirrhosis. Because these clinical manifestations are followed by a change in the gut microbiota, probiotics have been suggested as promising supplements as the part of the treatment of such liver diseases. After the administration of probiotics that alter the gut microbiota, lowered levels aspartate transaminase (AST) and alanine transaminase (ALT) in the blood of patients with liver diseases related with chronic alcohol consumption have been reported in numerous studies. Preparations including *L. plantarum* which decrease the inflammation in the intestine caused by increased oxidative stress are among the probiotics that have a potential therapeutic effect. On the other hand, bacteria-free culture supernatant of *L. rhamnosus* GG was also confirmed to suppress the alcohol-induced intestinal permeability, endotoxemia and liver injury. Thus, still it remains

uncertain whether live strains are compulsory or only the products of these bacteria are sufficient for the treatment these diseases (Sharma and Singh 2016, Sharma *et al*. 2013).

7. Hypercholesterolemia

The ability of probiotics to interact with bile acid via different mechanisms has led to the development of new strategies in the treatment of increased cholesterol levels (hypercholesterolemia) in the body. Deconjugation of bile acids by bile salt hydrolase (BSH) is the main mechanism of probiotic bacteria for decreasing the level of cholesterol. However, such a treatment relying on the BSH enzyme produced by probiotics has side effects on the human body. Further approaches for reducing the side effects of probiotics in this field are required in order for probiotics to be used in the treatment of hypercholesterolemia (Pavlović *et al*. 2012).

8. Cardiovascular diseases

New treatment strategies for cardiovascular diseases have currently been investigated since these diseases are one of the main causes of premature mortality worldwide. These new strategies include the use of probiotics for decreasing triglyceride and high-sensitivity C-reactive protein (hs-CRP), an indicator of atherothrombotic and cardiovascular disease risk, and enhancing high density lipoprotein (HDL) without any alteration in total cholesterol or low density lipoprotein (LDL) cholesterol levels. Beneficial effects of probiotics and the role of microbiome in cardiovascular diseases have not yet been clarified definitely. Therefore, more studies are needed to understand the relationship between probiotics and cardiovascular diseases so that new strategies for the prevention and the management of heart diseases would be available (Sanaie *et al*. 2013, Ettinger *et al*. 2014).

9. Peptic ulcer

Peptic ulcer disease whose prevalence is high in many parts of the world develops as a result of the inflammation of gastric or duodenal mucosa generally due to factors such as prolonged consumption of NSAIDs, *H. pylori* infection, smoking and alcohol intake. All of these factors decreases or inhibits the secretion of mucus and bicarbonate leading to increased acid secretion that results in mucosal damage. Probiotics including *L. acidophilus* and *S. boulardii* have been reported to accelerate the healing of ulcers and those including *Lactobacillus johnsonii* La1 have been used in the treatment of *H. pylori* infections (Vomero and Colpo 2014, Khoder *et al*. 2016).

10. Nervous system diseases

Central nervous system (CNS) and gut have an integrative physiology that includes gut-brain-axis and nutrient, endocrine and immunological signals between the CNS and GI

tract. CNS is influenced by microbial components of the microbiota. Regulation of satiety via CNS-gut-microbiome signalling is the best example of such an interference. The signalling, which is a result of satiation-signalling peptides, changes according the type of the food consumed since the diet affects the components of gut microbiota. In turn, metabolical by-products of gut microbiota affect the secretion of these signalling peptides. Peptides secreted by enteroendocrine cells in response to by-products of microbiome are transported through the blood to the brain finally affecting the satiety centre (Wang and Kasper 2014).

Another example of the relationship between the gut microbiome and the CNS is related with psychological disorders such as anxiety and depression. Probiotics, especially *Bifidobacterium* and *Lactobacillus* spp. or a mixture of *L. rhamnosus* and *L. helveticus* strains, have been reported to have anti-depressant activity. The action of mechanism of probiotics in depression may be due to attenuation of pro-inflammatory cytokines, increase in the tryptophan level and production of neuro-active substances (Zhang and Abdullah 2013). Dementia, Alzheimer's disease being the most common type, is a type of nervous system disease that affects the person's daily functioning. Relation of microbiota with dementia via various mechanisms (e.g., leading to cardiovascular disease which has been shown to be a risk factor for dementia or leading to the development of some metabolical abnormalities like high blood sugar and increase in the body fat) and the potential use of probiotics, especially those that lead to the production of B vitamins, in the treatment of dementia have recently been reported (Rashad *et al*. 2016).

11. Urinary tract infections (UTIs)

UTIs, one of the most commonly detected bacterial infections that may be responsible for renal failure in long term, are among the most important causes of health expenditure due to the need for the antibiotic treatment. In addition, the use of antibiotic in the treatment of UTIs is the main reason of the development of antibiotic resistance in bacteria, a worldwide public health concern that has been gradually increasing since the last decade. An alternative treatment method that would replace antibiotherapy would definitely lead to a decrease in the antibiotic resistance rate because it has been proved that the less the antibiotic consumption is, the lower the antibiotic resistance rate would be. Probiotics are therefore supplements which have gained interest as an alternative treatment for UTIs.

S. boulardii was reported to be possibly effective in the prevention of UTIs caused by *E. coli* indirectly, via leading to reduction in the number of *E. coli* colonizing the colon, since the source of most of *E. coli* cystitis is stool (Akil *et al*. 2006). In addition, probiotics consisting of

Lactobacillus spp. have been reported to be an effective prophylactic agent for the prevention of recurrent pyelonephritis in infants by preventing the adhesion of uropathogenic bacteria, changing the pH of the urinary tract towards acidic, leading to the accumulation of hydrogen peroxide that has antimicrobial activity in the urinary tract and regulating mucosal immunity (Lee *et al*. 2016).

In addition, when used together in combination with antibiotics, probiotics may prevent the side effects of antibiotics by decreasing the risk of super-infections of gut or vagina by *C. difficile* or *Candida albicans*, respectively (Reid 2006).

12. Cancer

Cancer, the result of abnormal proliferation of cells in the body, is one of the most common causes of human death worldwide and is a result of the combination of genetic and environmental factors such as physical, chemical, and biological carcinogens, dietary factors and lifestyle (Saber *et al*. 2016).

Several studies have reported that different dietary habits and lifestyles may be related with cancer, especially with colorectal cancer (CRC), because these factors can disrupt the balance of the components of intestinal microflora (Ucello *et al*. 2012, Raman *et al*. 2013). Moreover, in some of studies investigating the efficiency of probiotics in cancer prevention, it was reported that probiotics can be effective in the prevention of cancer via mechanisms including the induction of the host's immune system, competition with putrefactive and pathogenic microbiota that can be related with the development of cancer, regulation of apoptosis and cell differentiation via anti-proliferative effects, inhibition of tyrosine kinase signalling pathways and fermentation of undigested foods (Motevaseli *et al*. 2017, Ucello *et al*. 2012, Raman *et al*. 2013, de Moreno de LeBlanc et al. 2007). In addition to their ability of preventing cancer development, it has been reported in a systematic review that the use of probiotics (*Lactobacillus* or *Bifidobacterium* spp.) in cancer patients is also effective for reducing the frequency of diarrhea, the most frequently encountered side effect of chemotherapy or radiotherapy (Redman *et al*. 2014).

Some bacteria that reside in intestine can convert some pro-carcinogens into carcinogens that would lead to cancer. Probiotics may inhibit the growth of these harmful bacteria so that they lead to the reduction in the concentration of carcinogens. Such an action of mechanism of probiotics, especially lactic acid bacteria, has been reported in colon cancer and breast cancer cases (de Moreno de LeBlanc et al. 2007) .

Probiotics containing yeasts such as *S. cerevisiae*, *S. boulardii* and *Candida spp.* have been reported to be more resistant in terms of penetration of the upper parts of GI tract and to

be more effective in the stimulation of immune system when compared to bacteria containing probiotics. Therefore, they may protect the host against pathogenic bacteria and their toxic compounds much more efficiently than bacteria containing probiotics. In addition, some fungal products, such as β-glucan, have shown to have possible beneficial effects on cancer development via the induction of immune system. Whereas studies investigating the anti-cancer effect of bacteria containing probiotics are numerous, those related with anti-cancer effects of yeast containing probiotics are limited. Therefore, further evaluations of yeast containing probiotic related with the prevention of different types of cancer are required (Saber *et al*. 2016).

In addition to their possible beneficial effects on cancer development, probiotics have also been reported to have some possible side effects, some of which are serious, on cancer patients. Currently, neutropenic cancer patients in United Kingdom are suggested not to use probiotic preparations. *Saccharomyces* related fungemia and *L. acidophilus* related bacteremia have been reported in cancer patients using related probiotics. In addition to blood stream infections, probiotics have also been reported to be responsible for the progression of malignancy (Redman *et al*. 2014).

13. Children diseases

A lot of studies have estimated the role of probiotics in critically ill children especially for the treatment and prevention of necrotizing enterocolitis (NEC), otitis media (OM), AAD, ventilator-associated pneumonia (VAP), invasive candidiasis and candida colonization (Singhi and Kumar 2016, Niittynen *et al*. 2012).

Probiotics may be alternative choice in the prophylaxis and the management of infectious diseases. In some studies, probiotic nasal sprays containing *Streptococcus sanguis*, *S. oralis* and *S. mitis* has been reported as an alternative treatment for otitis media, a bacterial infection which is common in children, whereas no effect has been detected in other studies. Similar to adults, the administration of a mixture of probiotics for one week could prevent and treat AAD in children. Although probiotics have been shown to be effective in the treatment of some childhood diseases, more studies are needed to clarify the duration of treatment, cost effectiveness and effectiveness of a mix versus single-strain probiotics. In addition, the safety of probiotics (the risk of bacteremia, fungemia, and sepsis) in critically ill, especially immunocompromised children has not been evaluated yet (Singhi and Kumar 2016, Niittynen *et al*. 2012).

14. Pregnant and lactating women

Pregnancy is a period that contains many physiological and immunological changes in order to provide a suitable environment for the fetus. Physiological changes in the gut and vagina during pregnancy lead to changes in the microbiota in these locations affecting the health of pregnant women. Orally or vaginally administered probiotics have been found to be effective on women during early or late periods of pregnancy, and during the lactation period (Gomez Arango *et al*. 2015).

Recently, several studies have confirmed that probiotic supplements taken during the pregnancy enhance mucosal immunity, regulate vaginal and gut microflora, improve metabolic activity and decrease urogenital infections in women. Probiotics (especially those containing *Lactobacillus*) were found to be effective in pregnant women with constipation in the early stages of pregnancy without any increase in the adverse pregnancy outcomes (Lee *et al*. 2012). The data about the efficacy of probiotics in the late stages, especially the last trimester, of pregnancy is limited. Pregnant women in their last trimester using the probiotic VSL #3 (a mixture of *Lactobacillus*, *Bifidobacterium* and *Streptococcus* strains) have reported to have higher concentration of anti-inflammatory cytokines IL-4 and IL-10 when compared to those who do not use (Vitali *et al*. 2012). Probiotics can also be effective for pregnant women with diabetes and obesity via balancing the microbiota composition.

Bacterial vaginosis (BV), common inflammation of the vagina, is as a result of the reduction in the number of *Lactobacillus* spp. found in the normal flora of vagina. Probiotics, especially those including *Lactobacillus* spp., have been used to normalize the microbiota of vagina so that BV is eradicated. Moreover, the use of probiotics together with metronidazole in bacterial vaginosis has also been investigated. Patients who used vaginal or oral probiotics together with metronidazole were reported to be at lower risk for the recurrence of BV than those who used only metronidazole (Homayouni *et al*. 2014, Bodean *et al*. 2013, Onderdonk *et al*. 2016). However, further studies are required in order to clarify the efficacy of probiotics in these diseases.

In neonate perspective, probiotics were reported to be rarely absorbed systematically and couldn't reach into the breast milk leading to any adverse effect on infant (Elias *et al*. 2011). Moreover, probiotic use during pregnancy was reported to lead to a change in the cytokine composition of the breast milk and induce the secretory IgA production in infant resulting in the improvement of the gastrointestinal function of the infant (Baldassarre *et al*. 2016).

15. Other Applications

Apart from applications in human, probiotics have applications in veterinary medicine and aquaculture as well. Probiotics have been used as a dietary supplement in animals to prevent and control pathogenic bacterial colonization. The challenge facing scientists in this field is the presence of various different species of bacteria in the gut of different animals reflecting the diversity of the composition of fecal microbiota among animals. A mixture of probiotic strains is used to cover more types of microbial pathogens. The mixture has to have specific characteristics such as possessing antimicrobial activity, surviving in the gastrointestinal tract and adhesion (Gaggia *et al*. 2010). *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Lactococcus*, *Streptococcus* and *Saccharomyces* species have been studied as probiotics in animals. Probiotics have also been used as a tool to control diseases in aquaculture that is the cultivation of aquatic organisms in controlled water environment. More studies are needed to ensure the role of probiotics in both fields (Edun and Akinrotimi 2011).

DISCUSSION

Probiotics which have attracted high interest of consumers recently are among the most popular products on the nutraceutical market or pharmacies and are considered as a type of functional food that are easy to reach and have little side effects when used correctly (38). Evidence was present about the benefits of probiotics when used at the right dose, duration and when suitable strains and species are chosen for specific diseases. However, rigorous clinical trials to ascertain the health benefits of most of the commercially available preparations on many clinical manifestations have not been done yet. Most probiotic preparations are currently marketed as food ingredients, dietary supplements, or "medical food." Yogurt products labelled as containing "live and active cultures" are supplemented with one or more probiotics (Chen and Sears 2015, Berman 2015).

WHO and FAO define probiotics as live microorganisms that enhance the health of the host when consumed in adequate amounts (Chen and Sears 2015). The definition brings out the priority of scientifically supported data related with health benefits of these products.Therefore, health benefits of probiotics have to be documented in well-designed, controlled clinical trials. However, only a few of marketed probiotics meet this standard. Moreover, the safety issue of most of the probiotics is still unclear due to the lack of enough number of studies about the possible negative effects of probiotics on the host. Further researches related with probiotic development, use and safety are warranted (Chen and Sears 2015, Berman 2015, Sanders *et al*. 2010).

Nowadays, probiotics are widely consumed in many countries and clinical studies related with their efficacy in the treatment and prevention of various diseases have still been going on. However, further in-vitro and clinical studies are required for clarifying the their mechanisms of action, benefits and side effects (Boyle *et al*. 2006).For the future, there is a need for obtaining probiotic foods from non-dairy environments like almond milk fermentation. New non-dairy probiotic candidates like fruits and vegetables are being investigated (Bernat *et al*. 2015).

Gene technology and genomic studies will play a role in rapid search and the development of new strains which might increase insight into the mechanisms and the functionality of probiotics that would offer promise for development of novel therapeutics (Syndman 2008). Advancements in the immunological or physiological properties of probiotics can be succeeded by genetic modification leading them to be used as vaccine vectors or mucosal delivery systems. Such a use of genetically modified strains is still limited because of lack of safety related studies (Syndman 2008).

CONCLUSION

Even though there is a substantial increase in the number of studies related with probiotics, the need for high number of volunteers for in-vivo studies to be conducted, the high number of different species of microbes to be covered, cost and ethical considerations slow down the clinical trials. In general, health organizations accept probiotics as “food supplements”; *not as drugs*. Therefore, at least for now, probiotics should not be used to replace the antimicrobials for the treatment of any infection and the un-controlled use of probiotics should be avoided, especially for the diseases in which their efficacy has not been proved yet.

Although the preliminary studies are promising, because of the lack of health benefits and safety issues for most of the preparations, clinicians and pharmacists should be aware of the quality-control issues in probiotic manufacturing, the limitations of probiotic use in some patients (immunocompromised patients, individuals at extreme ages and for those with central venous catheters, disrupted mucosal barriers, short bowel syndrome, abnormal cardiac valves, prosthetic joints, valves or prosthetic materials) and potential adverse consequences of probiotics and explain such important topics to their patients. Further clinical trials related with probiotics will add to the field of new treatment strategies for various diseases.

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USE OF ANALGESICS AND REYE'S SYNDROME

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ABSTRACT

Non-steroidal inflammatory drug are commonly used as an analgesic, antipyretics and also anti-inflammatory agents by many people at all ages in the world .Non-steroidal anti-inflammatory drugs are useful to relief for pain ,fever inflammation but they show only palliative therapy which also have common and /or rare adverse effects as well as therapeutic effects. Reye's syndrome is rare, but very severe and serious side effect related to this group drugs.

Therefore in the present study. Reye's syndrome was examined in detail especially in children. Its prognosis, sign symptoms and reasons, treatment and relationship between use of the drugs and Reye's Syndrome, were evaluated. According to evidences about this problem, it is clear that there is between some analgesic group relationship group drugs and RS. Additionally serious the role and duties of health personnel especially pharmacist to prevent or reduce the risk are emphasized in this study

Key word: Reye's syndrome, Nonsteroidal anti-inflammatory drugs.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) which is using primary or secondary inflammatory, fever and pain. NSAIDs are among the most widely used for relieving with prescription or nonprescription among pharmaceutical agents in all age groups, in every country. Today NSAIDs are consumed about at least 30 million people in the world. This drugs usage increased abnormally for about 20 years. NSAIDs are used palliative treatment for rheumatoid arthritis, osteoarthritis, infectious and inflammatory diseases, menstrual cramps, sprains, slightly or normal pain, dysmenorrhea, juvenile rheumatoid arthritis and like this diseases. Using NSAIDs without prescription is possible and they are using for many disease with fever, pain and inflammatory so NSAIDs are chosen primary drugs by people. These drugs are using widely but they have many important side effects. One of them is Reye's syndrome which has occurred with the use of NSAIDs especially salicylates while viral infection occurs in children.

Reye's syndrome is rare form of acute non-inflammatory encephalopathy which is mostly brain and liver that usually follows an acute viral illness in children who is under 18 ages, and usually results in death. Although Reye's syndrome was described as early as 1929, it was not recognized as specific entity until 1963, when Dr.R Douglas Reye, an Australian pathologists, reported it as syndrome. The etiology of Reye's syndrome is uncertain. Drugs, some toxins and metabolic diseases are responsible. Ingestion of acetylsalicylic acid during or after a viral illness significantly reason of Reye Syndrome. The viral infections are mostly influenza B, influenza A and varicella. Currently, there is no conclusive data as to whether other forms of salicylates are associated with the development of Reye's Syndrome but the National Reye's Syndrome Foundation recommend that aspirin and combination products containing aspirin not be taken by anyone during viral illness. Moreover it is obscure point whether other drugs from this group cause Reye's syndrome or not.

Therefore major aim of the present study was to evaluate relation between analgesics usage and Reye's syndrome. Reye's Syndrome's ethiopathology, prognosis, which analgesics cause to the syndrome, frequently its reasons, treatment were extensively investigated. All evidences were assessed. In order to reduce risk of Reye's Syndrome especially in children. Finally, moreover responsibility of pharmacist and other health staff were determined.

DESCRIPTION OF ANALGESICS

Analgesics is a number of drugs purposed to relieve pain and used to acquire analgesia without causing the loss of consciousness, inhibiting the conduction of nerve impulses or varying the sensory perception. The primary classes of analgesics are the narcotics including additional agents that are chemically based on morphine molecule but have minimal abuse potential; Nonsteroidal anti-inflammatory drugs (NSAIDs) that includes the salicylates and Acetaminophen. Other drugs, notably the tricyclic antidepressants and anti-epileptic agents such as Gabapentin, have been used to relieve pain, particularly neurologic pain but are not routinely classified as analgesics. NSAIDs are among the most common analgesic medication in the World which is mostly preferred to relieve and reduce pain, fever and inflammation. NSAIDs are also preferred as non-narcotic analgesics, anti-inflammatory NSAIDs and non-opioid analgesics that have analgesic, anti-pyretic and anti-inflammatory effect. They have different kinds of classes but all of them have same therapeutic effects and adverse effects. In additionally, chemical structures of NSAIDs are different from each other but all of them have weak organic acid structure. Narcotic analgesics are also known as opioids that are all derived from opium family. This group of analgesics contain morphine, codeine and a number of semi-synthetics including meperidine, propoxyphene and others. All Narcotic analgesics are

effective in treatment of visceral pain when used in adequate doses. Their side effects are associated with their doses because this type of analgesics are showed addictive property so they are controlled under federal and state laws. There are some differences between these two types of analgesics. NSAIDs act primary in peripheral tissues to inhibit the formation of pain-producing substances such as prostaglandins so they are also known as milder form of analgesics. On the other hand, opioid analgesics have quite different mechanism of action of the NSAIDs that play directly role on the central nervous system so they are not only inhibit the incoming conceptive signals to the brain but also act at higher brain centers and controlling the affective component of the pain. As a result of, NSAIDs are class of non-addicting medication and they have less adverse effects when compared to the opioid analgesics. Acetaminophen is quite different them these two classes because that is non-narcotic analgesic with no anti-inflammatory properties. It is generally preferred for treating to mild to moderate pain. This drug is well tolerated in normal doses. However, it has toxic activity at high doses. Acetaminophen, salicylates and other non-steroidal anti-inflammatory drugs are found alone or in combination with other medicines in the composition of hundreds of medicines sold without prescription and over the counter medicines.

Description and History of Reye's syndrome

Reye's syndrome (RS) is very rare but it is a very serious, risky and life-threating condition which is characterized by viral illness and encephalopathy and fatty degradation of liver. It is describes as biphasic disease. First phase of disease is related with a non-specific viral-like illness that are respiratory tract infection or gastroenteritis .Besides that, encephalopathy is emerged with second phase of the illness which starts unpredictably with sensorial vomiting and sensorial changes. Reye's syndrome is a disease of infancy, childhood, adolescence and in some condition that may affect the adults but it occurs mostly in children depending on excessively usage of aspirin and some other analgesics during viral illness. Most of mitochondria, brain and liver are damaged in Reye's syndrome and these damages cause brain death and liver lubrication. Reye's syndrome is clinically begins after influenza like viral infections, upper respiratory tract diseases or gastrointestinal symptoms which is seen mostly after influenza especially Influenza B or Varicella in U.S. The health condition deteriorates after few days and recurrent severe vomiting is the most prominent symptom of this disease. This vomiting is the initiation of the encephalopathy and this situation may lead to the patient to loss of consciousness. A lot of factors can contribute to the development of Reye's syndrome. Salicylates which is taken during viral infections is the most trigger factor of the disease.

Reye's syndrome was firstly described in 1963 in Australia by RDK Reye. The occurrence of syndrome may have first been reported in 1929. In 1964, investigation of an outbreak of Influenza B that explained 16 children who developed neurological problems four of whom had a profile remarkably similar to Reye Syndrome was issued by Dr George Johnson and colleagues. According to some researches, this syndrome was defined as Reye-Johnson Syndrome. Although, it is commonly known as Reye's syndrome. Besides that, RS became reportable disease in 1973 in United State. Some studies such as Ohio and Michigan was shown that this syndrome was triggered depending on the use of Aspirin during upper respiratory tract or chickenpox infection. Beginning in 1980, physicians and parents were warmed about the association between the Reye's syndrome and use of salicylates in children and teenagers were warmed about the association between the RS and use of salicylates in children and teenagers with chickenpox or virus-like illnesses. Besides that, peak incidence was reported in 1979-80. In 1982, an advisory was published by U.S Surgeon Geed and in 1986, Reye's syndrome related warming label was required by the Food and Drug Administration (FDA) for all Aspirin containing medications (Daniel et.al. 2017).

Etiology of Reye's syndrome

The etiology of Reye's syndrome is not fully understood. Drugs, toxins and metabolic diseases are responsible for this disease. Besides that, it. There is thought to be linked to a viral infection. The viral infection which includes both Influenza B and Varicella are well-explained but the development of RS which contains each of these viral interventions is not widespread and it is not fully explained why specific induvial develop the disease. Also, researches shows that there is a link between the RS and use of salicylates. The salicylates which is taken especially during viral infections is increased the risk of the Reye's syndrome (John et.al. 1981).

Heterogeneity of Reye's syndrome

Reye's syndrome infection is a syndrome that is contained in a number of heterogeneous disorders caused by metabolic poison or drug. This process with suspicion is a critical process in diagnostics and usual renaissance syndrome and this syndrome requires a differential diagnosis.

In experimental animal models and environmental toxins such as aflatoxins, pesticides, insecticides and many chemical substances can cause symptoms like RS. Drugs containing salicylate, phenothiazine, metoclopramide, zidovidine, valproic acid, didanosine and various antiemetic agents can cause Reye's syndrome.

The viral-activated defense mechanism results in the primary isoforms of the cytochrome P450 (CYP 450). Some people who are genetically predisposed many even result in clinical

irregulities, even monitoring the therapeutic doses of a drug metabolized via the P450 cytokine. As a result, mitochondrial disorders can cause some disturbances in metabolism.

This is not a distinguishing factor for the liver. Most of energy-loaded drug metabolism occurs in the brain and skeletal muscles (Morgan et.al. 1963).

Causes of Reye's syndrome

The reason for the formation of the Reye's syndrome is not fully known but a number of studies Show that acetylsalicylic acid used in viral infection increases the risk of the RS in children and most of the symptoms of this disease are hidden (NIH Consense statement 1981).

•Viral infections: Acetylsalicylic acid used in children is known to be the most common cause of RS. These viral infections are Influenza A, Influenza B, Varicella zoster which are generally caused RS. In such diseases, ASA and similar medicines are taken to relieve the symptoms and at this condition, RS and its symptoms do not reveal (Schrör et.al. 2007).

The main pathogen of gastroenteritis is the Rotavirus which is very common in infancy and childhood in winter. The relation between the RS and Rotavirus has been reported. In a study conducted in UK between 1981 and 1992, 57 patients with viral infection, 9 patient with influenza us and 3 patient with rotavirus were detected. Rotavirus gastroenteritis is believed to lead to RS, there is no evidence to support this situation. Large-scale epidemiological and pathological studies are required. Other viruses that lead to Reye-like syndrome are defined as measles, herpes simplex, rubella and human herpes virus (NHS, 2017).

•Drugs:

Salicylates: Salicylates are drugs that are classically associated with Reye's syndrome. Many epidemiological studies have revealed the association of Salicylates with disease. Reye's syndrome developed in 0.1% children receiving aspirin but more than 80% of patients who received aspirin in the last 3 weeks were diagnosed with Reye's syndrome (NHS, 2017).

Paracetamol, experided tetracyline, valproic acid, zidavudine, didanosine and antiemetics have been associated with the Reye and Reye-like syndrome. A report of a child receiving antiretroviral therapy (didanosine and sstavudine) at over 3 months of high doses resulted in Reye's syndrome (Medscape, 2017).

•External factors without drugs: Reye and Reye-like syndrome, insecticides, herbicides, aflatoxins, paint-thinners, hepatotoxic fungi and acne-berry hypoglycemia included herbal-remedies containing atractylocite (NHS, 2017). According to a study done by the New Brunswick, many children are not only Reye's syndrome due to influenza, varicella or viral infection. Genetic and environmental factors sometimes cause the Reye's syndrome. The main suspect factors are chemicals used in aerial forest spray programs at New Brunswick. In which

the active substance is an organophosphate insecticide known as phenothiodin (Devulapalli, 2000).

•**Genetic factor theory:** Genetic disorders constitute Reye-like syndromes. Mostly fatty acid oxidation disorders and urea cycle disorders are identified but at the same time, amino and primary carnitine organic acid deprivation, primary carnitine deficiency and carbohydrate metabolism irregulaties are found. Sudden disturbances and recurrence of symptoms are depended on dietary and metabolic changes. Genetic disorders occasion family members of these symptoms. The rate of patients with RS was 0.4%. The proportion of patients' brother/sister with RS is 2.3%.It is likely that some of these patients will be caught in RS (NHS, 2017).

According to a theory, a viral infection can change in the immune system of child born with yet unknown susceptibility or genetic differences or it can damage when a child with a genetic predisposition to the theory receives aspirin, one of the components that damage the aspirin salicylate activity has changed and can cause severe destruction of the damaged immune system and destruction result in attacking healthy liver cells in the immune system but there is no clinical evidence supporting this theory (John et.al. 1981).

Risk groups for Reye's syndrome

Reye's syndrome can be seen in all ages of children but that is most common between 6-9 ages and 10-14 ages. 6-7 ages are very important and critical ages because this disease is peaked in this period. There is no discrimination between sexes. RS can be seen both genders (Belay et.al. 1999).

Reye's syndrome is seen between 5-9 ages with Varicella. On the other hand, it is seen between 10-14 ages with Influenza especially Influenza B (Kramer, 2009). Besides that, RS is very rare for newborns and for people over 18 years (Belay et.al. 1999).

Incidence of Reye's syndrome

Disease Control Center (CDC) says that only 10% cases of Reye's syndrome are recorded. The incidence of RS has decreased dramatically after health warnings relate on-aspirin delivery to children in 1980s (Belay et.al. 1999). In 1980s, there were 52 cases per year in England and Ireland but in 1990s this number has fallen to 17 cases. 597 cases are reported in UK between in 1981-1996 (Belay et.al. 1999). Similar rates were recorded in other countries. The case of RS has not been recorded in England and Wales since 2001 (NHS, 2017). The incidence of disease was recorded as 0.6/100.000 children in 1979. On the other hand, this ratio was dropped to 0.1/100.000 children in 1989. Patients were not reported more than 36 in US between in 1987-1993 in one year and patients were not reported more than 2 between in 1994-1997 in

one year (Belay et.al. 1999). 1207 cases were detected in total under 18 years of age between 1980 and 1997 in US. The incidence rate was reported 0.15-0.88/1.000.000 children in this period per year (Belay et.al. 1999). The incidence of RS was defined 0.797/1.000.000 children between at 1995-1996 in France. The disease can be seen very extremely during the season (December to April) when viral infections are on rise. Incidence of disease is 1 or 2 decibels in summer (Belay et.al. 1999).

Diagnostic Criteria for Reye's syndrome

Reye's syndrome is very rare disease. Firstly, beginning step in diagnosis is removed some diseases which are seen rarely and have similar symptoms with RS.

These diseases are;

• Meningitis

• Aflatoxin poisoning

• Encephalitis

• Urea cycle disorders

• Fatty acid oxidation disorders

Besides that, urine and blood test can be performed to determine if a toxin or bacterium has an increase in blood and whether the liver function is normal or abnormal (Praxis, 1994).

Signs and Symptoms of Reye's syndrome

Some signs and symptoms of Reye's syndrome are occurred about three to five days after onset of a viral infection such as influenza or chickenpox or upper respiratory infection such as cold. These signs and symptoms are including;

SIGNS and Symptoms of Reye's syndrome

Diarrhea Hallucinations

Rapid breathing

Weakness or paralysis in the arms and legs

Persistent or continuous vomiting Seizure

Unusual sleepiness or lethargy Excessive lethargy

Irritable, aggressive or irrational behavior Consciousness

Confusion Delirium

Disorientation fluctuating personality changes

Hyperammonemia High level of alanine aminotransferase and aspartate aminotransferase

Diarrhea and rapid breathing are generally first signs and symptoms of RS especially for children younger than age 2. Besides that, persistent or continuous breathing and unusual sleepiness or lethargy are seen in older children and teenagers. If the conditions and complaints

progree, the signs and symptoms can dramatically increase and cause hazardous or fatal consequences such as delirium, coma and death may occur at the end of the this disease. Figure 9 has been demonstrated some symptoms of RS (The New York Times, 2017).

Stages of Reye's syndrome

Basically, Reye's syndrome can be categorized into 5 different stages which are ordered according to severity of disease. Lovejoy explains the evolution of stage 1 to 5. Besides that, Hurwitz is added unclinically stage which is called as phase 0. Finally, Disease Control Center is used the Hurwitz's classification and he is only added phase 6 to this classification (Anochie, 2013). These are;

Stage 0: Abnormal history associated with Reye's syndrome and laboratory findings, clinical uncertainty.

Stage 1: Vomiting, laboratory evidence of liver dysfunction, lethargic, sleepy and headache are general symptoms of this stage.

Stage2: Deeply lethargic, restless, confused, delirious, combative, hyperventilation and hyperreflexia are symptoms that are seen in stage 2.

Stage3: Obtunded or in a light-coma, decorticate rigidity are general symptoms of stage 3.

Stage4: Deeping coma, seizures, decerebrate, rigidity, fixed pupils and loss of oculovestibular reflexes are seen this stage.

Stage5: Seizures, deep coma, flaccid paralysis, abset deep tendon reflexes, respiratory arrset and fixed, dilated pupils are symptoms of the stage 5.

Stage6: Patient who are not classified, cuartive and they are trying to change the level of consciousness with other drugs.

Some Complications of Reye's syndrome

Many complications are developed irreversibly. These complications are;

Electrolyte abnormalities Hypoglycemia

Acid-base disorders

Fluid impairment or uncontrolled secretion of antidiuretic hormone

Low blood pressure Cardiac arrhythmia

Bleeding; especially gastrointestinal

Hemorrhage Pneumonia

Deterioration in thermoregulation Coma

Death 30% permanent disability and impairment of motor functions in survivors.

Prognosis of Reye's syndrome

Reye's syndrome should be treated urgently as it can rapidly damage the lungs and brain. A child with RS should immediately receive an intense look to continue body operations. Survival rate due to developments in the treatment RS and its treatment is now estimated at 80% but brain may damage after this disease in some children (Butterworth, 1998).

Reye's syndrome mortality rate has decreased to 50% to 20% in recent years. According to CDC reports, the mortality rate was 31% in 1997 (Anochie, 2013). Some patients did not complete. Patients who are younger than 5 years have a relative risk about 1.8.

The level of ammonia that best describes the duration of disease's progression. Despite that fact that most reports correlate with a slight increase of 900mcg/dl. In 1999, the belief that the level of 45mcg/dl ammonia was the most accurate improvement with a relative risk of 3.4.

Ammonia level at 45mcg/dl, approximately 3% patients have neural sequelae and 11% have simple sequelae.

The mortality rate for stage 0 is 15% but for stage 5 is 90%.Survivors have a high rate of having long-term neurological disease in those with ammonia levels of more than 45mcg/dl, those with stage 2-5 disease or those under 2 years of age (Anochie, 2013).

Treatment of Reye's syndrome

Reye's syndrome does not have specific treatment. The patient must be taken to intensive care unit urgently during the treatment of the RS. The purpose of the treatment is minimized the symptoms of RS and supported to vital functions such as blood circulation and respiration. The majority of brain-injured end points are very important in preventing permanent damage to the brain.

As a intravenously treatment;

Glucose or Insulin, corticosteroids, diuretics, chemicals, sodium benzoate/sodium phenyl acetate and ondansetron are preferred for intravenously treatment of the Reye's syndrome.

• Glucose or Insulin: used for increasing the blood glucose levels.

• Corticosteroids: preferred for reducing the brain edema.

• Chemicals: used to correct blood chemistry and given to provide nutrients (Butterworth, 1998).

• Sodium benzoate and Sodium phenyl acetate: They may be effective in treating hyper ammonia. Hemodialysis is preferred when the ammonia level is above 500-600 mg/dl. Sodium benzoate and Sodium phenyl acetate can be used before the onset of hemodialysis or in conjunction with hemodialysis. Antiemetic agents are administered to reduce the vomiting in patients during the usage of sodium benzoate and sodium phenyl acetate.

• Ondansetron: It is used with Sodium benzoate and Sodium phenyl acetate to control nausea and vomiting associated with Reye's syndrome. Besides that, it is a selective Serotonin (5-HT3) receptor antagonist which blocks peripheral and central serotonin. It prevents nausea and vomiting in people who have been administered with intravenously sodium benzoate and sodium phenyl acetate (Anochie, 2013).

Hemodialysis is the most appropriate treatment for elevated ammonia level. Hemodialysis is recommended in patients who initially responded to Sodium benzoate and Sodium phenyl acetate. Hyper ammonia treatment increases nitrogen elimination. FDA has accepted sodium benzoate and sodium phenyl acetate in the treatment of hyper ammonia due to urease cycling disorder (Anochie, 2013). If the RS continues to progress seriously and the patient needs help in breathing, the tooling may need for the patient (Langford, 2002). Other body functions should return to normal in few days if brain edema is absent and the patient can recover for several weeks.

Relationship of analgesic consumption to Reye's syndrome.

ASA is the best known chemical agent related to the RS. After many studies conducted in America and England during the 1980s, ASA was proposed as major reason in RS cases.

After limitations on the consumptions of ASA in the 1980s were established, a dramatic decrease in the RS incidence has occurred (Prior et.al. 2000).

Aspirin and Reye's syndrome

After the discovery of the Aspirin in the 1800s, the patients were simply advised to 'take two aspirins and go to bed'. Aspirin is regarded as a panacea for many diseases. Being used as antiplatelet agent for cardiovascular diseases is one of aspirin's major roles.

The obtainability of aspirin with or without a prescription has caused it to be a popular analgesic and an anti-inflammatory agent. Its low risk profile and the fact that it can be taken on high dosages are the reason why the aspirin is frequently preferred. However, aspirin is far from a good medicine. Gastrointestinal and cerebral hemorrhages are risks for the elderly population. The consumption of aspirin for young people has been associated with the Reye's syndrome.

International Reye's Syndrome Foundation has prohibited the consumption aspirin by children or the young population (Langford, 2002).

There several factors in the development of RS however, aspirin consumed during a viral infection is indicated as the main causer of the disease. Its relationship to salicylates has been clarified by several world-wide epidemiological studies. RS has only developed in 0.1% of children but 80% of the RS patients backgrounds show that the patients has consumed aspirin within the last 3 weeks (Anochie, 2013).

The relation between the salicylate and RS was thought to be a prejudgment and the studies were limited however; after the suggestion made by healthcare organizations on not treating children with salicylates, the RS incidence decreased suddenly and dramatically.

. The causality between the RS and salicylates has never been fully established. However, in vitro studies show that when the fibroblastic culture and control groups of RS children are compared, the salicylates cause a decrease in long chain fatty acids, palmitates and beta-oxidation.

Studies show that consuming aspirin to prevent a viral disease also increases the RS development. If there is a viral disease, aspirin or other medicines consisting of aspirin should not be taken (Anochie, 2013).

Acetaminophen and Reye's syndrome

Acetaminophen is an analgesic and antipyretic agent which, show chemical similarities to aspirin.

After FDA and International Reye Syndrome Institution banned aspirin for due to Reye's syndrome, acetaminophen began to be prescribed as an analgesic and antipyretic. Frequency of Reye's syndrome cases decreased after the use of acetaminophen. A study conducted in Sidney Hospital where Reye's syndrome was first diagnosed showed that only 4 (8%) out of 49 patients with Reye's syndrome took ASA. This finding is related to limited salicylate use for viral diseases in Australia where acetaminophen being prescribed mainly to be used on children with viral diseases. Clinical and epidemiologic studies show a relation between acetaminophen and RS, however small. For example, a study conducted in Australia showed that 24% of patients with RS took acetaminophen. 41% of age-matched viral infection patients who were prescribed acetaminophen did not develop RS.

Crocker et al. think that ASA and acetaminophen worsen the condition when used for viral infections and potentially help RS develop (Prior et.al. 2000).

Ibuprofen and Reye's syndrome

Aspirin is considered a major reason for RS. When ibuprofen was first marketed and prescribed for children, the possibility of this new agent increasing RS risk rose. In a Boston University study about illnesses conducted on 55000 children, a relation between the medication and the illness was not observed.

RS incidence data results between 1977 and 1997 show that the dramatic decrease of RS is in correlation with increased ibuprofen sales of 1989-1997.

As ibuprofen usage became widespread, the researchers decided that there was no relation between ibuprofen and RS (Langford, 2002).

Ways to protect from Reye's syndrome and Recommendations

Unless your doctor suggests, you do not give acetylsalicylic acid or other medicines that contains this active ingredient for treatment to children under age of 18.

Other preparations containing acetylsalicylic acid;

• Acetylsalicylate

• Salicylic acid

• Salicylate

If your child has a flu or viral disease, paracetamol and ibuprofen should be given to reduce the pain. Besides that, it is not recommended to use ibuprofen in children with asthma and liver damage. You should consult your doctor and pharmacist if you are not sure.

DISCUSSION and CONCLUSION

Analgesics are widely used throughout the world. They include a very broad class that can be used both prescription and non-prescription. Analgesics are generally safe and are often consumed by many get groups as they exhibit fewer side effects than other drug classes, but occasionally have some adverse effects due to analgesic use. One of the most spectacular multipliers of there is the RS which takes especially children into the risk group.

Reye's syndrome is a rare but this syndrome usually results in a dramatic outcome, and the outcome of the disease may be death. For this reason it is necessary to have more knowledge and awareness about RS both doctors and pharmacists need to have more information about this subject. This should include in-vocational programs, lectures congresses, conferences on the RS After that, doctors and pharmacists should ensure that the information which is receiving the most appropriate way and understanding it by public. At this point, there is a great deal of duties dedicated to pharmacists. These roles are;

- Pharmacist should warn people in the interval especially December and April when viral diseases are seen more often. We need to have a brochure about Reye's syndrome in our pharmacy especially during these months.
- If doctors are prescribing medicines containing aspirin or aspirin, pharmacist should definitely look at diagnosis especially children under the age of 18. If there is a viral disease, pharmacist contact the doctor immediately.
- Pharmacist have to ask who gets the illness who wants to take aspirin without prescription if the medicines are used for child under the age of 18, pharmacist must be warned to patient.

Media organizations a play other major and critical role about the RS because visual works or news delivered via TV, radio, newspaper or internet will attract more attention from the public and will require the public to take more precautions.

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REVIEW ON PATIENT SATISFACTION IN PHARMACY SERVICES

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ABSTRACT

Patient satisfaction is one of the important quality determinants within the globally developing health-care industry. Various sectors of the health industry monitor patient satisfaction and depending on the results, they update their qualifications for better services. Community pharmacies are pharmacy services are one of those indispensible units within the healthcare system. Therefore, it is impossible to ignore patient satisfaction and its monitoring for pharmacy services concomitant to the dynamic improvement of patient needs. Regarding this, within this review study, we made a literature review to find out recent developments on the investigation between the pharmacy services and patient satisfaction. Our findings indicated the basic variables and determinants of patient satisfaction organized through the services provided by pharmacists. Although much of the information is valid, maybe through a century, the data shared on the literature point out that there are certain rules that pharmacists need to follow to guarantee patient satisfaction. Considering the increasing number of community pharmacies worldwide and the trade-based competition among them, it is obvious that those pharmacists paying attention to patient satisfaction will keep standing, since the opposite provides negative effects in competition with other pharmacy stores.

Key words: Patient satisfaction, Pharmacists, Pharmacy services

INTRODUCTION

Patient satisfaction is among the most studied topics in recent years. The basic definition offered for patient satisfaction might be summarized as the measurement of how a patient is content with the care he/she has been given for the exact treatment. (Atkinson, Sinha, Hass, Colman, Kumar, Brod & Rowland, 2004). It can be defined as the extent to which the health care services provided by the health workers are met (Rossiter, Langwell, Wan & Rivnyak, 1989). It is also the result of evaluating the health services or health care workers (Ware, Snyder, Wright & Davies, 1983). Patient satisfaction has been accepted that a crucial determinant to identify the achievement of health care professionals (e.g., doctors, pharmacists, and nurses) (Prakash, 2010). It has been found that patient satisfaction influences patient

compliance, use of health services, continuity of care, health status, clinical results, patient retention, medicinal negligence, claims timely, efficient, and patient-centered delivery of quality health care (Xiao & Barber, 2008; Prakash, 2010). The limit of patient satisfaction is quite large. Indeed, the ability to reach to patient care, the health-care providers and their qualifications, communication, the technical aspects of the healthcare provided are all the pieces of it. These parameters can create 60-70% variability depending on the case. (Ross, Steward, & Sinacore, 1993).

Although, patient satisfaction is a simple yet delicate topic, it varies among individuals. What does each patient actually expect? This is a question to ponder about in an attempt to provide improved quality of life for the beneficiaries of healthcare delivery systems. The outcomes of patient satisfaction measurement contribute to a variety of aspects in health programs provided to patients. The overall assessment of the quality provided, the drawbacks requiring improvement, and helping out the establishments in various aspects of statistics related to the consumers of a health care program are some of those results of the measurement of patient satisfaction (Rubin, Gandek, Rogers, Kosinski, McHorney & Ware 1993; Jackson, Chamberlin & Kroenke, 1997; Weiss & Senf, 1990). Based on these, it is logical to expect that health care systems organized on the evaluation of patient satisfaction not only have the skills to improve current health systems, strategy and decision making but also can make assessment on costs, financial issues, monitoring, health plans, and patient feedbacks (Al-Abri & Al-Balushi, 2014).Overall, all these parameters stating the importance of the results of the evaluation of patient satisfaction make them at the same time the quality indices of the system. (Al-Abri., & Al-Balushi,. 2014). A study found that quality in health care is generally known to be a fundamental health service expectation (Naidu, 2009). Since it is important for designing and managing health care, patient satisfaction is the most desirable outcome of health care services (Naidu, 2009).

LITERATURE REVIEW

The recent studies main topic is focusing on the investigation of the relationship between the patient and his/her pharmacist concomitant to the questioning whether the patient has enough understanding on the services provided by the pharmacy. (Malewski, Ream & Gaither, 2015).Although the results of these studies point out variances including the location of a pharmacy unit, the overall measurement indicates the satisfaction of patients (Malewski, Ream & Gaither, 2015). The evaluation also shows a significant issue that the mental status is also another critical parameter directly affecting the satisfaction.

In many studies, the reasons of satisfaction and dissatisfaction from pharmacy services have been mentioned. One of the important milestones on the topic was achieved by a recent study conducted in Malaysia, since the research results found out the critical determinants between the pharmacy service and its resulting satisfaction on patients. It was concluded that the study hours and its availability for patients, the reachability of drugs, particularly including the OTCs, the cost of drugs to patients, and the attitude towards the patient were found as the basic variables (Bahari & Ling, 2010). One of the drawbacks stated by the patients was the period that patients obliged to wait for the preparation of prescriptions (Belcher, Fried, Agostini & Tinetti, 1998). The majority of patients point out their short patience to have their drugs ready to go. Even, there are some ideas requested by patients to ask for pharmacists stay longer time in their pharmacy stores, including evening and weekend periods (Bahari & Ling, 2010).

One another important observation is that patients do not see community pharmacies as just for stores to buy drugs. In other words, patients are not willingly to drive variety of stores to get their needs, and therefore, they want to find out more material in pharmacy stores. These all imply that beside OTC medications, pharmacy stores are expected to have a wide range of readily available pharmacy related goods. Examples of such products include cosmetics, herbal treatments, nutritional supplements as well as dermatological products. Beside, pharmacists appear to have shorter action time to prepare medications to satisfy patience satisfaction (Bahari & Ling, 2010).

Some also resemble pharmacy services as a kind of retailing services, therefore, patient satisfaction and the creative and innovative aspects of pharmacist become critical from this perspective (Nzekwe 2008).

Previous reviews on the determinants of patient satisfaction also revealed that patients are also questioning price variability among the community pharmacies. For this purpose, they visit regional pharmacy stores to investigate prices, particularly for their routine (chronic employed) medications (Bahari & Ling, 2010). This also implies that the level of income or pricing is also important parameter for the customers or patients.

Communication skills are also important parameter for satisfied customers in pharmacy profession as well as in all other professions. Beside the occupational capacity of community pharmacy workers, these people are also expected to have different skills and these must be improved with educational programs (Kamei, Teshima, Fukushima, Nakamura, 2001). This basically includes the improvement of communication skills concomitant to direct and clear expressions of pharmacists to their patients (Kamei et al., 2001).

Additionally, the perceptions of patients about their health status as well as their perceived relationship with pharmacists are important determinants of patient satisfaction with pharmacy services (Malewski, Ream & Gaither, 2015). A pharmacist cannot ignore the basic understandings of patients (i.e., their perception and expectation), therefore it is also pharmacist job to pay extra attention to the requirements of patients (Al-Arifi, 2012). This means a pharmacist is expected to have emotional skills to understand possible hesitations of patient. Based on it, it is important to communicate with the patient at the correct time. It is pharmacist duty to appreciate the needs and the questions of the consumer (Al-Arifi, 2012).

There is also a research study comparing the organization of pharmacy stores located either in urban or in suburban places. Accordingly, the appreciation of pharmacists is independent from the location, however, patients state their compliance for easy access to community pharmacies (Malewski, Ream & Gaither, 2015). Patients agree on that convenience of pharmacy stores starts with the convenience of its location (Bahari & Ling, 2010).

In addition to these factors which are the most compelling factors talked about over, another four factors, i.e., offices, convenient area, accessibility of special services and medication record, are likewise fundamental and vital pharmacy functions that influence consumer satisfaction (Bahari & Ling, 2010). The impression related to the appearance is also important. Pharmacists are expected to provide spacious area both for waiting and consultation in their community pharmacies. It is suggested to pharmacists to keep their own records for their patients not only to monitor their improvement with their disease state but also to show their conscious to patience (Bahari & Ling, 2010).

It is noteworthy to express that there are other factors such as the financial status, insurance types of patients that affect the patient satisfaction. Although these create patient variances in terms of their perception, the pharmacists must be aware of these considerations (Lee, Godwin, Kim & Lee, 2015).

Outcomes of Patient Satisfaction in Pharmacy Profession

The loyalty of patients depend on his/her satisfaction and this depends on the total services provided by the community pharmacy. Knowing the possibility of a patient's next visit to the same pharmacy store is related to the measurement of patient satisfaction. (Rigolosi & Reed, 2001). Therefore, pharmacists must be aware of the patient satisfaction concept, that in turn, positively feedbacks the position of the community pharmacy within the total competition present within the health market (Rigolosi & Reed, 2001). There are scientific results that show the positive feedback to pharmacists regarding their follow-up the patient satisfaction measurement. These feedbacks are either financial or promotion-advertisement related both

triggering the economic return to a pharmacy store. Advertising stated here is different; in fact it is costless to the pharmacist, since it is happening through the suggestion of one patient to another. (Luo & Homburg, 2007). These recommendations boost more purchases, resulting in more economic wealth to the community pharmacy. Close relatives, family members, friends, and co-workers of patients are all the pieces of this quiet, costless but very effective advertisement. Although this looks a good situation for pharmacists, the opposite of the case is as serious as positive issues discussed. Patient dissatisfaction is a very threatening issue for the continuation of pharmacy activities. This definitely ends up with the discontinuation of the pharmacy store (Ross, Frommelt& Hazelwood, 1987). Based on this it is easy to say that the organization within the community pharmacy must be patient related rather than considering the business as patient care and quality healthcare should be the sole goal of any healthcare delivery system (Ross, Frommelt & Hazelwood L, 1987). Consumer loyalty toward using the same service providers can be regarded as a measure of patient satisfaction (Odili, Ihenyen & Okhawere, 2017; Sansgiry & Jayawant, 2005). Health care organizations that focus on patient satisfaction demonstrate a willingness to build long-term relationships with their consumers and, thus, achieve a competitive advantage (Odili, Ihenyen & Okhawere, 2017). To monitor their performance for quality improvement and quality management, health care organizations would conduct consumer evaluations on a regular basis (Sansgiry & Jayawant, 2005). Moreover, as a general acceptance for trade-based organizations, the positive feedback obtained from the satisfaction of customers have also remarkable effect on the workers of the establishment (i.e., for community pharmacy this is true for the pharmacist and the employers). Overall, patient satisfaction acquired through the services provided by a community pharmacy result in good patient-pharmacist relationships, loyalty to the same pharmacy store, and a much better treatment of diseases with respect to the intact adherence to medical regiment (Castro & Ruiz, 2009; Crosby, Evans & Cowles, 1990; Ware & Snyder, 1975; Yi, 1990; Bartlett, Grayson, Barker, Levine, Golden & Libber, 1984).

CONCLUSION

Poor patient satisfaction comes with a few less than desirable consequences. According to the study of Medical Executive Council (2016), for every patient who complains, 70 percent of them who receive perceived deficient care will not visit that facility again;75 percent of dissatisfied health care consumers talk about it, and will tell nine family members or friends.

It is proven that great patient satisfaction comes with benefits for the staff too, which includes the possibility to enhance staff satisfaction and quality care, reduce provider malpractice risk, and increase health organizations financial development where patient satisfaction is

completely depend on the services provided by the pharmacy store and the workers of it. It is also known that patient satisfaction saves some costs such as advertising costs and also giving concern to patient satisfaction helps reduce the risk of marketing myopia which makes the pharmacy have a consumer driven service rather than product driven service and in the long run boost its sales and profits as all business is primarily because of profits. Patients who keep visiting the same pharmacy store concomitant to good interaction with the pharmacist are typical clinical examples to patient satisfaction, which in turn, guarantees the adherence to the medical protocol offered by a doctor. While patient's dissatisfaction will lead to the adverse of the satisfaction where by patient would not visit again and lead to decrease in sales.

As still for other areas health industry is also a dynamic area, routinely welcoming new developments. Therefore, patient satisfaction is a routine part of this dynamics. The more pharmacists follow up the patient satisfaction the more will be the quality as the quality is an always ascending parameter. This is the way to reply patient's expectations. As defined by Prakash "a satisfied patient is a practice builder" (Prakash, 2010).

The critical challenge for health care managers is to find and select the appropriate methods to measure overall patient satisfaction and its components. This challenge is made more complex by the fact that the quality of the service product is determined by the individual patient and his or her behavior as well as the technical quality and service quality provided by the organization. Consequently, what is perceived as merely acceptable services by one person may be a "wow" experience to another and totally unacceptable to a third. One note to keep in mind is that quality is not objective, it is personal, and therefore, finding out the right services for the community pharmacy is a challenging process requiring appropriate measurement (Ford, Bach & Fottler, 1997).

To cope with low Satisfaction and enhance better results, some steps should be taken by the pharmacist or other healthcare provider. Health Care providers should understand that improving patient satisfaction is about systems just as much as it is about smiles and that in order to improve, they should strive to create a blame-free environment (Rolig, 2015). Also, healthcare organizations should teach their employees, every single one, how to handle a patient or family member's complaint or concern (Rolig, 2015). Moreover, the correct language and the true communication determine the basics of patient satisfaction. Therefore, pharmacists must pay attention to use appropriate language and good verbal expressions (Jiao, 2015).

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ORALLY DISINTEGRATING TABLETS: A SHORT REVIEW

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ABSTRACT

The oral route is widely accepted and common method of drug delivery. Nowadays, with the rising the patient compliance and ease of drug administration, especially for pediatrics, new dosage forms are being introduced. When the ODT (oral disintegrating tablets) are placed on the tongue, with the help of saliva they disintegrate and then they are absorbed into the bloodstream from the oromucosal cavity without the need for water. These dosage forms have some advantages over the conventional oral dosage forms due to the fact that,amongst all other advantages, they bypass hepatic metabolism, which means that more of the drug is absorbed into the systemic circulation, leading to higher bioavailability and higher therapeutic efficacy. Novel techniques have been investigated to formulate ODT's in order to achieve desired tablet characteristics to improve API compatibility and patient acceptance with this oral dosage form.

Keywords: Oral dosage forms, oral disintegrating tablet, hepatic metabolism, novel techniques.

INTRODUCTION

Orally disintegrating tablet (ODT) is a dosage form that contains active ingredients and disintegrates without extra water when placed into oral cavity rapidly (Bi et al., 1996).

There are some variations related to the definition of the ODT's in different pharmacopoeias and FDA. According to FDA; ODT's are solid dosage forms that disintegrate in a few seconds after they are placed on the tongue (Davtyan and Voronkina, 2016).

The active ingredient is released, dissolved, or dispersed in the saliva in the oral cavity, and then after swallowing, it can be absorbed to blood circulation. ODTs are distinguished from classic sublingual tablets, which take more than few minutes to dissolve in oral cavity (Hu et al., 2013). To formulate a convenient oral dosage form for oral administration, we have to put into consideration swallowing difficulties, especially for geriatrics and pediatrics, leading to low patient observance (Handa et al., 2016). To solve the swallowing problem, ODT's have been developed. These rapidly disintegrate tablets in the oral cavity, after that are swallowed easily without extra water that is a significant advantage over classic type oral dosage forms (Desai et al., 2016)

In recent years, some new ODT technologies allow high drug loading and they provide an acceptable taste of the formulation after oral administration (Hooda, 2012). ODT's have been evaluated for their potency in developing bioavailability especially for drugs which have solubility problem by improving the dissolution profile of the formulation (Sharma et al., 2015).

Orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, rapid dissolving tablets, and fast dissolving tablets are names used to describe orally disintegrating tablets (Desai et al., 2016).

Advantages of ODT's

1. Increased bioavailability and faster onset of action: Oromucosal absorption leads to pre gastric absorption, especially for formulations where the active ingredient dissolves rapidly. Any pre gastric absorption avoids hepatic metabolism and this has a great edge over drugs that get metabolized fairly (Hannan et al., 2016).

2. Gastric and buccal regions are absorption areas for a lot of active ingredients. The buccal area has high amount blood circulation, but its permeability property is not high as the sublingual area. Drugs are quickly absorbed into the circulatory system under the oral mucosa. (Bhati and Nagrajan, 2012).

3. Enhanced safety drug profile that produce high quantity of toxic metabolites mediated by first pass hepatic metabolism, and for active ingredients that have important parts of absorption in oral cavity and gastrointestinal system (Sharma, 2013).

4. Increased patient compliance in ODT's due to:

• Removal of pain related with injection and convenience of administration compared to parenteral formulations.

• Ease of administration to patients having difficulty in swallowing (Klancke, 2003).

• Convenience where water is not available (Sharma et al., 2015).

5. Useful for pediatric and geriatric patients (Sharma, 2013).

6. It provides fast drug delivery because there is the large surface area contact with the oral cavity.

7. Enables high drug loading (Abdelbary et al., 2005).

Limitations in ODT's

1. One of the crucial disadvantages of ODT's is related to the mechanical strength of the tablets: ODT's have a porous and soft molded matrix and are compressed in a tablet form with low compression, which creates a friable and brittle tablet that is difficult to handle (Sotoyama et al., 2017).

2. Bitter drugs are not easy to formulate as ODT's. Therefore, taste masking materials should be used before formulating this kind of drugs (Baber, 1994).

3. Several ODT formulations may be hygroscopic and in this case, they cannot protect their physical integrity from humidity. Hence, they require specialized packaging (Sharma, 2013).

4. Decreasing the amount of saliva which can occur as a result of taking drug formulations like some antidepressants, can directly affect the bioavailability of the ODT formulations in a negative way (Mathew, 2015).

5. Dosage form stability (Abdelbary et al., 2005).

Target population for ODT's

Oral disintegrating tablets are more suitable for child and elderly patients who cannot swallow conventional solid dosage forms. Some examples of target population for Orodispersible tablets include:

• Patients who are non-compliant due to fear of choking (Pseudodysphagia).

• Infants and children.

• Patients undergoing radiation therapy who may be too nauseous to swallow (Sotoyama et al., 2017).

Technologies used for ODT formulations

The technologies used in preparation of ODT'S can be mainly categorized into two groups. These are: Conventional technologies and patented technologies. The latter is composed of more methods from the former. (Rao and Venkatachalam, 2010)

Conventional Technologies

1. Lyophilization: Lyophilization is a process that allows the drying of heat-sensitive active ingredient under low temperature by the application of vacuum to remove water by sublimation. Active ingredients are dissolved in an aqueous solution, transferred to preformed blisters and subjected to flush to freeze out with nitrogen, then placed in a refrigerator to complete the process (Davtyan and Voronkina, 2016).

2. Addition of Disintegrant: This method involves the addition of a material which has superdisintegrant property like microcrystalline cellulose derivatives and crosscarmellose sodium to the ODT formulations to obtain fast disintegration.

3. Molding: A Hydroalcoholic solvent and a water soluble material are used for this technique. Then, this mixture molded into tablets under low pressure than used in conventional tablet compression. (Davtyan and Voronkina, 2016).

4. Sublimation: Easily evaporated solid ingredients like camphor are used in the ODT formulations and the mixture is compressed into tablets. Then, a volatile material is evaporated from the formulation by sublimation method in order to obtain ODT formulation.

5. Spray-Drying: Spray-drying technique is achieved by utilizing gelatins as supporting agents, mannitol as a bulking agent, crosscarmellose as disintegrating agents and acidic and alkali materials to increase the deformation of ODT formulations (Manivannan, 2009).

6. Cotton candy process: This method includes the polysaccharides matrix of melting suddenly. Then, this candy matrix is blended with an active material and other formulation ingredients to ODT formulation.

7. Melt granulation: Hydrophilic waxy binder is used in this method. PEG-6-stearate is commonly used as a binder. But PEG-6-stearate is not used as a binder to increase physical strength of the formulation but it also used as a disintegrant in the ODT formulation (Mishra et.al, 2006).

Patented Technologies

Diverse techniques have been developed for ODT formulations. Finished ODT formulations are evaluated according to theirs different parameters like mechanical resistance, stability, and bioavailability. (Nagar et al., 2011).

Some examples of patented technologies are:

1. ZYDIS®:

Process involved: Lyophilization

Patent owner: R.P.Scherer Inc

Advantages: Easy dissolution, increased bioavailability on ODT.

Disadvantages: Costly technique, and stability problem at high temperature.

Brand name drugs: Loratidine (Claritin Reditab®) (Baber, 1994).

2. ORASOLV®:

Process involved: Tablet compression.

Patent owner: Cima Labs Inc.

Advantages: Taste masking is twofold and rapid dissolution on ODT.

Disadvantage: Low mechanical strength.

Brand name drugs: Paracetamol (Tempra Quicklets®), Zolmitriptan(Zolmig Repimelt®) (Bi et al., 1999).

3. DURASOLV®:

Process involved: Molding

Patent owner: Cima Labs Inc.

Advantages: Higher mechanical resistance.

Disadvantage: Cannot be used for active ingredient with low potency.

Brand name drugs: Hyoscyamine Sulfate (NuLev®), Zolmitriptan (Zolmig ZMT®) (Hannan et.al, 2016)

4. FLASHTAB®:

Process involved: Lyophilization

Patent owner: Ethypharm.

Advantage: Only conventional tableting technology.

Brand name drugs: Ibuprofen (Nurofen, Flashtab®) (Sastry et al., 2000).

5. ORAQUICK®:

Process involved: Micro-mask taste masking.

Patent owner: KV Pharm. Co., Inc.

Advantage: Easy production and appropriate for heat-sensitive APIs.

Brand name drugs: Hyoscyamine Sulfate® ODT (Velmurugan and Vinushitha, 2010).

6. FLASHDOSE®:

Process involved: Cotton candy method.

Patent owner: Fuisz Technology.

Advantage: High surface area on ODT.

Disadvantage: It needs high temperature for melting the matrix.

Brand name drugs: Tramadol HCl (Relivia Flash dose®) (Mishra et.al, 2006).

Quality controls of ODT's

The quality control tests which are conducted over ODT's are almost identical with conventional tablets, including: Weight variation, hardness, friability test, in-vitro, in-vivo disintegration tests, uniformity of dispersion are performed for the purpose of ensuring uniformity in the weight of tablets in a batch. The hardness of a tablet indicates its resistance Kg value of the applied force for breaking the tablet is determined of the ODT tablet (Thyssen et al., 2007).

As distinct from conventional tablets, according to FDA, in-vitro and in-vivo disintegration time of ODT's should be less than 30 second (Kraemer et al., 2012).

Differences in quality control of ODT's what should be highlighted are wetting time and taste sensation/mouth feel.

The determination of wetting time of tablets can be performed easily. For this aim, tissue papers are put in a Petri-dish containing 0.2% w/v solution. Then, sample tablet is placed on the

surface of the paper.The time needed for the tablet to develop a blue color on the upper surface is noted as the wetting time (Zhang and Carlin, 2010).

Mouth feel is an important parameter for ODT's as patients may sometimes reject tablets with an unpleasant mouth feel. The sample tablet is applied on the tongue in order to evaluate of its mouth feel. Then, healthy volunteers evaluate the tablet taste with using different score values like 0 = good, 1 = tasteless, 2 = slightly bitter, 3 = bitter, and 4 = awful. (Bhati and Nagrajan, 2012).

CONCLUSION

As a conclusion; when we compare the ODT's with conventional oral dosage forms, we can say that they have important advantages like higher bioavailability and patient compliance. Nevertheless, ODT's have some disadvantages like limited tablet weight, short disintegration time, high cost, and packaging problems. Orally disintegrating tablets may be evaluated as a first option for pediatric and geriatric patients who have swallowing problem.

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